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Southern African Journal of HIV Medicine

- Guideline: management of mental health disorders in HIV-positive patients
- Is it lawful to offer HIV self-testing to children in South Africa?
- Perceived adherence barriers among patients failing second-line ART
- Impact of ART on pregnancy outcomes
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Sincerely,
Landon Myer

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MESSAGE
From the Editor

This issue features a diverse sampling of HIV medicine from across South Africa (SA). Several contributions provide a glimpse into the future of the HIV epidemic in the country, and in turn, our responses.

In the area of the prevention of mother-to-child transmission (PMTCT) of HIV, the use of triple-drug antiretroviral therapy (ART) regimens in HIV-infected pregnant women is becoming standard of care – whether as short-term prophylaxis against mother-to-child transmission or as lifelong treatment. In Europe and North America, the use of ART in pregnancy has raised concerns around potential toxicities in HIV-exposed pregnancies and infants. It is important to remember that almost any such toxicity is likely to be uncommon in comparison to the risk of vertical HIV transmission. Still, with more than 200 000 pregnant women exposed to ART each year across SA, the possibility that *in utero* ART exposure may contribute to adverse pregnancy or child health outcomes requires consideration. Aniji *et al.*[1] report the outcomes of a small cohort of HIV-exposed pregnancies from Limpopo Province. While the sample is small and there are limitations to the design, the findings for no association between early *in utero* ART exposure and either prematurity or low birthweight appear somewhat reassuring. There are a number of major, ongoing studies across the country investigating these issues, and with the 2013 revisions to the PMTCT guidelines in full implementation, additional evidence is eagerly anticipated.

In thinking about health systems, we know that nurse-driven services form the basis of primary healthcare across SA, and most HIV-positive individuals are managed through nurse-initiated management of antiretroviral therapy (NIMART) services. One of the core challenges to NIMART services is providing appropriate clinical support to nurse practitioners. In this regard, the National HIV & TB Health Care Worker Hotline serves as a valuable resource. Swart *et al.*[2] present a descriptive analysis of the queries that the hotline has received recently from nurses. Their report provides readers with valuable insight into the types of questions that arise in primary care, and with this, a valuable basis for future training interventions.

There is considerable excitement in public health circles about human papillomavirus (HPV) vaccination across SA and its eventual impact on cervical cancer epidemiology, particularly in HIV-positive women. However, the manifestations of HPV in men have been largely neglected. Delany-Moretlwe *et al.*[3] review the epidemiology and natural history of HPV in men, emphasising the role of circumcision and vaccination in future prevention efforts. In addition, self-testing for HIV infection has been controversial, both locally and internationally, as a strategy to increase awareness of individual HIV status. Strode *et al.*[4] comment on the ethico-legal aspects of HIV self-testing in adolescents, and raise important questions about the risks v. benefits of allowing self-testing in young people – clearly a double-edged sword.

Inevitably, the number of patients initiating second-line ART regimens is growing in most parts of the region, and following from this, a small but increasing number of patients are found to be failing second-line regimens. Failure of a second-line regimen is considered grounds for specialist referral in many settings, but this is certainly not always possible. This issue features two contributions regarding the management of patients on second-line regimens in primary care settings in Cape Town. First, in a group of 69 patients with sustained viraemia on a second-line regimen, Garone and colleagues[5] report that a substantial proportion appeared to re-suppress with targeted adherence support. In parallel with this, Barnett *et al.*[6] present a qualitative study using a unique photo-based methodology to suggest that the barriers to adherence in this group of patients vary notably between patients and providers, underscoring the complexity of supporting patient adherence. This research is from small, local studies, but is surely a harbinger of the kinds of issues that the national ART rollout will face in the years to come.

Finally, few among us would question the role of mental health as part of long-term health outcomes in HIV-positive patients, including the interplay of mental disorders and treatment adherence, as well as the neurocognitive effects of HIV disease. However, many providers struggle with practical steps to support the mental health of their patients. To help fill this gap, the Southern African HIV Clinicians Society has produced a valuable guideline[7] on the management of different types of mental health disorders in HIV-positive patients. The guideline is at once comprehensive but accessible – an impressive feat given the breadth and complexity of mental disorders – and hopefully readers will be able to put it to good use in practice.

Happy reading.

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MESSAGE
From the Executive

I have spoken before about where we are in the HIV epidemic in South Africa (SA) today. The heady days when there were scientific breakthroughs every few months are over. The excitement surrounding increased treatment access, improved antiretroviral therapy (ART) regimens and nurse-initiated management of antiretroviral therapy (NIMART) have settled; HIV no longer makes the news every other day. What we have achieved is truly remarkable: SA has the largest antiretroviral (ARV) programme in the world, with estimates of as many as 2.4 million people receiving ART. HIV healthcare workers can be proud of the contributions they have made – and continue to make – to lessen the burden of this disease.

Now that the excitement has passed, it is time to get on with the slog of rolling out and sustaining a massive treatment programme. What we are finding is that this may actually be our greatest challenge yet. In this issue of *SAJHIVMED* you will find an insert highlighting key points from a national survey conducted by the Stop Stock Outs Project assessing ARV and tuberculosis drug stockouts at the facility level. As you will see, the report found that the problem is far beyond previous estimates, and affects most provinces. The telephone survey, which took place during September and October 2013, obtained information from over 2 000 health facilities. Around one in every five facilities in SA reported a stockout or shortage during the 90-day period covered in the survey. Free State, Limpopo and Mpumalanga provinces were the worst affected, with 54%, 41% and 26% of facilities affected, respectively. In 20% of facilities facing stockouts, patients were sent away with no medicine.

To some of you these results won't be surprising at all, as you are negotiating medicine shortages and stockouts on a daily basis. What the report makes clear is that stockouts are so common, that they represent a credible threat to the success of the national ARV programme.

The report is also a reminder that although the fight may be over, the battle is far from won. As we begin 2014 and prepare to mark ten years of ART in the public sector, we must celebrate what we have achieved, but not become complacent about where we need to be. As healthcare workers we must redouble our efforts and contribute our part to strengthening the health system, whether it's reporting medicine stockouts, corruption or inefficiencies within the system. What we have accomplished in ten years is no less than remarkable; what is possible for us to achieve in the next ten is truly inspiring.

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Call for submissions

A decade of antiretroviral therapy in the public sector

As 2014 marks the 10-year anniversary of the public sector rollout of antiretroviral therapy (ART) services in South Africa, *SAJHIVMED* is planning a special edition to reflect on the lessons learned and celebrate the achievements during this time.

As part of this, *SAJHIVMED* is calling for submissions from healthcare workers, policy makers and researchers towards 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, often under difficult circumstances.

These submissions can take the form of editorials of 500 - 1 000 words or longer, 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 15 January 2014 via the journal website (http://www.sajhivmed.org.za) or email the Editor directly (landon.myer@uct.ac.za).

FORUM

Is it lawful to offer HIV self-testing to children in South Africa?

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Health-facility-based HIV counselling and testing does not capture all children and adolescents who are at risk of HIV infection. Self-testing involves conducting an HIV test at home or in any other convenient space without the involvement of a third party. It is increasingly being argued that it should be incorporated into national HIV-prevention programmes as one of a range of HIV counselling and testing approaches. Although this model of HIV testing is being seen as a new way of reaching under-tested populations, no studies have been conducted on offering it to children. HIV self-tests are now available in South Africa and are sold without the purchaser having to be a certain age. Nevertheless, all HIV testing in children must comply with the norms set out in the Children's Act (2005). Here we explore whether offering self-testing to children would be lawful, by outlining the four legal norms that must be met and applying them to self-HIV testing. We conclude that, although children above the age of 12 years could consent to such a test, there would be two potential obstacles. Firstly, it would have to be shown that using the test is in their best interests. This may be difficult given the potential negative consequences that could flow from testing without support and the availability of other testing services. Secondly, there would need to be a way for children to access pre- and post-test counselling or they would have to be advised that they will have expressly to waive this right. The tests are more likely to be lawful for a small sub-set of older children if: (*i*) it assists them with HIV-prevention strategies; (*ii*) they will be able to access treatment, care and support, even though they have tested outside of a health facility; and (*iii*) psychosocial support services are made available to them via the internet or cell phones.

S Afr J HIV Med 2013;14(4):151-154. DOI:10.7196/SAJHIVMED.987

Globally, in 2010, 3.4 million children aged <15 years were HIV-positive, 90% of whom were living in sub-Saharan Africa.[1] In 2011, UNAIDS estimated that in South Africa (SA) alone there were about 460 000 children aged 0 - 14 years living with HIV. Health-facility-based HIV counselling and testing (HCT) does not capture all children and adolescents who are at risk of HIV infection.[2-5] The large number of children not treated suggests that there are still relatively low rates of testing among children.[6] Children are either being missed by the prevention of mother-to-child transmission of HIV (PMTCT) services, are surviving past two years of age without being tested, or are infected after birth through child abuse or health-service-acquired infection. In addition, children aged >12 years may be at increased risk because of their own sexual activity.[7-9] Similarly, rates of testing among adolescents are particularly low, especially among young males, despite this being an at-risk population.[9] This highlights the need for new, targeted, innovative, age-appropriate counselling and testing services for children and adolescents.[10]

Low uptake of HIV testing is attributed to both supply and demand factors. On the supply side, key factors include inconvenient clinic hours, the inaccessibility of health facilities and the high cost of travelling to clinics.[11] In terms of demand, even if testing services are available, these do not always translate into willingness to test.[12] Research has shown that deep-seated concerns regarding stigma, discrimination and the fear of positive results act as barriers to increased uptake of HIV-testing services in high HIV prevalence settings.[13]

HIV self-testing (HST) refers to the performance of a simple saliva or blood-based test similar to a pregnancy test in the privacy of a home or in any other convenient space without the involvement of a third party.[14,15] Richter *et al.*[16] point to four potential benefits of such testing; it could: encourage regular HIV testing, allay fears of stigma and possible breaches of confidentiality, decrease the overall costs of HIV testing through removing the need for face-to-face counselling, and facilitate earlier diagnosis and access to treatment. Based on increasing evidence from feasibility and acceptability studies, activists and public health policy-makers have argued that HST should be incorporated into national HIV-prevention programmes as one of a range of community-based HCT approaches.[17,18] Community-based HCT models such as home-based and mobile testing have significantly improved testing uptake and have reached higher rates of first-time testers in sub-Saharan Africa.[19-23]

HIV self-tests are now available in SA. They sell for approximately R100 at pharmacies and have a shelf-life of two years. They can also be ordered via the internet.[24] Detailed instructions are in the packaging and they generally require the user to place a drop of blood on a test strip; if a dark line develops on the strip, it indicates that the person is HIV-

positive.[24] Highly accurate oral self-test kits exist with a sensitivity of 92% and a specificity of 99.9%.[17,24] While some HIV self-tests are available in SA, the distribution and use of these tests is largely unregulated as the country's legal and policy frameworks do not specifically allow for their dissemination.[16] This means that there are no specific regulatory restrictions on the sale of such products to persons aged <18 years. Nevertheless, all HIV testing in children must comply with the norms set out in the Children's Act (2005), and accordingly, regardless of the model of testing, must meet these minimum standards.[25]

Although this innovative model of HIV testing is being seen as a new way of reaching under-tested populations, no studies have been conducted on offering HST to children. There has also not been any conceptual work exploring: (*i*) whether this is an appropriate model of testing to offer to children; and (*ii*) if it was found to be acceptable, whether there would be country-specific legal barriers to providing it to them. Here we explore whether offering self-testing to children would be lawful in terms of the Children's Act, by outlining the four legal norms that must be met and by applying them to HST.

The legal framework

The Children's Act (2005) describes the rights of children to consent independently to a number of health interventions.[26] It provides expressly for *when* and *how* HIV testing may be done with children. The drafters of the Act considered HIV testing to be an area in which children's rights were being abused and special protection was needed. Accordingly, sections (s) 130 - 133 of the Children's Act create four norms regulating HIV testing. These are that a child: (*i*) may only be tested for HIV in specific circumstances (s 130(1)(a) - (b); (*ii*) must be counselled before and after the HIV test (s 130(1)(a) and 132); (*iii*) can consent independently to an HIV test from the age of 12 years (s 130(2)); and (*iv*) has a right to privacy regarding their HIV status (s 133).

The circumstances in which a child may be tested for HIV

Parliament has expressly limited the circumstances in which HIV testing may be undertaken with children.[25] The Act provides that, other than in exceptional circumstances, HIV testing in children will only be lawful if it is in the best interests of the child and is undertaken with consent.[25] This means that, unlike most other health interventions where children of a certain age or with a particular level of capacity can autonomously choose the intervention, with HIV testing it must be demonstrated that taking the test is in their best interests.[26]

Our courts have generally held that in determining the best interests of the child, an effort must be made to establish if a decision will promote a child's physical, moral, emotional and spiritual welfare.[27] Furthermore, it should be seen as a flexible standard which is applied with due consideration to the individual circumstances of the child.[28] The Children's Act gives substance to this assessment by listing a number of factors that should be used in such an analysis. These include: the effect that the decision will have on the child's circumstances, its impact on their physical and emotional security, as well as the need to protect the child from physical or psychological harm.[25]

If we apply these principles to HIV testing generally, we would argue that testing undertaken for prevention or treatment purposes would be in the best interests of the child as it promotes their right to basic healthcare services in terms of s 28 of the Constitution.[29] However, HIV testing aimed at discovering a child's HIV status and using this information to discriminate against the child, by e.g. withholding a bursary for tertiary education, would be contrary to the child's best interests.

If we apply these principles to HST specifically, we submit that the following factors would need to be taken into account in establishing whether it could be in the child's best interests: (*i*) the emotional impact of a child discovering their HIV status on their own, and potentially without support; (*ii*) the possibility that adults could use self-testing to coerce children to be tested for HIV; (*iii*) the confidential nature of such testing, which may meet the needs of some adolescents with privacy concerns; (*iv*) the availability and accessibility of other forms of HIV testing; (*v*) the child's age, level of maturity and ability to cope with this particular form of testing; (*vi*) the views of the individual child on HST; and (*vii*) the capacity of the child to consent to the HIV test.

If we weigh and balance the above factors, we would argue that HST could not be considered to be in the 'best interests' of all children. Our reasons are: Firstly, several authors have suggested that many would be too young to cope with the impact of receiving an HIV test result on their own. Secondly, others have suggested that in the absence of pre- and post-counselling there is potentially a risk of suicide for an individual who might be distressed.[30] Thirdly, a study conducted in Kenya[31] revealed that the main challenge of a self-testing programme was providing links to support services. Napierala Mavedzenge *et al*.[32] highlight how HST delinks testing and counselling, potentially depriving individuals of access to a range of critical services.[32] Furthermore, if other testing services are accessible and available, it would seem more appropriate that young children use such services where they can be assured of both support and access to treatment. Fourthly, there are some concerns in the literature that self-testing may not be in the best interests of children in that it could be used in a coercive way in the home environment and could possibly result in an abuse of individual rights. It appears that the authors are alluding to the possibility of the test being used by adults to test children at home as, e.g., 'punishment' for being sexually active. Given that the test is done in private, it would always be difficult to ensure that it is not being undertaken for the benefit of third parties. However, there are no data available to support this potential risk.[32,33]

Nevertheless, it is possible that for certain older children (aged ≥16 years) who are at high risk of HIV infection, this may be a testing model that appeals. We base this on the emerging evidence on self-testing for adults. Several studies have documented high acceptability, uptake and accuracy of oral self-testing.[20,34] Furthermore, adult users of HIV self-tests have found them easy to use, the instructions comprehendible,[35] and that they have a high level of accuracy (99.2%).[20] This model of testing offers high levels of personal control to children with the capacity to consent to testing and privacy for those who wish to establish their HIV status without the involvement of a third party. If accompanied by alternative forms of support such as telephone counselling or internet-based advice, children may not necessarily be lost to care.

Consent

The Children's Act states that children aged >12 years can consent independently to an HIV test.[26] Given that there is no express capacity requirement for HIV testing, it is presumed that all children aged >12 years can make this decision.[27]

If we apply these principles to HST, it means that children as young as 12 years could theoretically consent without assistance to an HIV self-test, provided that the other obligations in the Children's Act relating to

the best interests of the child and counselling are met. One issue raised in the literature is the possibility of such consent being coerced.[33] Accordingly, it has been submitted that to avoid this possibility, laws and policies should be put in place to ensure that vulnerable groups such as children are not tested against their will.[36]

Pre- and post-test counselling

The Children's Act (s 132) requires pre- and post-test counselling by an appropriately trained person. The Act does not describe the manner in which the counselling should be provided or the information that must be given to children during the counselling processes. McQuoid-Mason[37] submits that this provision simply means that 'during pre-test counselling the benefits, risks and social implications of an HIV test must be explained to the child, while during post-test counselling the implications of the results must be explained'.

The lack of accompanying counselling is a key concern in the literature on self-testing.[36] It has been argued that pre-test counselling provides an opportunity to make informed decisions on whether to test or not, while post-test counselling informs individuals of their HIV status, provides information on HIV prevention, encourages them to test regularly, reduces the risk of HIV transmission to others, and offers psychosocial or referral support to HIV-positive clients.[36]

Counselling is a mandatory requirement in the Children's Act, which means that testing without counselling is unlawful unless a child waives their right to this service. This therefore serves as an obstacle to self-testing by SA children. The Act does not specify the nature of the counselling; thus, it is possible that, e.g., telephone counselling could suffice. The National HIV Counselling and Testing Policy also does not specify that counselling must be face to face. Instead, it provides a list of the minimum information that should be provided in pre-and post-test counselling sessions.[38]

Confidentiality

The Children's Act (s 133) provides that children have the right to confidentiality regarding their HIV status.[26] Furthermore, information on a child's HIV-positive status may only be disclosed with the consent of that child if they are aged >12 years.[37]

A key strength of the self-testing approach is that it ensures that confidentiality is maintained. A study conducted in Singapore[39] found that confidentiality was a key reason why people preferred to buy over-the-counter HIV test kits. The right to confidentiality in the Children's Act is therefore not a barrier to self-testing.

Conclusion

There is some preliminary evidence that HST could be a valuable new HIV-prevention strategy in that it gives persons at risk of HIV infection another way of discovering their HIV status. Although no research has been undertaken on whether this model is suitable for children, we argue that this work needs to be done as a matter of urgency, as they are a group at high risk of HIV infection.

This review of the SA legal framework has shown that the law does not expressly prohibit or regulate the offering of self-tests to children. Nevertheless, the way in which self-testing was offered would have to comply with the Children's Act. This means that only children aged >12 years could use an HIV self-test on their own, as below this age they do not have the capacity to consent. Furthermore, there would be two potential legal obstacles. Firstly, it would have to be shown that using an HIV self-test is in their best interests. This standard may be hard to meet, given the potential negative consequences that could flow from testing without support and the availability of other forms of HIV testing. Secondly, there would need to be a way for children to access pre- and post-test counselling or for children to be advised that they will expressly have to waive this right. Thus, simply offering self-HIV tests to all children aged >12 years would not be lawful, unless it could be shown that it was in their best interests and that counselling was provided.

Given these legal obstacles, we would suggest that it is only a small sub-set of children for whom such testing would be considered lawful. We argue that for older children (aged >16 years) self-testing may be in their best interests if: (*i*) it assists them with HIV-prevention strategies; (*ii*) they will be able to access treatment, care and support even though they have tested outside of a health facility; and (*iii*) psychosocial support services are made available to them via the internet or cell phones.

It is submitted that although self-testing in children is an under-explored issue, it requires further debate and discussion. Policy guidance is needed on when a self-test would be in a child's best interests and how children who choose such a testing model can receive counselling and appropriate referral to services, if required.

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GUIDELINE
Management of mental health disorders in HIV-positive patients

by the Southern African HIV Clinicians Society

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

These guidelines are intended as a reference document to assist HIV nurse and doctor clinicians in managing mental health disorders. It is intended to improve awareness, knowledge and capacity to support patients living with HIV and mental health disorders.

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1. Introduction

'*There is no health without mental health*'.[1,2] Mental disorders are highly prevalent among people living with HIV/AIDS (PLWHA), with major depressive disorder (MDD) occurring almost twice as frequently among this group than in the general population.[3] Mental disorders may increase an individual's risk for HIV infection through increased social vulnerability, altered risk behaviour, associated substance misuse and loss of control within sexual relationships. Conversely, such disorders may also arise as a direct result of HIV neuro-invasion or psychosocial stressors, or due to complications of antiretroviral therapy (ART).[4,5]

Despite their prevalence, mental disorders are often under-diagnosed or inadequately managed in PLWHA. The impact of untreated mental disorders on health outcomes is substantial. It is imperative that clinicians caring for HIV-positive individuals actively screen for, diagnose and manage mental disorders in this population.[6]

2. Overview of the guideline

This guideline is intended to improve primary care HIV clinicians' knowledge and capacity to manage mental health disorders. It is also intended to heighten HIV clinicians' awareness of the need to integrate HIV and mental healthcare within their daily practice.[7]

The following conditions and issues are addressed here:

- HIV testing in the context of mental disorders
- common mental disorders (CMDs)
- severe mental disorders (SMDs)
- HIV-associated neurocognitive disorders (HANDs)
- grief
- healthcare worker (HCW) burnout and vicarious trauma.

These guidelines do not encompass substance use disorders or triple diagnosis (HIV/mental disorder/substance use disorder), or mental disorders among children and adolescents; these topics will be covered in separate, future guidelines.

3. Principles of HIV testing in patients with mental disorders

- All patients with mental disorders (in-/out-patients, voluntary/involuntary patients admitted under the Mental Health Care Act) should be offered HIV testing, HIV-prevention/risk-reduction education and access to condoms
- The presence of a mental disorder does not automatically equal incapacity to consent to HIV testing
- Capacity to consent to HIV testing must therefore be assessed on an individual basis, particularly in patients with SMDs
- For capacity to consent, patients should be able to:
  - understand why they are being tested
  - understand and report on the consequences of a negative or positive test result
  - report how they are likely to respond to either result
- Patients should be included in decision-making about their HIV testing, as far as possible in all cases
- If the patient is assessed as being incapable of giving informed voluntary consent (e.g. active psychosis, dementia), then proxy consent may be sought
  - Proxy consent
    - Consent is given by someone else acting in the best interests of the patient, e.g. a senior clinician in charge of the case
    - The reasons for testing and the process must be documented carefully
    - If the patient regains capacity, then disclosure of the results is paramount

  - There may be a need to disclose the results to the carer, if the patient has irreversible neurocognitive impairment, with cognisance of potential stigma/discrimination
- Disclosure
  - All medical information should be kept confidential at all times
  - Information should preferably be released only with patient consent, unless the information is relevant to clinical management/medical aid procedures
- The procedure to follow when testing for HIV in patients with mental disorders is shown in Fig. 1.[8,9]

4. Assessment and diagnosis of CMDs

The term 'common mental disorder', used to describe disorders that are highly prevalent in the general population (usually occurring at rates >10%), typically includes:

- depressive disorders
- anxiety disorders
- substance use disorders (not included in this guideline).[10]

Box 1 provides an overview of CMD prevalence. In South Africa (SA), 26 - 38% of PLWHA have a CMD (v. 12.6% of the general population).[6] CMDs have not decreased in prevalence with the introduction of ART.

Box 1. Overview of CMD prevalence

- Two-fold increase in prevalence in HIV-positive individuals[3,8]
- In SA, 26 - 38% of PLWHA have a CMD (v. 12.6% of the general population)[9]
- Some 20 - 60% of PLWHA are affected by some form of psychiatric disorder[10] (depressive disorders are most common)
- CMDs are **not** decreasing in the ART era
- CMD prevalence is influenced by viral central nervous system (CNS) pathology, concomitant psychosocial stressors and the nature of HIV as a life-threatening and stigmatised illness
- CMDs often go undiagnosed and untreated in this population

4.1 Screening

Clinicians should screen routinely for CMDs, because patients rarely volunteer information about their mental state. Box 2 includes three questions to ask patients. Due to the high prevalence of gender-based violence (GBV) in SA, we recommend clinicians also incorporate screening for GBV.[11]

Box 2. Screening for depression and GBV

Brief routine screening questions for depression

- How have you been in the past month/since your last visit?
- Have you been feeling more stressed than usual?
- Have you been feeling down, low, heart-sore or depressed?

Brief screening questions for GBV

- How are things going in your relationship with your partner?
- Have you ever been emotionally, sexually or physically victimised?

Certain patients may require more intensive screening, including:

- those at their first ART assessment
- those responding poorly to ART (detectable viral load (VL)/adherence issues)
- those exhibiting worrying behaviour (looking anxious/depressed, expressing suicidal ideation or self-harm).

Patients who respond positively to one of the brief screening questions should be administered a validated screening tool that is appropriate for primary healthcare settings, such as the Patient Health Questionnaire (PHQ)-9 (Fig. 2).[12]

4.2 Risk assessment

It is important to assess suicide risk. Clinicians should always ask about suicidal ideation in patients with depressive symptoms. High risk is indicated by:

- a clear plan for ending life
- an identified lethal method
- a previous suicide attempt
- a lack of social support
- severe (psychotic) depressive disorder.

See also the 'SAD PERSONS' scale (Fig. 3).[13]

4.3 Mental state assessment

Assessing the patient's mental state is as important as a physical examination. Clinicians should conduct and document a 'mental state examination' (Box 3) at each visit.

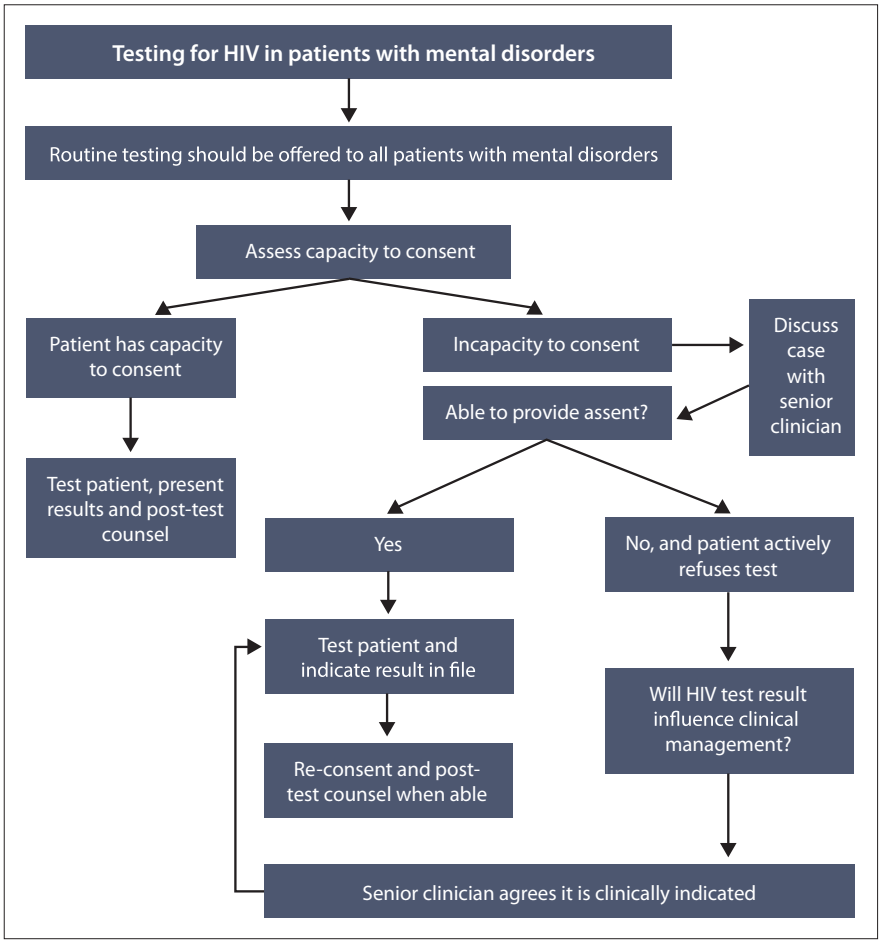

Fig. 1. Testing for HIV in patients with mental disorders.[8,9]

Box 3. Recording the mental state examination

Document the mental state examination, as for physical examination:

- appearance and behaviour: grooming, eye contact, motor activity, etc.
- level of consciousness: orientation for time, person, place
- cognitive function (see section 6: HANDs)
- mood: objectively euthymic, depressed, elevated
- speech, form and content of thinking: flow of speech, coherence and content of thinking (delusions, pre-occupations, ruminations)
- perceptual abnormalities: evidence of hallucinations
- insight into own condition

4.4 Depression in PLWHA (including MDD and less severe types)

Up to 25% of PLWHA in SA are thought to suffer from some form of depression during the course of the illness. Severe depression, also known as MDD, occurs in about 5 - 10% of patients, while minor depressive disorders are diagnosed in about 15 - 20%.[6,10] Even mild depression can lead to erratic adherence, poor care engagement and ultimately to more serious outcomes. Major depression is diagnosed by the presence of five or more of the symptoms listed in section 4.4.1 for at least two weeks, while minor depression is diagnosed when fewer symptoms are present and/or for shorter periods.

4.4.1 Symptoms of depressive disorders

Depressive disorder is characterised by five or more of the following occurring together in a two-week period:

- **EITHER:** depressed mood almost all day every day
- **OR:** loss of interest or enjoyment of usually pleasurable activities for most of the day
- **AND (occurring nearly every day):**
  - significant weight loss when not dieting or due to medical illness, or weight gain (e.g. >5% body weight change in a month), or decreased/increased appetite
  - insomnia or hypersomnia
  - psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or of being slowed down)
  - fatigue or loss of energy
  - feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) – not merely self-reproach or guilt about being sick
  - diminished ability to think or concentrate, or indecisiveness (either by subjective account or as observed by others)
  - recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation

Over the past 2 weeks how often have you been bothered by any of the following problems	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling or staying asleep; or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things such as reading the newspaper or watching TV	0	1	2	3
8. Moving or speaking so slowly that others could have noticed. Or the opposite - being so fidgety and restless that you have been moving around a lot more than usual	0	1	2	3

Over the past 2 weeks how often have you been bothered by any of the following problems	Not at all	Several days	More than half the days	Nearly every day
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Add columns				
Total				
0 - 4: No depression 5 - 9: Mild depression 10 - 14: Moderate depression				
15 - 19: Moderately severe				
20 - 27: Severe				
	Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
If you checked any of the problems, how difficult have these problems made it for you to do work, take care of things at home, or get along with other people				

Total score:

Total score	Depression severity
0 - 4	No depression
5 - 9	Mild depression
10 - 14	Moderate depression
15 - 19	Moderately severe depression
20 - 27	Severe depression

Fig. 2. Patient Health Questionnaire (PHQ)-9.

S	Sex: male gender represents a higher risk
A	Age: extremes of age are at higher risk (e.g. <18 years and >55 years)
D	Depression or other psychiatric comorbidity are at higher risk
P	Previous attempts: those with a past history of [suicide] attempts are at higher risk
E	Ethanol/alcohol or other substance use/abuse
R	Rational thinking loss, e.g. psychosis with command hallucinations
S	Social support: no social support confers a higher risk
O	Organised plan
N	No spouse
S	Sickness: medical or psychiatric illness may confer a higher risk
Score card	
0 - 2 points	This patient may be sent home but one needs to ensure follow-up in the future
3 - 4 points	Close follow-up needs to be ensured and hospitalisation considered
5 - 6 points	Hospitalisation is strongly considered
7 - 10 points	Ensure hospitalisation and consider involuntary admission if necessary

Fig. 3. 'SAD PERSONS' scale (yes for any letter = 1 point).

without a specific plan, or a suicide attempt or a specific plan for committing suicide.[14]

Psychotic symptoms may occur in severe depressive disorders. These usually consist of delusions (guilt, nihilistic, of death, occasionally paranoid) and occasionally hallucinations (these are usually transient).

If the screen is positive for a CMD, conduct and document a mental state examination (see Box 3).

4.4.2 Differential diagnosis of depression

- Minor or sub-threshold depressive disorders are characterised by the presence of some symptoms, but do meet all criteria for MDD
- Major depression
- Adjustment disorder: a depressive reaction to psychosocial stressors including HIV diagnosis
- Bereavement (see section 7)
- Mood disorder secondary to a medical condition/substance, e.g. HIV, hypothyroidism, efavirenz (EFV), alcohol
- Bipolar disorder: there is usually history of a previous episode of elevated mood resulting in abnormal behaviour, e.g. reduced sleep, increased energy/libido/risk-taking, etc.

4.4.3 Management of MDD (moderate to severe depression according to the PHQ-9)

4.4.3.1 Hospitalisation

The patient requires hospitalisation:

- if there is a high suicide risk
- in complex cases: the presence of psychosis and/or minimal social support and/or a poor response to out-patient treatment and/or a diagnostic dilemma
- in complex medical comorbidity (to monitor antidepressant medication)
- in the event of severe psychomotor retardation or no eating/drinking.

4.4.3.2 Initiation of antidepressant treatment

The initiation of antidepressant therapy in patients with CMDs is based on a step-wise approach, using the PHQ-9 as a guide to diagnosis, management and follow-up (Box 4). It is essential to remember that one 'starts low and goes slow' as patients with HIV/AIDS are often more sensitive to side-effects of medication.

Box 4. Introducing an antidepressant: 'Start low and go slow'*

- Initiate 20 mg fluoxetine (or similar) at the lowest available dose and refer to psychosocial support services where available
- Reassess using the PHQ-9 at 2 - 4 weeks and for side-effects (e.g. irritability, nausea, headache, disturbed sleep patterns); most side-effects settle within 2 weeks
- If after a total of 6 - 8 weeks there is no/minimal improvement, then increase the dose and reassess with the PHQ-9 in 4 - 6 weeks
- If after reassessment there is still no improvement, then up-refer

* Fluoxetine and amitriptyline are the only antidepressants on the primary-level essential drugs list. Nurses are not currently permitted to prescribe – refer to a doctor. If unsure at any point, then phone the referral centre for advice. If the depression worsens at any point, or if suicide risk increases, then refer the patient.

4.4.5 Psychotherapy[15]

- If available, patients should be referred for psychological assessment and treatment
- Evidence-based psychotherapy interventions for PLWHA and depression include:
  - cognitive-behavioural therapy (CBT): a form of psychotherapy addressing dysfunctional emotions and maladaptive ideas through a goal-directed systematic process
  - interpersonal therapy (IPT): a form of psychotherapy that is time-limited and encourages patients to regain control of mood and functioning through the therapeutic alliance
  - group IPT (IPT-G): a form of therapy that employs the same basic structure and focus of individual IPT, though modified to capitalise on the group format
- Key determinants of successful therapy include the motivation of patients to attend multiple sessions and the access to clinics/times.

4.5 Anxiety disorders

Anxiety disorders in PLWHA are common. Some studies report that between 20% and 60% of HIV-positive adults suffer from some form of psychiatric disorder. The most recent general population study of the prevalence of mental disorders in SA was the SASH study, which reported a combined 12-month prevalence of depressive and anxiety disorders of 12.6%.[6] It is important to recognise and treat anxiety disorders as they have been associated with increased rates of poor treatment compliance and high-risk behaviour. Quality of life is also adversely affected by anxiety disorders (Table 1).

5. SMDs and HIV/AIDS

These disorders occur less frequently in the general population (usually at rates <5%) and include:

- schizophrenia
- bipolar mood disorder
- MDD with psychotic features.

Box 5 describes the prevalence and impact of SMDs.

Box 5. Prevalence and impact of SMDs

Prevalence

- HIV among those with SMDs: 2.6 - 59.3% in sub-Saharan Africa[8]
- SMDs in the HIV-positive population: up to 15%
- New-onset psychosis among the HIV-positive population: 0.2 - 15.2%[16]

Impact

- SMDs lead to an increased risk of acquiring and transmitting HIV
- SMDs may impact adherence to psychiatric treatment and ART
- HIV disease progression can be associated with secondary psychiatric disorders, which often improve with ART
- **Integrated** care of both conditions improves outcomes[7]
- Successful ART is more likely if there is:
  - no substance abuse
  - no history of homelessness/incarceration
  - retention in psychiatric care
  - adherence to psychiatric treatment[16]
- Regular mental health visits decrease the risk of ART discontinuation

5.1 Diagnosis of SMDs

SMDs in PLWHA can often be classified as 'primary' or 'secondary'. Primary SMDs often occur prior to HIV infection while secondary

Table 1. Common anxiety disorders

Anxiety disorder*	Features	Medication options	Psychotherapy
GAD	• Pervasive physical and psychological symptoms of anxiety interfere with normal functioning (work, studying, activities of daily living, socialising) and/or cause significant distress	Medication options for all anxiety disorders include: • SSRI antidepressant at doses as for MDD • short-term (2 weeks) benzodiazepines, e.g. 1 - 2 mg lorazepam nocte/prn, 10 - 30 mg oxazepam daily	• CBT
PD	• Recurrent panic attacks (acute severe anxiety/panic: palpitations, sweating, tremor, feelings of choking, inability to breathe, feelings of impending doom, fear of death from symptoms) • First panic attack often unexpected and unrelated to external stimulus • Subsequent attacks may become associated with particular situations, leading to avoidance, e.g. fear of crowded places (agoraphobia) • Isolated panic attacks can occur as part of GAD and depressive disorders • Frequently associated with substance use disorders	• As above	• CBT
PTSD	• Onset after experiencing or witnessing a serious traumatic event (rape, assault, accidents) • Symptoms may occur soon after the event or with delayed onset: intrusive memories (reliving, flashbacks, nightmares), hyper-arousal (increased startle response, anxiety symptoms) and avoidance (avoiding situations which remind the person of the traumatic event, numbing, and feelings of a foreshortened future)	• As above	• Trauma counselling • CBT • Note: those recently exposed to trauma should not receive once-off debriefing or prescription benzodiazepines as these may increase the risk of PTSD
OCD	• Irrational thoughts or fears which are intrusive (obsessions), commonly fears of contamination or of not having completed an activity correctly, which results in compulsive rituals, e.g. repeated hand-washing, checking of activities	• As above	• CBT

SSRI = selective serotonin reuptake inhibitor; MDD = major depressive disorder; CBT = cognitive-behavioural therapy; GAD = generalised anxiety disorder; PD = panic disorder; PTSD = post-traumatic stress disorder; OCD = obsessive compulsive disorder.

SMDs arise as a consequence of HIV infection. Both are responsive to a combination of psychotropic medication and ART.

A careful approach will help to differentiate primary SMDs (with comorbid HIV) (Fig. 4a) from secondary SMDs resulting directly from HIV or an opportunistic infection (Fig. 4b).

Clinicians must:

- conduct a thorough history: presenting symptoms, temporal relationship to HIV diagnosis, family/past psychiatric history
- conduct a comprehensive physical and neurological examination: this is essential to exclude underlying medical causes for psychiatric symptoms, e.g. opportunistic infections (particularly CNS pathology – toxoplasmosis/tuberculosis or cryptococcal meningitis), delirium or medication side-effects
- perform the following investigations: vital signs, urine dipstix, blood glucose, full blood count (FBC), creatinine and estimated glomerular filtration rate (eGFR), $CD4^+$ count, lumbar puncture; may also perform alanine transaminase (ALT)/liver function tests (LFTs), syphilis serology, thyroid stimulating hormone (TSH), VL testing and a computed tomography (CT) scan, if these are indicated on the basis of history and examination findings.

5.2 Management of SMDs

- Requires a multidisciplinary team approach, and where possible, integrated care including the involvement of community members and allied professionals
- Adherence support via treatment supporter/support groups and careful monitoring are key; patients should be educated/counselled regarding mental disorders and HIV to improve insight
- Poly-pharmacy (antidepressants, anticonvulsants, antipsychotics and ART): try as far as possible to rationalise to once daily dosing; patients on complex regimens should be reviewed regularly with a view to simplification
- Patients are more vulnerable to medication side-effects (e.g. extra-pyramidal side-effects while receiving antipsychotics) and should be monitored closely.
- See Table 2.

5.3 Starting ART in SMD: Use of EFV

Clinicians should follow standard national guidelines when initiating patients with SMDs on ART. EFV can often be used safely in patients with CMDs and in most with SMDs.[17] Routinely avoiding EFV for fear

Table 2. Commonly used drugs and their interactions[19,20]*

Class and drug	Dosage	Possible side-effects	Possible drug interactions
SSRIs			
Fluoxetine	20 - 60 daily	Headache, nausea, vomiting, irritability (initially), sexual dysfunction	EFV: potential increase in EFV levels Monitor for worsening of neuropsychiatric conditions
Citalopram/ Escitalopram	10 - 20/5 - 10 mg daily	Headache, nausea, vomiting, irritability (initially), sexual dysfunction	Generally nil clinically significant drug interactions PIs: potential for decrease citalopram dose
Sertraline	50 - 100 mg daily	Headache, nausea, vomiting, irritability (initially), sexual dysfunction	Generally nil clinically significant drug interactions; however, EFV may decrease dose of sertraline so titrate to effect
TCAs			
Amitryptaline	25 - 100 mg nocte	Sedation, anticholinergic side-effects – urinary retention, worsening confusion in older patients, constipation Fatal in overdose	Amitryptaline and PIs may increase the concentration of amitryptaline; potential cardiac arrhythmia abnormalities due to increased dose of amitryptaline
SNRIs			
Venlafaxine	75 - 225 mg daily	Potential for withdrawal syndrome if stopped quickly Initial irritability and GI side-effects Sexual side-effects	Generally well tolerated EFV and NVP may decrease venlafaxine concentration PIs may increase venlafaxine concentration
Tetracyclic antidepressants			
Mirtazepine	30 - 60 mg nocte	Sedation, weight gain	NVP and EFV potentially increase mirtazepine clearance
Trazodone	50 - 150 mg nocte	Sedation	NB: PI/r may increase trazodone dramatically – monitor carefully
NDRIs			
Bupropion XL	150 - 300 mg daily	Irritability, anxiety, tremulousness, paraesthesias, insomnia, seizures	EFV and PIs: potential for decreasing the dose of bupropion
Antipsychotics			
FGAs			
Haloperidol	0.5 - 5 mg nocte	EPSEs (dystonia, tremor, akathisia, cogwheeling, bradykinesia), NMS	PI/r may increase haloperidol concentration EFV may decrease haloperidol concentration
Chlorpromazine	25 - 200 mg in divided doses	Sedation, anticholinergic side-effects, NMS	PI/r may increase chlorpromazine concentrations
SGAs			
Risperidone	0.5 - 4 mg nocte	EPSE, sedation	Risperidone levels may increase with PIs Monitor for EPSEs and NMS EFV and NVP may decrease risperidone concentrations
Quetiapine	25 - 600 mg	Sedation, cardiac issues (QT prolongation – rare)	PI/r: potentially increased levels of quetiapine with increased sedation EFV and NVP may decrease levels of quetiapine
Olanzapine	5 - 20 mg	Sedation, metabolic syndrome – recommend lipogram if available	Probable interactions with PIs PIs: decreased concentration of olanzapine, may need to increase dose or choose alternative agent
Aripiprazole	5 - 30 mg	Akathisia, sedation	PI/r could potentially increase aripiprazole concentrations EFV and NVP could decrease aripiprazole concentrations
Clozapine	25 - 250 mg	Neutropaenia Best to avoid without specialist support	Probable interactions with PIs Possible increased concentration with PIs and possible increased risk of sedation and seizures EFV and NVP may decrease clozapine concentrations

continued...

Table 2 (continued). Commonly used drugs and their interactions[19,20]*

Class and drug	Dosage	Possible side-effects	Possible drug interactions
Mood stabilisers			
Lithium	400 - 800 mg	Lithium toxicity that may be life-threatening Monitor levels regularly once steady state is reached	Relative contraindication to avoid with TDF Potential risk for increased acute kidney injury
Sodium valproate	200 - 800 mg	Sedation, thrombocytopenia, toxic valproate levels if not monitored regularly	Interaction with AZT (increased AZT levels) PI/r may decrease valproate and increase PI Monitor levels closely
Lamotrigine	25 - 200 mg	SJS	Possible interactions with PIs; decreased dose of lamotrigine May need to increase/titrate doses of lamotrigine
Carbamazepine	100 - 200 mg bd	Sedation, syndrome of inappropriate ADH, skin rash, cognitive dulling, decreased white cell count	NVP and EFV: decreased carbamazepine, decreased EFV PI/r: increased carbamazepine, decreased PI
Benzodiazepines			
Alprazolam	1 - 2 mg daily	Sedation, dependence	PIs increase concentration of alprazolam
Diazepam	10 - 30 mg/day	Sedation, respiratory depression and ataxia	PIs increase diazepam

SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; SNRIs = serotonin noradrenaline reuptake inhibitors; GI = gastrointestinal; NDRIs = noradrenaline dopamine reuptake inhibitors; FGAs = first-generation antipsychotics; SGAs = second-generation antipsychotics; EPSEs = extra pyramidal side-effects; NMS = neuroleptic malignant syndrome; ADH = antidiuretic hormone; EFV = efavirenz; NVP = nevirapine; AZT = zidovudine; TDF = tenofovir; PIs = protease inhibitors; PI/r = ritonavir-boosted PI; SJS = Stevens-Johnson syndrome.

* See http://www.druginteractions.org

of worsening psychosis/depression is not warranted, especially since EFV has a more favourable side-effect profile, lower pill burden and fewer drug-drug interactions with psychiatric medications than other available alternatives (nevirapine and lopinavir/ritonavir).

Milder neuropsychiatric side-effects of EFV (vivid dreams, dizziness), which typically resolve within 2 - 4 weeks, can be managed with reassurance.[18] Should a patient develop new-onset or worsening of pre-existing psychosis with a temporal relationship to EFV introduction, and the psychosis persists despite psycho-pharmacological management, then the clinician should consider switching from EFV to an alternative agent. If a patient cannot tolerate EFV side-effects, then it may be necessary to switch to an alternative ARV.

The use/initiation of EFV in patients who are currently psychotic or severely depressed remains controversial. If available, consider alternative regimens as there currently is no published literature on the outcomes of EFV in psychotic/depressed individuals. If alternatives are unavailable, contraindicated or involve significant drug-drug interactions, then initiate EFV and monitor carefully.

5.4 Diagnosis and management of secondary SMDs

It is helpful to establish whether the SMD (psychosis or manic episode) is due to an underlying primary mental disorder or is secondary to HIV infection. Primary disorders require the initiation of psychotropic treatment and an assessment of whether HIV disease is currently contributing to the disorder. If patients do not meet National Department of Health (NDoH) criteria for ART initiation and are not considered to have HIV-associated SMD, then they can be referred to out-patient HIV services when discharged. Where the SMD is either thought to be secondary to HIV or where a primary SMD is being aggravated by HIV, ART and psychotropic treatment should be given in hospital.

5.5 SMDs secondary to HIV infection

- SMDs secondary to HIV infection are often associated with:
  - cognitive impairment (memory deficits and psychomotor slowing)
  - significant immune-compromise: stage III/IV WHO disease, $CD4^+$ counts <350 cell/µl and/or high VLs
  - some atypical mental state features, e.g. irritability, non-auditory hallucinations (i.e. visual or other), and a lack of personal or family history of mental disorders (i.e. no or little genetic loading)
  - no/poor response to psychotropic treatment.
- Management includes:
  - commencing ART in line with the NDoH guidelines
  - using low-dose anti-psychotics (haloperidol, risperidone, quetiapine) for psychosis
  - patients with mania due to HIV may respond well to second-generation antipsychotics (SGAs) (risperidone, quetiapine, olanzapine, aripiprazole)
  - considering mood stabilisers in persistently manic patients (consult with a psychiatrist).

6. HIV-associated neurocognitive disorders

HIV-associated neuropathological disease presents with a characteristic sub-cortical deficit pattern including: psychomotor slowing, impaired memory, attention, language, executive functioning and behavioural apathy. In patients receiving ART, a mixed cortical-subcortical picture is observed (less psychomotor slowing, more executive function, language and visuo-spatial difficulties). Classification into various HAND categories (Box 6) is determined by the extent of neurological and functional impairment:

- mild neurocognitive disorder (MND)
- HIV-dementia (HIV-D).[21]

Box 6. MND v. HIV-D

Incidence

- HIV-D in untreated HIV: 35/1 000 person years
- HIV-D in patients receiving ART: 3/1 000 person years

Prevalence (SA)

- MND, pre-ART: 42.4%
- MND, while receiving ART: 25.4%[22]

Impact

- HIV-associated neuro-invasion results in a spectrum of neurological effects, ranging from subclinical to advanced dementia
- Milder (or subclinical) HAND, which often persists during ART, has significant effects on functional outcomes, e.g. poor adherence, unemployment
- Increasing HIV testing uptake, earlier access to ART and adherence support will positively impact rates of HAND in HIV-positive populations

6.1 Screening

- Without screening (excluding HAND sufferers presenting to hospital with confusional states/psychosis), many patients with gradual neurodegenerative changes are undiagnosed due to infrequent self-reporting of functional impairment/ decline
- Such milder HAND needs to be detected as it may precede to further neurodegeneration that can potentially be prevented by ART
- In pre-ART patients with CD4$^+$ counts >350 cells/μl, screening should be performed in wellness clinics approximately annually; patients with clear neurocognitive disorder should be referred for confirmation and initiation of ART
- At ART initiation, patients with cognitive problems may require additional treatment support; a baseline assessment allows tracking over time of progress/recovery
- Once receiving ART, patients with HAND may require additional adherence support
- HAND may progress or fail to recover despite ART
- Should be offered as part of adherence support or may be offered annually, or where resources are limited, reserved for those with clinical problems (treatment failure, poor adherence, on-going depression, self-reported functional impairment).

6.2 Approaches to screening for HAND

- There is no globally accepted screening policy or practice

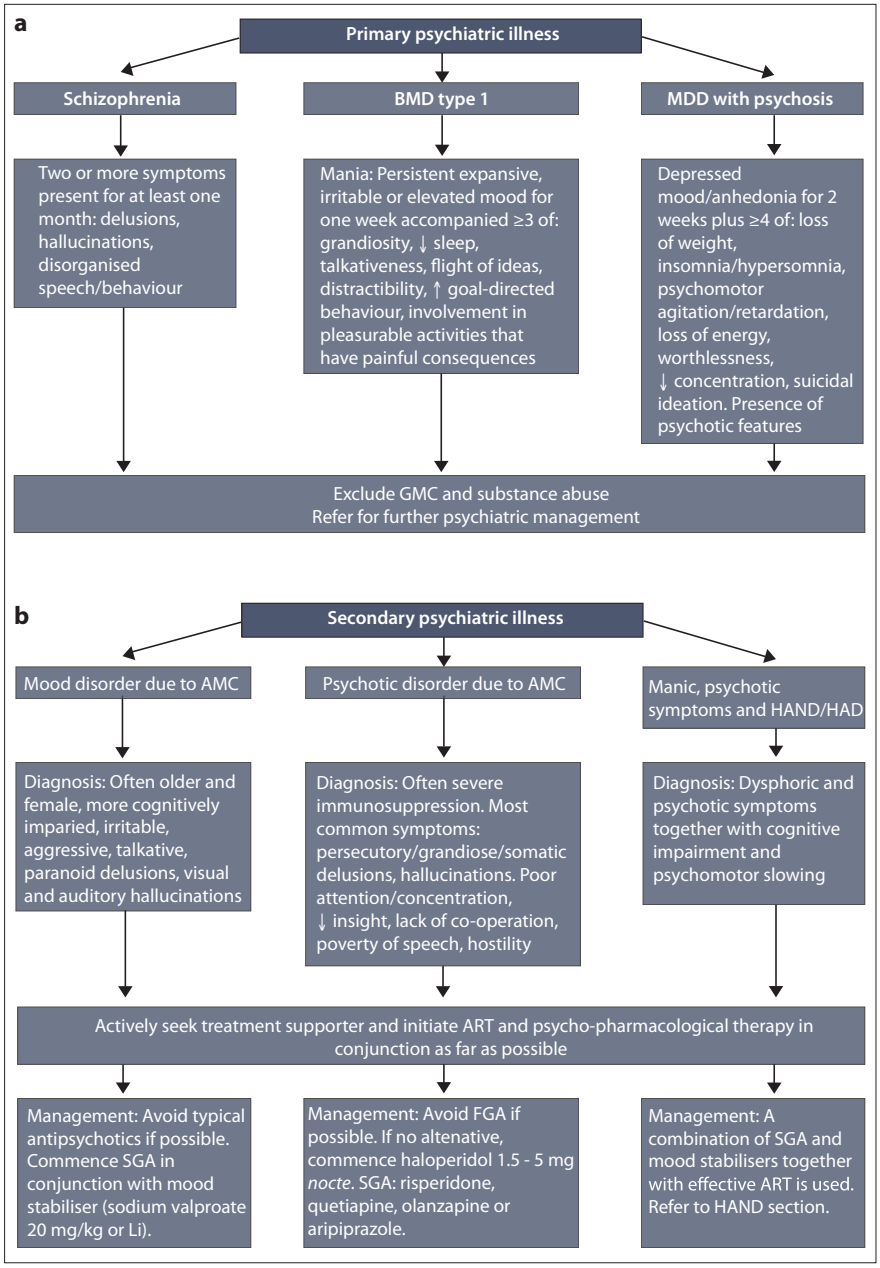

Fig. 4. Recognising (a) primary and (b) secondary SMDs. (BMD = bipolar mood disorder; SMD = severe mental disorder; HAD = HIV-associated dementia; AMC = another medical condition; HAND = HIV-associated neurocognitive disorder; ART = antiretroviral therapy; MDD = major depressive disorder; SGA = second-generation antipsychotic; FGA = first-generation antipsychotic.)

- An ultra-brief symptoms-based tool[23] may detect more severe cases (see Table 3)
- Other tools proposed for use include:
  - International HIV Dementia Scale (IHDS) (validated in SA) (http://www.europeanaidsclinicalsociety.org/Guidelines/G2_pC.htm)
  - Montreal Cognitive Assessment (MOCA) (http://www.mocatest.org)
  - the HIV-Dementia scale (http://www.turkpsikiyatri.org/arsiv/category/3-eng.html?...93:hiv-dementia)
  - Cognitive Assessment Tool – Rapid Version (awaiting validation) (http://www.hivmentalhealth.co.za/.../Cognitive-Assessment-Tool-paper-version2.pdf)
- A positive screen does not equate to a diagnosis of HAND; three further steps are required for clinical confirmation (Table 4).

6.3 Management (Fig. 5)

- Pre-ART, with confirmed HAND: commence ART, irrespective of CD4$^+$ count; engage family/partner for treatment support; and diagnose and treat confounding conditions
- Receiving ART, with HAND: usually mild/

Table 3. Simioni Neurocognitive Symptom Questions[23]

Ask the patient the following questions. Each answer should include one of 'never', 'hardly ever', or 'yes, definitely'. Any one 'yes, definitely' answer equals a positive screen.

Question	Never	Hardly ever	Yes, definitely
Do you experience frequent memory loss (e.g. do you forget the occurrence of special events, even more recent ones, appointments, etc.)?	☐	☐	☐
Do you feel that you are slower when reasoning, planning activities or solving problems?	☐	☐	☐
Do you have difficulties paying attention (e.g. to a conversation, a book or a movie)?	☐	☐	☐

Table 4. Three-step diagnostic approach to HAND in clinical practice

Step*	None	Mild - moderate	Severe
1. Is neuropsychological impairment present? (use symptom questions and at least one brief objective measure e.g. IHDS, MMSE, HDS, MoCA)	☐	☐	☐
2. To what extent are confounding illnesses contributing to the neurocognitive disorder? (depression, alcohol abuse, head injury, epilepsy, nutritional deficiency, CNS OI and neurosyphilis)	☐	☐	☐
3. Is functional impairment present? (measure basic daily activities including pill-taking and complex tasks, e.g. cleaning, cooking, shopping, money management, work tasks or driving)	☐	☐	☐

IHDS = International HIV Dementia Scale; MMSE = mini mental state examination; HDS = HIV dementia scale; MoCA = Montreal Cognitive Assessment; CNS = central nervous system; OI = opportunistic infection; HIV-D = HIV-dementia; MND = mild neurocognitive disorder; NP = neuropsychological; HCWs = healthcare workers; CT = computed tomography.

Clinicians then need to confirm whether HIV-D or MND is present:
- HIV-D: severe NP impairment + at least mild - moderate functional impairment +/- mild - moderate contribution from confounders.
- MND: either Severe NP impairment + no reported functional impairment, or mild - moderate NP impairment + at least mild - moderate functional impairment.

* Notes: Step 1: Clinicians may perform more advanced neuropsychological testing or combine bedside tests. Primary HCWs may refer patients for such detailed assessment.
Step 2: If clinical examination reveals no focal abnormality or comorbid medical conditions, lumbar puncture, CT scanning and blood tests rarely add diagnostic information. If delirium, confusion or psychiatric/behavioural symptoms are present, these further investigations are mandatory. Actively manage underlying confounding conditions.
Step 3: The extent of functional impairment is often under-rated – seek objective measures including third-party reports and clinical assessment of simple tasks where possible.

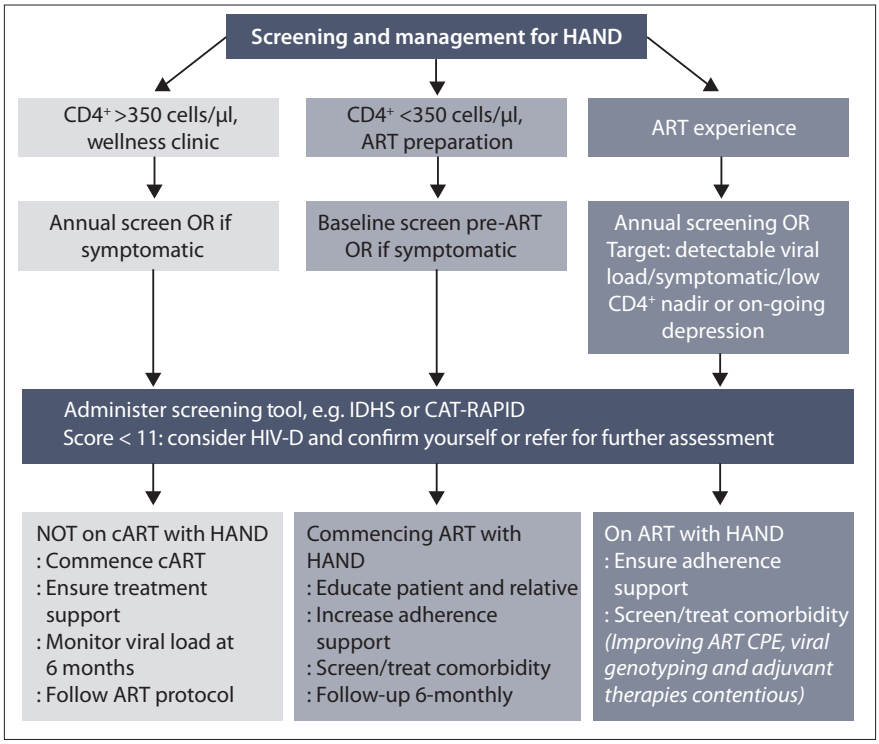

Fig. 5. Screening and management of HANDs. (CPE = CNS penetration effectiveness.)

moderate disease but, with ageing populations, more advanced disease may develop
- Routine VL monitoring with enhanced support, if adherence is poor
- Screen and treat comorbidities including age-related dementia
- Adjusting the ARV regimen to enhance CNS penetration (CPE) is not recommended, as the evidence in this regard is conflicting
- Measure the cerebrospinal fluid VL if viral compartmentalisation is suspected (low CD4+ nadir, severe impairment, confusional symptoms, increased tone and psychomotor slowing despite viral suppression in plasma)
- Augmentation strategies, including memantine, are not recommended due to the lack of robust supporting evidence and cost
- Sodium valproate or lithium may be used if there is neuropsychiatric comorbidity.

7. Grief and loss in the context of HIV

Grief is a normal, non-pathological response to any type of loss, not just death. The grief response is highly individualised as it is influenced by individual, cultural, religious, familial, community and societal factors. Grief arising from a loss related to HIV may be particularly complicated; complicated grief is defined as a prolonged period of intensified grief symptoms that disrupt daily functioning.[24]

7.1 Screening

- Screen for common symptoms of grief:
  - emotional: enduring sadness, shock, anger, anxiety, loneliness, yearning, guilt,

Table 5. Differentiating grief/bereavement from depression[25]

Grief/bereavement	Depression
Expected, culturally accepted response to loss	Only diagnose depression if the griever experiences depressive symptoms persisting for ≥2 months
Guilt is focused on an aspect of loss	Guilt is preoccupied with a negative self-image
Moments of pleasure/happiness	Feelings of emptiness and despair are constant
Preoccupation with deceased	Preoccupation with self
Not demoralising or humiliating	Demoralising and humiliating
Overt expression of anger	Anger not as pronounced
Diminishes in intensity over time	Consistent sense of depletion
Suicidal gestures are rare	Suicidal gestures are not unusual
Responsive to support	Unresponsive to support
Elicits sympathy, concern and desire to embrace	Elicits irritation, frustration and a desire to avoid from others
Usually functions	Inability to function at work, home and/or school

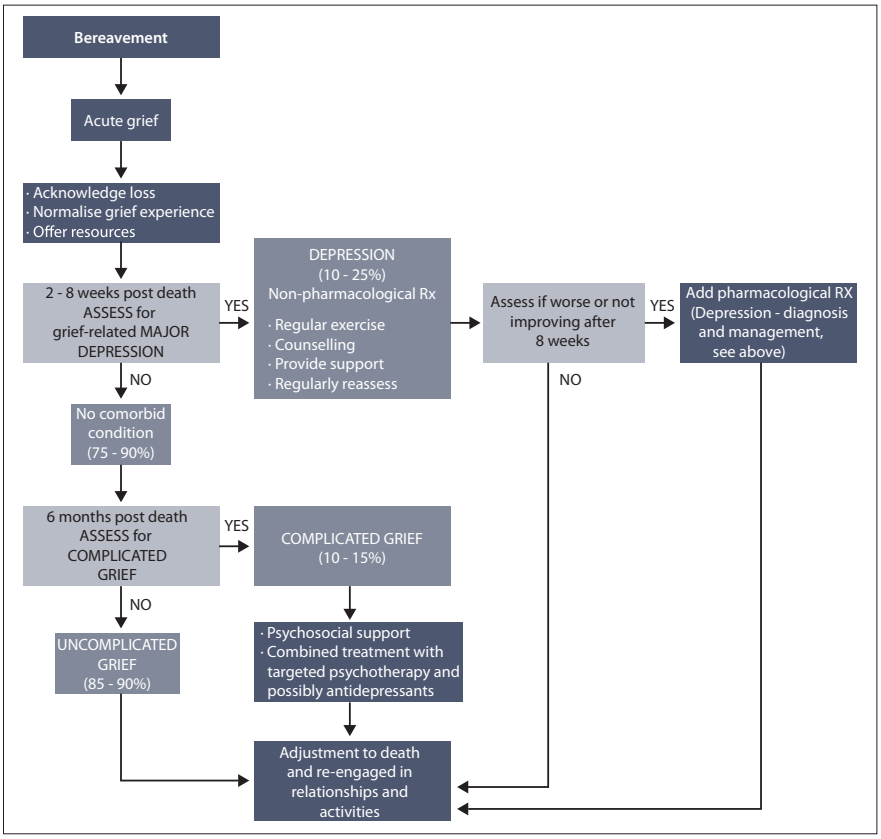

Fig. 6. Management of grief and bereavement.[26]

fear, withdrawal, feeling worthless, apathy, irritability, appetite disturbances
- physical: fatigue, tightness in the chest, shortness of breath, lack of energy, numbness, nausea, body aches, panic attacks, insomnia
- psychological/cognitive: disbelief, confusion, sense of presence, lack of concentration, auditory hallucinations (hearing the voice of the deceased), intrusive thoughts, anxiety about death, mental fatigue
- spiritual distress: questioning faith or the meaning of being a survivor
- Explore the nature and relationship of the loss/death and its impact
- Assess if the grief reaction is appropriate for the setting/cultural context
- Assess the griever's coping style, support network, and previous experiences of loss or death
- Assess for barriers to effective grieving, e.g. a lack of support, multiple losses, mental health issues, a complex relationship with the deceased, the manner of death, etc.
- The screening of children and adolescents needs to be age-appropriate and cognisant of the multiple subsequent losses that can arise following parental/caregiver death, e.g. separation from siblings, new school/friends, new home, etc.
- Clinicians may have trouble distinguishing grief and bereavement from depression (see Table 5; refer to Fig. 6 for the management of acute grief and bereavement)

8. Burnout and vicarious trauma

HCWs may also experience emotional and psychological effects from exposure to cumulative challenges within the health sector. While taking care of oneself is a prerequisite to taking good care of others, stigma persists for HCWs acknowledging burnout and vicarious trauma. Table 6 highlights key symptoms indicative of burnout and vicarious trauma.[29]

8.1 Burnout

- Prolonged involvement in emotionally demanding situations results in gradual progression towards: (*i*) emotional exhaustion; (*ii*) depersonalisation; and (*iii*) a reduced personal accomplishment and commitment to one's profession
- Risk factors include: a high patient load; difficult patient circumstances; HCW empathy, own experiences, age, training, lack of control and failure to care for oneself; and organisational characteristics (a lack of support/recognition/fairness, low salaries)
- Failure to recognise burnout may lead to depression or chronic fatigue[27]
- Burnout can be assessed officially using the Maslach Burnout Inventory (MBI) (http://www.mindgarden.com/products/mbi.htm) or the Oldenburg Burnout Inventory (OBI) (http://www.bma.org.uk/burnoutquestionnaire).

Table 6. Symptoms of HCW burnout and vicarious trauma

Burnout	Vicarious trauma
Individual level	**Individual level**
• Overextended emotionally and physically by his/her work environment	• Feeling overwhelmed/helpless when hearing patients' trauma stories
• Responds to colleagues/patients in an impersonal way	• Feeling ineffective, unskilled and/or powerless
• Feels no sense of accomplishment in anything that he/she does	• Intrusive imagery of the trauma stories that they hear about
• Physical exhaustion: fatigue; insomnia; weight fluctuations	• Hyperarousal
• Emotional exhaustion: feeling responsible; psychosomatic symptoms	• Avoidance of places, people or work
• Psychological exhaustion: compassion fatigue	• Feeling angry and irritable
• Absenteeism	• Disconnect from other staff members
Organisational level	**Organisational level**
• Absenteeism and high staff turnover	• Impact of trauma stories on staff not acknowledged/recognised
• Disengaged from colleagues/patients	• Disengaged from colleagues/patients
• Increased team conflict	• Increased team conflict/poor teamwork
• Insufficient staff training/technical ability and lack of resources	• Insufficient training of staff to manage emotional impact of trauma

8.2 Vicarious trauma

Repeated exposure to patients' traumatic stories may result in intrusive imagery, avoidance/hyperarousal, experiencing symptoms similar to the patients' trauma response (confusion, tearfulness, isolation, anger, irritability, powerlessness, hopelessness), increased vulnerability and/or survivor guilt.[28]

8.3 Management

- The individual clinician can manage burnout by following the 3 'r' approach:[30]
  - **r**ecognise: watch carefully for signs of burnout
  - **r**everse: undo damage by using stress-management techniques and employing support from fellow HCW and family
  - **r**esilience: build resilience to stress by looking after your physical and mental health
- When recovering from burnout: slow down; re-evaluate goals and priorities; and get support.

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ORIGINAL ARTICLE

Perceived adherence barriers among patients failing second-line antiretroviral therapy in Khayelitsha, South Africa

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Background. The recent scale-up of antiretroviral therapy (ART) coverage in resource-limited settings has greatly improved access to treatment. However, increasing numbers of patients are failing first- and second-line ART.
Objective. To examine factors affecting adherence to second-line ART from the perspective of clinic staff and patients, assessing both individual and structural perceived barriers.
Methods. Research was conducted at a large primary care tuberculosis (TB)/HIV clinic in Khayelitsha, a peri-urban township in Cape Town, South Africa. Participants were drawn from a Médecins Sans Frontières-run programme to support patients failing second-line ART. A qualitative research approach was used, combining multiple methodologies including key informant interviews with staff (n=11), in-depth interviews with patients (n=10) and a Photovoice workshop (n=11). Responses and photographs were coded by content; data were transformed into variables and analysed accordingly.
Results. Staff identified drinking, non-disclosure, not using condoms and pill fatigue as barriers to ART adherence, while patients identified side-effects, not using condoms and a lack of understanding concerning medication timing. With respect to service delivery, staff identified a need for continued counselling and educational support following ART initiation. Patients were concerned about missing medical records and poor staff attitudes in the clinic.
Conclusion. These findings identify discrepancies between provider and patient perceptions of barriers to, and facilitators of adherence, as well as of service delivery solutions. This highlights the need for on-going counselling and education following ART initiation, improved quality of counselling, and improved methods to identify and address specific barriers concerning medication adherence.

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In 2010, the World Health Organization estimated that 34 million people were living with HIV/AIDS (PLWHA) – of whom more than 30 million were living in low- and middle-income countries.[1] Around 9.7 million were receiving antiretroviral therapy (ART) in 2012, more than a 30-fold increase in ten years.[2] With an increased number of people receiving ART, first- and second-line treatment failure has become more common.[1,3]

Treatment failure results in increased morbidity and mortality for PLWHA, with larger numbers requiring more expensive second- and third-line treatment, and an increased risk of HIV transmission, including drug-resistant strains.[3] For ART to be effective, adherence rates must be between 90%[4,5] and 95%.[6,7] Studies also indicate that many failures are the result of suboptimal adherence, rather than due to the development of antiretroviral (ARV) resistance, suggesting a potential for continued efficacy with improved adherence, especially on protease inhibitor (PI)-based regimens.[8-10] Patients failing second-line regimens have no further treatment options available in the public sector in sub-Saharan Africa, as third-line regimens are too costly.[11] There is an escalating need to mitigate failure rates and improve the effectiveness of ART within existing public health structures.[12]

We sought to investigate: (*i*) major barriers to, and facilitators of ART adherence in this population; and (*ii*) areas of ART service delivery that shape patient behaviour. We examined the experiences of patients who failed both first- and second-line ART, identified through routine viral load (VL) testing. The most commonly cited barriers to adherence included: side-effects; regimen complexity; sociocultural factors such as complex dosing schedules, alcohol and substance abuse; economic factors; and patient-provider relationships.[13-17] No studies specifically addressing barriers to, or facilitators of adherence in patients with multiple episodes of treatment failure and re-adherence were identified. The majority of patients in this study achieved successful re-suppression following second-line ART failure. Further

work is needed to better understand the successful re-suppression of HIV in these patients.[8]

Methods

Setting

This study was conducted at Ubuntu Clinic, a public sector primary care HIV/TB clinic in Khayelitsha, a peri-urban township in Cape Town, South Africa (SA). Khayelitsha, with more than 500 000 residents, has one of the highest burdens of HIV infection nationally and worldwide, with an antenatal HIV prevalence of >26% in 2010.[18] ARVs have been available since 2001 and currently there are more than 20 000 PLWHA in the area receiving ART.[19] Ubuntu Clinic serves the biggest and oldest cohort of ART patients in Khayelitsha. By the end of 2011, 6 296 patients were receiving ART, of whom 463 (7.4%) were receiving second-line treatment. Currently, 20 new patients per month are starting second-line ART.[18]

Treatment success is assessed through VL testing. Provincial guidelines recommend that a VL test is performed at four and 12 months after treatment initiation and on a yearly basis thereafter.[11] After an initial high VL (defined as >1 000 copies/ml), patients attend adherence counselling and a follow-up VL is taken three months thereafter. Two consecutives VLs >1 000 copies/ml confirm virological failure, after which patients should be switched to a second-line ART regimen. At Ubuntu Clinic, after five years of receiving ART, an estimated 14% of patients experienced virological failure and 12% were switched to a second-line regimen.[20,21] Previous studies have found second-line failure rates in SA to be as high as 33%[22] and 40%,[25] respectively. The latter study conducted viral genotyping at Ubuntu Clinic and found that only two of 37 second-line failure patients had developed drug resistance.[23]

Médecins Sans Frontières (MSF) is an international non-governmental organisation that has worked closely with the Western Cape Department of Health during the scale-up of ART coverage in Khayelitsha. In 2010, MSF, in collaboration with Ubuntu Clinic staff, developed and implemented a patient-centred model of care for patients failing second-line ART. The programme provides a dedicated space, and individual and group counselling support. At the time of this study (August 2011), 49 patients were enrolled in the second-line failure clinic. This population allowed a first look at a small, but growing group of patients with multiple treatment failures in a setting with one of the highest HIV burdens worldwide.

Study population

Patients in MSF's second-line failure programme (patients with at least one VL >1 000 copies/ml) were approached to participate in the study. Of the 49 patients meeting these criteria, 12 were included based on availability and willingness to participate. Nurses, counsellors and doctors were selected from both the MSF programme and Ubuntu Clinic staff as key informants; they were purposively sampled to include those with the most exposure to patients receiving second-line ART.

Data collection

This study used multiple methods including in-depth patient and key informant interviews and a Photovoice workshop.[24] Semi-structured interviews were developed with input from all co-investigators on the project. Key informant interviews focused on staff perspectives regarding reasons for treatment failure and barriers in healthcare delivery. Patient interviews focused on individual reasons for treatment failure and perceptions of clinic service delivery.

Patients also engaged in a Photovoice workshop, a participatory qualitative research method where participants are given disposable cameras to take photographs of predetermined themes, and then engage with each other around the meanings and experiences behind the photographs.[24] Participants took part in two day-long workshops. The first introduced Photovoice and, with the participants, developed themes to explore the relationship between treatment and the people, places and ideas in their daily lives. Participants were then given two weeks to take photographs and return the cameras to the research team for development. In the second workshop, participants chose three of their photographs to share, and researchers facilitated discussion and the identification of themes. Twelve patients consented to be in the study, all took part in the Photovoice workshop; however, two could not be found for in-depth interviews following multiple attempts. One had relocated from the area, and another could not be located.

Data analysis

Interviews were conducted in English (n=3) and isiXhosa (n=7), depending on participant preference, with the aid of a translator. Interviews and Photovoice sessions were tape-recorded and transcribed; each was conducted by one of two separate investigators. Interview content and photographs were analysed to identify recurring themes. The initial analysis was done by a single investigator, and the review of themes identified was performed by all co-investigators. A process of coding and categorisation of data content assisted in bringing meaning to the responses and photographs.[25,26] Data were transformed into variables, with interviews and Photovoice data analysed separately.

Ethical approval

The study was approved by the Human Research Ethics Committee and Institutional Review Board of the Faculty of Health Sciences, University of Cape Town. Each participant gave written consent for their involvement in the study, including consent to publication of their photographs.

Results

Sample characteristics

Of the 10 patients interviewed, nine were female and one was male. All lived in Khayelitsha. The patients received first-line ART for a mean of 32 months (range 13 - 63) and second-line ART for a mean of 38 months (range 10 - 72). After being switched to second-line ART, patients experienced their first elevated VL (>1 000 copies/ml) at a mean of 12 months (range 4 - 41). Of the 11 key informant interviews, three were nurses, four were counsellors and four were doctors. Staff had worked a mean of 66 months (range 6 - 168) in the clinic.

Barriers and enablers to adherence

Patient-cited barriers

No patient responded that a single barrier caused their treatment failure and the majority (n=6) stated that they had made an active decision to stop taking their medication due to the barriers identified. The top reasons for ART failure (each cited by 3 patients) were side-effects, not using condoms, a lack of understanding around medication timing, didanosine (DDI) time delay between medication and food intake, and large pill size (Table 1).

Key-informant-cited barriers

The main adherence barriers cited by staff were patient drinking (n=9), non-disclosure (n=8), not using condoms (n=6), pill fatigue (n=5) and forgetting to take medication (n=5) (Table 1).

Table 1. Barriers to ART adherence cited patients and key informants

Issue	Barriers, *n* (%)	
	Key-informant-cited (*n*=11)	Patient-cited (*n*=10)
Drinking	9 (82)	1 (10)
Disclosure	8 (73)	1 (10)
Not condomising	6 (55)	3 (30)
Pill fatigue	5 (45)	1 (10)
Forgetting	5 (45)	2 (20)
Patients not honest with clinic staff	3 (27)	-
Stigma	3 (27)	-
Side-effects	3 (27)	3 (30)
Lack of food in the home	2 (18)	-
Life stress	2 (18)	2 (20)
Insufficient support	2 (18)	-
Treatment partner not working	1 (9)	-
Didanosine/one-hour delay*	1 (9)	3 (30)
Denial	1 (9)	-
Feeling better	1 (9)	-
Embarrassed about defaulting	1 (9)	-
Timing of medication	1 (9)	3 (30)
Staff shouting	1 (9)	-
Gave up	-	1 (10)
Has not accepted HIV status	-	1 (10)
Unable to keep appointment	-	1 (10)
Pills too large	-	3 (30)

*Refers to the time delay between medication and food intake when didanosine was prescribed.

Side-effects

One-third of patients identified side-effects as a reason for treatment failure, citing nausea, vomiting, stomach pains and cramping: 'I have this diarrhoea in my stomach and it's cramping … it started my viral to go up and up and up because I skip now because I'm scared that maybe I'm going to the church and my stomach maybe want to run.' (P06)

'Patients are not taking three of the tablets, taking two because one has got side-effects.' (KI02)

Another patient on second-line ART stopped because she did not realise her VL would go up quickly and was surprised when it became detectable. One-third of key informants also identified side-effects as a barrier.

Not condomising

One-third of patients blamed their failure on not using condoms: 'I had a boyfriend and didn't condomise with the boyfriend. After that I … failed and was changed to second-line.' (P04)

Not using condoms also emerged as a central theme in the key informant interviews, with six of 11 respondents citing it as a reason for non-adherence. Key informants did appear to understand this risk to treatment success as a consequence of transmission of resistant strains. However, they seemed to inflate the risk of this occurring. One key informant described a tendency of staff to defer to an 'easy' explanation for treatment failure.

Timing of medication

At the time of ART initiation, counsellors instructed patients to take their pills twice daily at exactly the same time in the morning and evening. This is laid out as one of the 'rules' of ART adherence and is presented in a concrete format, allowing very little scope for the patients when times clashed with their schedules: 'To keep the time is too difficult. I take my pills at 7 but sometimes wake up at 8 and the time has passed.' (P05)

One patient (P04) stated that she often missed doses because of her work schedule. Another blamed his counsellor for not telling him to take his medication twice daily, e.g. at 07h00 and 19h00. One-third of patients indicated that they had defaulted on first-line ART due to such strict parameters: 'Before they said to us, if you used to take your tablets at 8 o'clock in the morning or night you can't take it at 9 o'clock because it's too late. But [MSF counsellors] said it's not late, you must take the tablets. If you forget, maybe it's two hours or one hour, you can take your tablets.' (P02)

Many patients cited this increased latitude around timing as helpful to becoming re-adherent, allowing them more freedom to adjust timing around their schedules. Only one key informant mentioned timing of medication as a barrier to patient adherence.

DDI time delay

Until 2009, SA guidelines recommended DDI as part of its second-line ART regimen. This required patients to take the medication one hour before eating. This time-delay was identified by one-third of patients and one key informant as a reason for treatment failure.

'You must leave [medication] for the hour and then you forget to take other tablets after that. You take it maybe at 6 o'clock; you have to run at 7 o'clock for the train … You think okay that time is past, so you have to drink at night. That's why your viral load is so grown.' (P06)

'We picked up that they were having the problem with the DDI delay and forgetting.' (KI01)

Pills too large

One-third of patients stated that they had difficulty taking their medication because of the large pill size. Two of these patients discontinued taking their second-line regimen for this reason: 'It was getting so difficult to take second-line. It was a big pill and I decided to stop.' (P04)

Pill size was not noted in the key informant interviews as a reason for non-adherence.

Patient drinking

One patient identified drinking as a factor in her treatment failure. In the key informant interviews, however, alcohol use emerged as the most cited reason for failure (cited by 9). Staff said that this affected adherence in two ways: Firstly, patients often forget to take their medication when drinking. Secondly, staff reported that, as with the timing of medication, patients understood that they could not drink and take their ARVs literally and stopped treatment altogether: '[The patient] sees that he

is much better and he will start to drink again. It's whereby most of them are failing because when they are drinking, they don't take their medication, they stop their medication.' (KI02)

Non-disclosure

One patient identified non-disclosure as a barrier, citing the difficulty of maintaining ART without support at home where she felt she had to hide her medication: 'Some of them they don't tell their partners that they are positive and are on treatment. They need to disclose to friends, to partners.' (KI10)

Eight of the 11 key informants indicated that non-disclosure was problematic. Many of their patients felt the need to hide their medication and would often not take it when travelling or if others were present at work or at home.

Pill fatigue

One patient identified pill fatigue as a reason for defaulting, noting: 'I just keep getting tired sometimes. To take treatment everyday is not nice.' (P03); 'Second-line patients are more likely to have problems because of pill fatigue.' (KI09)

Five of the 11 key informants identified pill fatigue as a barrier.

Forgetting

Five of the 11 key informants identified patients forgetting to take their pills as a barrier. This was often cited with various reasons, ranging from patients being busy with work or family obligations, travelling without medication, and the lack of a plan for treatment adherence (alarm or friend/family to remind them).

Two of 10 patients identified forgetting as a barrier.

Service delivery barriers

Patient-cited clinic obstacles

Interviews with patients revealed difficulties with healthcare delivery at Ubuntu Clinic, with some patients citing missing medical records (n=6) and clinic staff shouting at patients (n=6). Few, however, cited these problems in response to questions on defaulting or suboptimal adherence. Rather, many seemed to view them as an expected part of clinic attendance; two patients stated that clinic problems affected their adherence or their attendance at the clinic: 'Sometimes they will shout you if you ask something … shouting at the top of their voices. You feel not happy and you go home and feel unhappy. And next time you say I'm not going to this clinic anymore.' (P02)

Key-informant-cited clinic obstacles

Staff identified a lack of continued counselling support following ART initiation (n=8) and insufficient education for patients (n=3) as key obstacles. One counsellor noted: 'The point where we are failing is to really find out exactly why [the patient] is failing and try to fix the thing that makes them to fail first-line … there is no time to focus on the problem, instead we are just providing the medication without support.' (KI09)

Staff also highlighted the need for increased follow-up to catch adherence issues earlier on. One clinician identified counselling as a critical but under-utilised component: 'There is so much pressure for roll-out of getting more patients onto ARVs, getting nurses dishing out ARVs … counsellors are being overlooked but they are a critical part of the whole process.' (KI08)

Three of the 11 key informants responded that there was no need for improvement and seven did not think that the clinic needed more time or resources for patients. These staff felt that patients should engage better with the healthcare system, that many obstacles faced by patients are difficult for the clinic to solve, or that current resources could be managed better.

Patient perspectives on the MSF programme

Patients cited feeling more comfortable and free to share problems (n=7), shorter wait times (n=6), seeing the same staff (n=4) and support groups (n=2) as reasons why they preferred MSF's programme to the larger clinic: 'I feel free now that on this side of the clinic. I can share everything … when I come here I feel at home because before when I was taking medicine on that side [larger clinic], I was afraid whether I had done right or done wrong.' (P04)

A more patient-centred environment enabled more open discussion of barriers to adherence and facilitated the resolution of issues.

Fig. 1. The daughter of a patient reminds her mother to take her medication.

Fig. 2. A counsellor explaining medication parameters to a patient.

Fig. 3. A patient who struggled with an alcohol abuse problem depicts herself pouring out the remaining alcohol in her home.

Table 2. Frequency of themes of photographs shared on patients' perspectives of ART adherence

Main photo theme	*n*
Support of family/friends	12
Importance of treatment in lives	5
Gratitude towards MSF staff	3
Difficulty of treatment	3
Religion as a source of strength	2
Overcoming a drinking problem	2
Poor living environment	2
Food insecurity	1
Regret for losing previous wealth	1

MSF= Médecins Sans Frontières.

Photovoice patient perspectives

The Photovoice component of the study elicited a different patient perspective on treatment compared with the interviews. The photographs and the workshop discussion became a platform for sharing successes and sources of strength. Each patient chose three pictures to share (Table 2). Of 33 total photographs shared, only nine illustrated negative aspects of patients' lives, such as poor living conditions, difficulty remembering treatment, poor clinic service and not having family support. Yet, when presented by patients, these negative aspects were often treated as barriers overcome or obstacles to get past.

The remaining photographs (24/33) showed supportive family and friends (*n*=11) (Fig. 1), the importance of treatment (*n*=5), gratitude towards the MSF clinic staff (*n*=3) (Fig. 2), religion as a source of strength (*n*=2), and overcoming drinking problems (*n*=2) (Fig. 3). There was a notable difference in the themes presented by patients as part of the Photovoice analysis and those that emerged in the interviews. This is likely due to the difference in methodology and format. Photovoice involved individual presentation to the full group; patients seemed to experience this format as a type of support group with a focus on sharing positive experiences, often to encourage others in the group by describing facilitators to adherence and sources of support: 'I believe in tablets, because it's my life and I will be taking treatment for life. Not for me, but for the kids too.' (P04)

Discussion

South Africa's *National Strategic Plan on HIV, STIs and TB: 2012 - 2016* calls for 80% of PLWHA to be receiving ART by 2016,[27] expanding from the 56% of those eligible who were receiving ART in 2009.[28] However, this focus on initiating patients on treatment has largely ignored the rising numbers of patients failing treatment.[11,29] We aimed to identify barriers and facilitators to long-term ART adherence in the context of second-line treatment failure from the perspective of staff and patients.

Interview themes most frequently identified as barriers to treatment adherence differed between patients and staff. Staff identified drinking, non-disclosure, not using condoms, pill fatigue and forgetting to take medication as barriers to adherence, while patients identified side-effects, not using condoms and a lack of understanding around medication timing. With respect to service delivery, staff identified a need for continued counselling and educational support following ART initiation. Patients were concerned about missing medical records and poor staff attitudes in the clinic.

Patients as well as staff had a tendency to blame treatment failure on factors that were external to themselves and their role in treatment adherence. This is consistent with previous findings in a similar setting, where ART patients who adhered tended to ascribe this to internal strength, whereas when they failed, external factors were identified.[30] In the current study, the principal patient-identified barriers were side-effects, not condomising, DDI, large pills and not understanding medication – all but condomising point toward obstacles external to the patient; whereas, staff identified patient drinking, not disclosing, not condomising and pill fatigue most frequently – all of which focus more on patient behaviour.

In the principal obstacles identified, the only one common to both patients and staff was not using a condom. When staff were questioned further on this topic, it became clear that they seemed to understand not condomising as contributing to the spread of resistant HIV strains within the population. However, given the small numbers of those failing second-line ART, the likelihood was very low of any patients in this sample contracting a resistant strain rather than failure resulting from non-adherence. Given the complexities involved in identifying behaviours that contribute to non-adherence, one explanation is that both patients and staff found not condomising a factor that is easily identifiable and relatively easily addressed, causing both to over-emphasise its role. This over-emphasis adds to the knowledge gap patients experience in understanding the reasons for treatment failure, reducing their ability to address and identify actual adherence issues.

For some patients, ART failure resulted from a lack of understanding around the parameters of their medication. For others, the issues were psychosocial in nature, involving bad living environments or a lack of support at home. Yet, some patients made an active decision to stop taking medication and became re-adherent when issues such as side-effects, pill size or time delay were addressed.

Patients enrolled in the second-line failure clinic receive patient-centred support with individual and group counselling. Unpublished data show a high VL re-suppression rate among those enrolled in the programme. This is likely due to improved access to staff, continuity of staff and more supportive clinic environment, allowing for quicker follow-up and more open discussion of issues affecting adherence. This is consistent with findings from similar studies where strong and open relationships between patients and healthcare providers facilitate adherence.[30]

There is currently an information gap between patients experiencing difficulties with treatment and clinic staff addressing those issues. There are personal and structural reasons for this, stemming from patients not informing staff when experiencing difficulties, not understanding which behaviours will lead to raised VLs and not feeling comfortable with staff. The most patient-cited clinic obstacle was staff shouting at patients; however, some patients also highlighted the benefit of feeling open and able to share their issues with the MSF programme staff. This serves to emphasise the importance of trust and communication between patients and staff, particularly between patients and counsellors; patients' difficulties with treatment remained unresolved until the clinic environment changed, allowing for open discussion and management of those issues. Though previous research has shown similar barriers to adherence including poor patient-staff relationships, untimely addressing of adherence issues and inadequate counselling following initiation of ART,[31] the patient population in this study showed that improving these issues within service delivery can lead to improved adherence and VL suppression.

Many staff responded that there was no need for an improvement in service delivery and that the clinic had sufficient resources

to serve its patient population, highlighting a tendency among some staff not to be critical of the *status quo* or look for methods to improve current service delivery. The present focus on increasing ART coverage and the relatively few patients who are failing treatment has concentrated efforts to increase the number of patients receiving ART, leaving little time to focus on the increasing rate of ART failure.

Study limitations

Interviews conducted in isiXhosa were translated during the interview in real time by MSF staff, which may have influenced patient response, either limiting patient openness due to the presence of clinic staff or limiting the interviewer interaction because of the language barrier. The high proportion of female respondents limited the generalisability of the study findings, suggesting that our results may only be appropriate to a female population failing second-line ART. Though the proportion of females attending the second-line ART clinic at the time was 68%, participation of males was low due to difficult schedules and willingness to participate. Only one male participated in the study, making it difficult to determine whether responses were gender-biased. The study population comprised a small group of patients who had a very specific context of care delivery within a programme separate from standard government clinical care. Thus, their experiences within a more adequately resourced environment than public clinical care is certain to have affected their perspectives on service delivery as well as their high level of re-adherence. Moreover, because of the relatively low numbers of patients failing second-line ART, the large bulk of staff experience is with patients receiving first-line ART. As the number of patients failing second-line ART increases, so will staff experience with these patients, offering a future opportunity to assess staff perspectives on barriers to, and facilitators of adherence.

Study significance

This study focused on a patient population that included among the first patients in SA who have experienced virological failure on second-line ART medication. Yet, many of these patients have been able to suppress their VLs within the MSF-run programme. This success highlights the importance of both counsellors and clinicians providing the necessary patient support – to ensure that patients are adequately equipped to initiate ART successfully and to serve as the front line for identifying problems as they arise. Many of the patients who became re-adherent benefitted from open relationships with clinic staff, enabling discussion and management of adherence issues. Prioritising patient-staff relationships and strengthening support mechanisms to identify adherence issues early on offers an opportunity for the current system of ART initiation and support to improve patient outcomes. The largely positive themes elicited by Photovoice illustrate that many multiple-failure patients feel positively about their treatment and lives and, with improved support mechanisms, this can translate into improved adherence and outcomes. Although some patients did make an active decision to stop taking ART, all continued to attend the clinic and engage with the healthcare system, demonstrating an opportunity for clinic staff to reduce failure rates in a patient population with no treatment option following failure of a second-line ART regimen.

Recommendations

The frequency with which not using condoms was cited as a factor contributing to ART failure should be examined further at the staff and patient level to ensure that messaging is not misleading and that patients address all behaviours affecting adherence. Continued follow-up, especially with regards to easily altered behaviour or misunderstood medication parameters (e.g. timing, missed doses, forgetting) should be explored to identify how best to equip patients for ART regimens. Continuity of care and patients' comfort with staff is another area that could be explored to identify whether and how that may have contributed to improved patient outcomes in this group. Though few patients were found to have resistant HIV strains following genotyping at Ubuntu Clinic, the incidence of primary or secondary infection with resistant strains should be explored. This is likely to become an increasingly important aspect of ART failure as the prevalence of resistant strains increases.

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ORIGINAL ARTICLE

High rate of virological re-suppression among patients failing second-line antiretroviral therapy following enhanced adherence support: A model of care in Khayelitsha, South Africa

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Objective. To describe and evaluate the outcomes of a support programme for patients with virological failure while receiving second-line antiretroviral therapy (ART) in South Africa.
Method. We described a comprehensive medical and counselling patient support programme for patients receiving second-line ART and with two consecutive viral loads (VLs) >1 000 copies/ml. Patients with >3 months follow-up and at least one VL measurement after inclusion in the programme were eligible for analysis.
Results. Of 69 patients enrolled in the programme, 40 had at least one follow-up VL and no known drug resistance at enrolment; 27 (68%) of these re-suppressed while remaining on second-line ART following enhanced adherence support. The majority (18/27; 67%) achieved re-suppression within the first 3 months in the programme. Five patients with diagnosed second-line drug resistance achieved viral re-suppression (<400 copies/ml) after being switched to third-line ART. Seven patients (7/40; 18%) did not achieve viral re-suppression after 9 months in the programme: 6 with known adherence problems (4 without drug resistance on genotype) and 1 with a VL <1 000 copies/ml. Overall, 3 patients (4%) died, 3 (4%) were lost to follow-up and 2 (3%) were transferred out.
Conclusion. Our experience from a routine programme demonstrates that with targeted adherence support, the majority of patients who were viraemic while receiving second-line ART returned to an undetectable VL within 3 months. By increasing the time receiving second-line ART and decreasing the need for genotypes and/or third-line ART, this intervention may reduce costs.

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At the end of 2012, 35 million people were estimated to be living with HIV worldwide – most in sub-Saharan Africa.[1] Antiretroviral therapy (ART) was first introduced in South Africa (SA) through pilot projects in 2001. In 2004, the country launched its public sector ART programme, now the largest ART programme in the world. By mid-2013, approximately 2.5 million people had initiated ART free of charge through the public sector.[2]

As increasing numbers of patients are enrolled in treatment regimens, there is an increase in the number failing first-line ART and being switched to second-line ART.[3-6] The durability of second-line regimens is not well-established and there is growing concern in SA and elsewhere regarding the management of second-line failure, given the high cost of third-line ART and limited treatment options. In one study conducted in Soweto, SA, about one-third of patients receiving the second-line lopinavir/ritonavir (LPV/r)-based regimen were found to be viraemic.[7] In another study in Khayelitsha, SA, patients receiving second-line ART were less likely to be virologically suppressed than patients remaining on first-line ART at equivalent durations of treatment (odds ratio (OR) 0.51; 95% confidence interval (CI) 0.26 - 1.01).[8]

North American and European ART guidelines recommend that genotyping governs decisions on the appropriate treatment for patients failing second-line ART.[9] In Khayelitsha, where routine viral load (VL) testing is available, targeted genotyping and switching to third-line ART has been implemented

in 2011 on the basis of expert advice. The most recent SA ART guidelines, published in 2013, recommend that specialist systems be created within programmes to guide clinical management and access to third-line regimens based on genotype resistance testing and expert opinion.[10]

Previous studies have found that only a minority of second-line patients with virological failure in the Khayelitsha programme had major protease inhibitor (PI) mutations necessitating third-line ART.[11] This suggests that the high VL measurements observed may largely be explained by adherence difficulties. In this study, we describe an enhanced patient support programme and short-term outcomes for patients with sustained viraemia on second-line ART regimens in the largest ART site in Khayelitsha.

Methods

Study setting

Khayelitsha sub-district (population ~500 000 inhabitants) is located on the outskirts of Cape Town, SA, and has one of the highest burdens of HIV and tuberculosis (TB) in the country. In 2010, antenatal HIV prevalence was measured at 26%; the TB case-notification rate reached nearly 1 500/100 000 inhabitants, and the TB/HIV co-infection rate was close to 73%.[12]

The Khayelitsha programme was the first in SA to provide ART at the primary care level in the public sector. The programme was established in 2001 by Médecins Sans Frontières (MSF) and the Provincial Government of the Western Cape (PGWC) and has been described previously.[8,12,19] MSF's role evolved from the provision of first-line ART to piloting models of primary care for drug-resistant tuberculosis (DR-TB), long-term ART and vulnerable groups such as children, youth, pregnant women and men. By the end of 2011, over 20 000 patients remained in ART care provided by the Department of Health in Khayelitsha.[12]

Ubuntu Clinic, the study site with the largest and oldest cohort of patients receiving ART in Khayelitsha, had initiated over 6 000 patients on ART, of whom 482 (7%) were receiving second-line PI-based regimens (mainly LPV/r-based) at the time of the study.

The PGWC ART guidelines recommend a first VL measurement four months after ART initiation. Follow-up VL monitoring is recommended 12 months after treatment initiation and annually thereafter. Patients with a VL ≥1 000 copies/ml and no medical reasons for a virological breakthrough receive adherence counselling and a follow-up VL measurement three months later. Virological treatment failure is defined as having two consecutive VLs ≥1 000 copies/ml. Such patients are switched to an appropriate second-line LPV/r-based regimen.

Second-line support clinic

Prior to the introduction of the intervention, and as is common in this setting, patients with a detectable VL routinely received at least one adherence session performed by clinic counsellors. These sessions focused on re-educating patients on treatment literacy rather than problem-solving around specific adherence barriers. Clinicians and counsellors often found it challenging and frustrating to deal with patients who were failing treatment and had no further treatment options.

In 2010, MSF partnered with the PGWC to pilot a 'second-line failure clinic' intervention at Ubuntu clinic, targeting patients receiving second-line ART and with two or more consecutive VL measurements ≥1 000 copies/ml.

All patients enrolled in the programme were offered a comprehensive package of medical and counselling support (Fig. 1), and were followed up by clinical staff (doctor and/or nurse). Counsellors conducted a simple screen for substance abuse and depression at the enrolment visit and referred patients for additional services accordingly. A typical visit would consist of a medical visit, an individual adherence support session and a group support activity.

Medical visits carried out by a clinician (medical officer or professional nurse) focused on clinical issues relating to treatment failure, such as opportunistic infections, drug interactions, side-effects and possible drug resistance. The clinician also engaged in adherence support and HIV drug resistance tests were only performed when patients failed to obtain virological re-suppression after all adherence barriers were addressed. Individual adherence support sessions were conducted by counsellors. During these individual sessions, the patient's specific adherence barriers were identified and assistance was provided to problem-solve these issues. During monthly follow-up visits, patients were encouraged to report back on the progress that they had made or the difficulties that they still faced in adhering to treatment. Adherence barriers and plans made were noted in the patient's folder to aid follow-up.

In addition, patients were invited to attend support group sessions facilitated by a counsellor. Grouping patients with similar difficulties encouraged patients to share their barriers and solutions, and also promoted openness and honesty.

After a period of three months in the second-line failure intervention, a VL measurement was repeated. Patients who achieved virological suppression were then referred back to routine clinic care. Patients who did not achieve virological suppression were retained in the intervention and assessed for HIV drug resistance testing.

This intervention ensured that the small number of patients who were struggling on second-line ART were identified, temporarily removed from the normal flow of the clinic, and given enhanced attention and support, which is challenging to offer to all patients in a busy ART clinic.

Outcome evaluation

The primary outcome was virological re-suppression, defined as achieving a VL ≤400 copies/ml after having two consecutive VL measurements ≥1 000 copies/ml. Patients who had no contact with the clinic for 6 months were regarded as lost to follow-up (LTFU). Those patients who requested transfer to another health facility were considered transferred out (TO). Data for each patient on the date of first-line ART initiation, initiation of second-line therapy, VL measurements and the dates of VL tests were extracted from routinely collected data in the electronic patient register in the clinic. Date of registration in the clinic was

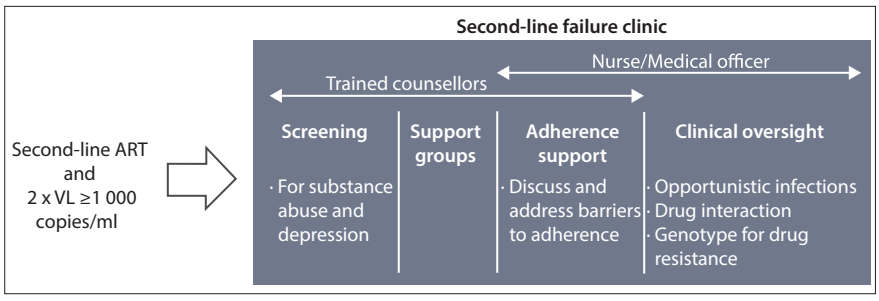

Fig. 1. Key elements of the second-line ART failure clinic. (VL = viral load.)

captured from the paper register used by the doctors to track patients in care. Information regarding barriers to adherence was extracted from counselling notes.

Statistical analysis

Enrolled patients with less than three months of follow-up and patients who did not have a follow-up VL measurement in the programme were excluded from the analysis. We described the treatment and VL history of patients during the study period with frequencies for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. The following variables were included: duration of first-line ART, type of first-line ART, duration (years) receiving first-line ART before the first and second of two consecutive VLs >1 000 copies/ml, duration and choice of second-line treatment, and duration in the second-line failure programme. The analysis of routine cohort data was approved by the University of Cape Town's Research Ethics Committee.

Results

From January to December 2011, a total of 69 patients were enrolled in the programme (Fig. 2); 29 were excluded from the analysis as they had not had a follow-up VL. Four patients who had known drug resistance at the time of enrolment were also excluded from the analysis. The median duration on first-line treatment was 3.4 years (IQR 2.1 - 4.3). The median duration of the first-line regimen before two consecutive elevated VLs was 1.7 years (IQR 0.9 - 2.5). Once switched to a second-line regimen, the median time to the first detectable VL measurement was 0.7 years (IQR 0.4 - 1.1).

Overall, during 9 months of follow-up, 27 of the remaining 40 patients (68%) achieved virological suppression while remaining on second-line treatment. One patient was switched to third-line ART after genotyping showed PI resistance. Seven patients (18%) continued to experience viraemia, either with known adherence problems or having been genotyped and found to be treatment-sensitive; none of these patients was switched to third-line ART and all continued in the programme. Five patients left the programme due to death, LTFU or TO.

Timing of virological re-suppression

Eighteen out of 40 patients (46%) achieved virological re-suppression within 3 months, 7 (18%) within 6 months, and 2 (5%) within 9 months. One patient underwent genotyping, was found to have PI resistance and was switched to third-line ART, subsequently re-suppressing within 3 months.

After re-suppression, 19% (5/27) of patients experienced a recurrence of viraemia: 3 of the 18 who suppressed at three months, and two of the seven patients who suppressed at six months. Of the seven patients who failed to re-suppress, four were genotyped and found to have a drug-sensitive virus; two had known adherence issues (one due to alcoholism, one for unspecified reasons) and one had a VL of 400 - 1 000 copies/ml, and could therefore not be genotyped.

Obstacles to adherence

The four main obstacles to adherence reported by patients entering the programme were: issues regarding the dosing schedule and not having a fixed routine; ignorance about the need for good adherence; a previous negative experience with clinic staff; and simply forgetting to take the drugs as needed. The action plans to address these barriers were: changing the dosing schedule; treatment education through support groups; specific clinic staff dedicated to patients with treatment failure; and reinforced counselling support.

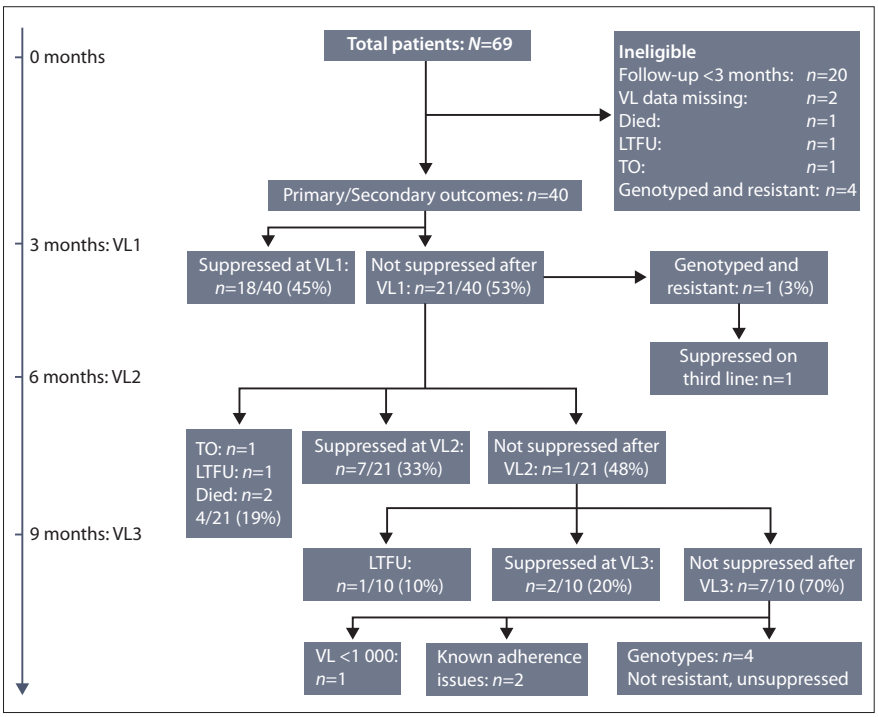

Fig. 2. Flow diagram of outcomes of patients failing second-line antiretroviral therapy enrolled in a comprehensive medical and counselling patient support programme at a primary healthcare clinic, in Khayelitsha, South Africa in 2011. (TO = transfer out; LTFU = loss to follow-up; VL1, VL2, VL3 = first, second and third VL measurements after enrolment into the programme.)

** 3 patients experienced a VL >400 copies/ml at VL2.*

*** 2 patients experienced a VL >400 copies/ml at VL3.*

Discussion

In this routine programme, more than two-thirds of patients failing second-line ART achieved virological re-suppression without changing regimen and following an enhanced patient-support intervention. The majority of patients re-suppressed within three months after enrolment in the programme.

Our findings are important for a number of reasons. Firstly, patients failing second-line ART have limited treatment options available as third-line regimens are extremely costly. In our study population, the median duration of the first-line regimen before two consecutive elevated VLs was 1.7 years and the median time to the first detectable VL measurement after being switched to a second-line regimen was 0.7 years. This suggests that these may be patients with significant barriers to adherence. Remaining on a failing ART regimen without acting on the reasons for treatment failure could compromise the efficacy of future treatment options. Failure rates of second-line therapy are higher than reported rates of failure of first-line therapy.[13] A systematic review and meta-analysis of treatment outcomes of patients receiving

second-line ART in resource-limited settings found a high proportion with virological failure, with most failures occurring within six months after initiation of second-line therapy.[14] For long-term health to be maintained in resource-limited settings where treatment options are limited, it is important to maximise the clinical benefits derived from each regimen. This has implications for the wide-scale rollout of ART in SA as well as in other resource-limited settings. The enhanced patient-support programme requires additional resources for a small number of specific patients, but may avoid unnecessary and costly regimen switching. The outcomes of this pilot programme are now informing the implementation of an adherence-support programme for patients at risk of failing first-line therapy.[15]

Adherence to ART is a key factor for achieving successful treatment outcomes in individual patients and for the success of large-scale ART programmes.[16] To maintain virological suppression, evidence suggests that individuals are required to take at least 80% of their medication for PI-based therapies,[17-19] and at least 95% of non-nucleoside-based therapies.[16] An emerging challenge for large ART programmes is maintaining patient-centred care while enrolment is on-going and total patient numbers are constantly increasing.[20] Our findings suggest that providing continuity of care for a period of time under the same healthcare staff may promote adherence.

Access to genotyping and third-line regimens remains a major challenge for public sector programmes. As has been reported by a previous study from the same and other programmes,[21,22] most of the samples genotyped remained susceptible to PIs due to a lack of drug exposure, with adherence problems constituting the major issue. In another study conducted in Khayelitsha,[11] only two of 37 genotyped samples had major PI mutations. Nevertheless, some second-line virological failures do have major PI mutations that confer resistance and third-line ART will likely become a growing concern. The model of care described here provides an approach to limit the need for costly genotyping by identifying those patients who are non-adherent. In our cohort, only five out of 40 possible samples were genotyped, and 20% of those were found to be resistant. In this way, such a model may be cost-saving.

Five patients experienced virological rebound after VL re-suppression and 18% of all patients did not achieve re-suppression while remaining in the programme. These patients chose to remain in the programme as they experienced continued value in the adherence support received. Adherence problems and/or treatment barriers were identified, highlighting the need for further research on optimal adherence support.

Conclusion

Our findings from an operational setting within routine care are promising, as they demonstrate that patients failing second-line treatment can become adherent with programmatic support. Our study resulted in increased durability of the second-line ART regimen, decreasing the need for costly third-line regimens and preventing many unnecessary genotypes by early identification of, and action on barriers to adherence. While our descriptive study shows satisfactory short-term outcomes, the long-term impact is as yet uncertain and remains to be evaluated.

Acknowledgements. We thank Ubuntu clinic patients and staff for their collaboration with our study.

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ORIGINAL ARTICLE
Impact of antiretroviral therapy on pregnancy outcomes

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Background. The majority of HIV-positive women in South Africa are of reproductive age, and pregnancies among women using antiretroviral therapy (ART) are common. However, there are mixed data regarding the impact of ART on pregnancy outcomes.
Objective. To examine the impact of ART on pregnancy outcome according to the timing of initiation of treatment.
Methods. A retrospective cohort study was conducted among women delivering at a tertiary hospital from 1 October 2008 to 31 March 2009.
Results. A total of 245 mothers were receiving ART: 76 mothers (31%) started ART pre-conception and 169 mothers (69%) started ART after the first trimester. No significant differences were observed in the rates of preterm delivery and low birth weight (LBW) between the pre- and post-conception groups (21% v. 24% and 21% v. 25%, respectively).
Conclusion. In this cohort of women receiving ART in pregnancy, timing of ART initiation did not have any adverse effect on the measured pregnancy outcomes such as preterm delivery and LBW.

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South Africa (SA), like many countries in sub-Saharan Africa, has a high HIV disease burden. According to 2008 reports by the World Health Organization (WHO) and the Joint United Nations Programme on HIV and AIDS (UNAIDS), an estimated 6 million adults and children were living with HIV in SA by the end of 2007, including approximately 3.2 million (54%) women aged ≥15 years.[1,2] This has a significant impact on vertical transmission and maternal mortality. The *Fourth Report on Confidential Enquiries into Maternal Deaths in South Africa 2005 - 2007* showed that pregnancy-unrelated infections, mostly HIV/AIDS, were responsible for 43.7% of all reported maternal deaths.[3-5]

Varied results have been reported on the risk of adverse pregnancy outcomes in HIV-positive women treated with antiretroviral therapy (ART). Several studies from Europe have suggested that the initiation of ART during pregnancy may be associated with an increased risk of preterm delivery, particularly with protease inhibitor (PI)-containing regimens.[6-8] However, these findings have been contradicted by studies from Brazil and North America showing no association between maternal ART use and pregnancy outcomes.[9-12]

In Africa, there have been some studies that evaluated the impact of ART on pregnancy outcomes. In a Cote d'Ivoire study[13] it was highlighted that ART in pregnant women with advanced HIV disease substantially reduced mother-to-child transmission, but was associated with low birth weight (LBW). A matched case-control study conducted in Nigeria[14] found that HIV-positive women were significantly more likely to have intrauterine growth restriction, preterm labour and LBW babies than HIV-negative women.

Given the large number of HIV-positive pregnant women in SA, and the importance of ART use for promoting maternal and child health in

Table 1. Comparison of maternal age, parity and mode of delivery between the pre- and post-conception ART groups

Variable	Pre-conception (*N*=76)	Post-conception (*N*=169)	*p*-value
Age, mean (±SD)	31.4 (±5.3)	29.2 (±5.4)	0.003
Parity, *n* (%)			
0	4 (5.3)	31 (18.3)	0.003
1 - 2	49 (64.5)	118 (69.8)	0.378
≥3	23 (30.2)	20 (11.8)	0.047
Mode of delivery, *n* (%)			0.568
Vaginal	52 (68.4)	113 (66.9)	
Caesarean section	24 (31.6)	56 (33.1)	

ART = antiretroviral therapy; SD = standard deviation.

Table 2. Comparison of gestational age and birth weight between the pre- and post-conception ART groups

Variable	Pre-conception (*N*=76)	Post-conception (*N*=169)	*p*-value
Gestational age, *n* (%)			0.348
Pre-term	16 (21.1)	41 (24.3)	
Term	60 (78.9)	128 (75.7)	
Fetal weight (g),* *n* (%)			0.945
≥2 500	60 (78.9)	128 (75.7)	
1 500 - 2 499	13 (17.1)	35 (20.7)	
1 000 - 1 499	2 (2.6)	4 (2.4)	
500 - 999	1 (1.3)	2 (1.2)	

ART = antiretroviral therapy.

*Fisher's exact test.

this population, it is pertinent to investigate any effects that ART may have on pregnancy outcomes.

The aim of this study was to investigate the impact of ART on pregnancy outcome, according to the timing of initiation of treatment, in a cohort of HIV-positive pregnant women at Dr George Mukhari Hospital (DGMH) in Ga-Rankuwa, SA.

Methods

We performed a retrospective medical record review of HIV-positive pregnant women who delivered at DGMH from 1 October 2008 to 31 March 2009. DGMH has a large academic obstetric unit with approximately 8 500 deliveries per annum. The study included HIV-positive pregnant women who booked at the antenatal clinic at DGMH and had either been receiving ART before pregnancy (pre-conception ART group) or started ART after the first trimester of pregnancy (post-conception ART group). Women with multiple pregnancies and those who defaulted ART and/or antenatal clinic visits were excluded from the analysis.

Data on demographic and obstetric characteristics and ART use were collected from the labour ward delivery register, patients' antenatal cards and/or hospital records. Data were analysed using SPSS (version 17.0). Term delivery was defined as birth at a gestational age of ≥37 weeks, where ultrasound was used to date the pregnancy before 20 weeks' gestation; or a birth weight of ≥2 500g in cases where pregnancy was not dated with ultrasound before 20 weeks' gestation. All statistical tests were performed using two-sided tests at the $p \leq 0.05$ level of significance.

Ethical approval for the study was obtained from the Medunsa Research and Ethics Committee of the University of Limpopo.

Results

A total of 245 mothers were receiving ART during the study period; 76 (31%) were receiving ART pre-conception and 169 mothers (69%) started ART post conception after the first trimester. The average age of the participants was 31 and 29 years in the pre- and post-conception groups, respectively (p=0.003). Significantly more women in the post-conception group were primigravidae than in the pre-conception group (18% v. 5%, respectively; p=0.003). The rate of caesarean sections was similar in the pre- and post-conception groups (Table 1).

In the pre-conception group, 73 women were on a regimen of two nucleoside reverse transcriptase inhibitors (NRTIs) with a non-nucleoside reverse transcriptase inhibitor (NNRTI), while 3 women were on PI-containing regimens. The duration of treatment prior to conception ranged from 4 to 60 months. All the women in this group were in relatively good health, with sustained viral suppression prior to conception. In the post-conception group, 161 women were using two NRTIs with an NNRTI, while 8 women were on PI-containing regimens. All women in this group had $CD4^+$ counts <200 cells/µl per the national ART guidelines at the time of the study. The duration of treatment before delivery ranged from 2 to 22 weeks.

Table 2 compares pregnancy outcomes between the two groups. Results indicated that preterm delivery rates were similar between the pre- and post-conception groups (p=0.348). With regards to LBW, the rate was slightly lower (21%) in the pre-conception group than in the post-conception group (24%), but the difference was not significant (p=0.945).

Discussion

We investigated the effect of ART on pregnancy outcomes according to the timing of initiation of treatment. Accordingly, we did not find any

negative impact of this therapy on pregnancy outcomes, regardless of the timing of treatment initiation.

Those women who were receiving ART prior to conception, irrespective of the duration of treatment, had a similar rate of preterm delivery compared with those who commenced ART after the first trimester of pregnancy. A study conducted in the USA[10] also reported a non-significant difference in the rate of preterm delivery between pre- and post-conception ART groups. It would seem that in this study population, the use of antiretrovirals did not have any effect, whether positive or negative, on the rate of preterm deliveries. It is important to point out that the use of illicit drugs, alcohol abuse and cigarette smoking – all important causes of preterm labour – were negligible in this setting.

However, our results are in contrast to the findings of some other studies conducted in Europe, Cote d'Ivore and Nigeria, which concluded that patients who were receiving ART prior to conception had an increased risk of preterm delivery compared with those who commenced ART post conception.[8,12-14]

With regards to LBW in our study, the rates were similar: 17.1% and 20.7% in the pre- and post-conception groups, respectively. This result is in line with other studies conducted in Brazil and the USA,[11,15] both of which did not find any association between birth weight and the use of ART. However, contrasting results from Europe, Cote d'Ivore and Nigeria indicated higher rates of LBW among women receiving ART.[8,13,14]

Study limitations

This was a retrospective study that focused on women delivering live infants in health facilities and did not account for early pregnancy loss or home deliveries, thus constituting an important potential bias. Several other factors with known influence on pregnancy outcome including other infectious diseases, socioeconomic information of the mothers (e.g. educational level and employment status) were not measured and could not be evaluated in this study.

Conclusion

In summary, the results of this study suggest that ART initiated before or during pregnancy does not have any adverse effect on measured pregnancy outcomes such as preterm delivery and LBW.

Acknowledgement. We thank all members of staff in the labour ward for their efforts in entering data into the maternity records, and the clerks in the records department who assisted with patient file retrieval.

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ORIGINAL ARTICLE

Analysis of queries from nurses to the South African National HIV & TB Health Care Worker Hotline

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Background. Since 2008, the Medicines Information Centre (MIC) has run the South African National HIV & TB Health Care Worker Hotline which provides free information on patient treatment to all healthcare workers in South Africa. With the introduction of nurse-initiated management of antiretroviral therapy (NIMART) in the public sector, the need for easy access to HIV and tuberculosis (TB) information has increased, especially among nurses. The hotline aims to provide this, most importantly to nurses in rural areas, where clinical staff often have little access to peer review.
Objective. To describe the queries received from nurses by the hotline between 1 March and 31 May 2012 and identify problem areas and knowledge gaps where nurses may require further training.
Methods. All queries received from nurses during the study period were analysed. An experienced information pharmacist reviewed all queries to identify knowledge gaps.
Results. During the study period, the hotline received a total of 1 479 HIV- and TB-related queries from healthcare workers. Of these, 386 were received from nurses, of which 254 (66%) were NIMART-trained. The most common query subtopic was initiating antiretroviral therapy (ART) (20%), followed by adverse drug reactions (18%). The most common knowledge gap identified was the ability to interpret laboratory results before initiating ART (10%).
Discussion. We conclude that the hotline is providing clinical help to an increasing number of nurses on the topic of treating HIV and TB throughout South Africa. In addition, queries directed to the hotline may assist in identifying knowledge gaps for the further training of nurses.

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The Medicines Information Centre (MIC), situated within the Division of Clinical Pharmacology, Department of Medicine, Faculty of Health Sciences, University of Cape Town, is the only clinically based medicines information centre in South Africa (SA) and provides information to both public and private sector healthcare professionals. Established in 1980, the MIC's objective is to support rational prescribing in SA, by promoting the safe and effective use of medicines through the provision of unbiased, evidence-based information to its users.

SA healthcare workers see large numbers of HIV- and/or tuberculosis (TB)-infected patients. A large percentage of patients are HIV/TB co-infected, resulting in additional complexities. Many of these patients' care has been devolved to clinic level where they are managed by nurses. The management of such patients is often complicated, and the need for a clinical hotline to provide immediate advice is self-evident. Although the current hotline partially meets this need, expanded use is required to improve the care of HIV/TB-infected patients across SA.

Following the decision by the Minister of Health to expand the number of health facilities providing ART significantly in April 2010,[1] various institutions offered training to enable nurses to initiate and maintain patients on ART. These courses varied in length with standardised curriculum topics including HIV and TB diagnosis and management, interpreting laboratory results and clinical findings, ART regimens, clinical record-keeping and reporting. By the end of 2011, 10 541 nurses had attended such a nurse-initiated management of antiretroviral therapy (NIMART) training course.[2]

After the theoretical component of the NIMART course, it was intended that these nurses would work under the supervision of an experienced mentor. In practice, however, regular mentor visits were not always possible, and many of the doctors who visited the clinics had themselves not received training in HIV/AIDS.[3]

In March 2008, in collaboration with the Foundation for Professional Development (FPD) and the US President's Emergency Fund for AIDS Reflief (PEPFAR)/US Agency

for International Development (USAID), the MIC established the toll-free National HIV & TB Health Care Worker Hotline, to provide information to all healthcare workers in SA on all aspects concerning the treatment of HIV and TB.

The hotline received 2 035 calls between March 2008 and February 2009 (year 1) and 5 449 between March 2011 and February 2012 (year 4) – a 2.6-fold increase. The percentage of calls from nurses increased from 8% during the first six months of the service in 2008 to 28% of total calls during the six months ending in February 2012 (Fig. 1).

Queries received by the hotline cover a range of topics including HIV testing, post-exposure prophylaxis, the management of HIV in pregnancy, prevention of mother-to-child transmission (PMTCT) of HIV, when to initiate ART, regimen selection, laboratory and clinical monitoring, interpreting and responding to laboratory results, management of adverse events, drug interactions, treatment and prophylaxis of TB and opportunistic infections, drug availability and adherence support.

During many of the NIMART courses, nurses were encouraged to make use of the toll-free National HIV & TB Health Care Worker hotline for advice with any drug-related problems.

The objectives of this study were: (*i*) to describe the queries received from nurses by the hotline between 1 March and 31 May 2012; and (*ii*) to identify knowledge gaps where nurses require further training.

Methods

The queries directed to the hotline are handled by four specially-trained drug information pharmacists. They have direct access to the latest information databases and reference sources and to a network of experienced clinicians and consultants across SA. Queries requiring clinical input are discussed with clinicians experienced in HIV management.

All queries received between 1 March and 31 May 2012 were included. Only queries received from nurses were analysed. Queries were recorded using standardised data-capture sheets and were entered into a Microsoft Access database.

The following was recorded:

- province
- whether or not the answer was given immediately
- when the answer was provided immediately, how long the telephone conversation lasted
- when not immediately answered, how long before the answer was given
- subtopic(s) of question in 25 pre-defined subject areas
- how many times the same nurses called the hotline during the study period
- how many queries received from nurses needed a specialist consultant's input
- whether or not the querying nurse had been NIMART-trained.

To identify specific gaps in the medical knowledge of nurses making use of the hotline, an experienced information pharmacist manually reviewed all the questions during the study period.

Ethical considerations

The study was approved by the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town. The confidentiality of patients was maintained throughout.

Statistical analysis

Associations between categorical variables were explored by cross-tabulation, using the χ^2 test. Statistical significance was assumed at $p \leq 0.05$.

Results

During the study period, a total of 1 479 HIV- and TB-related queries were received by the

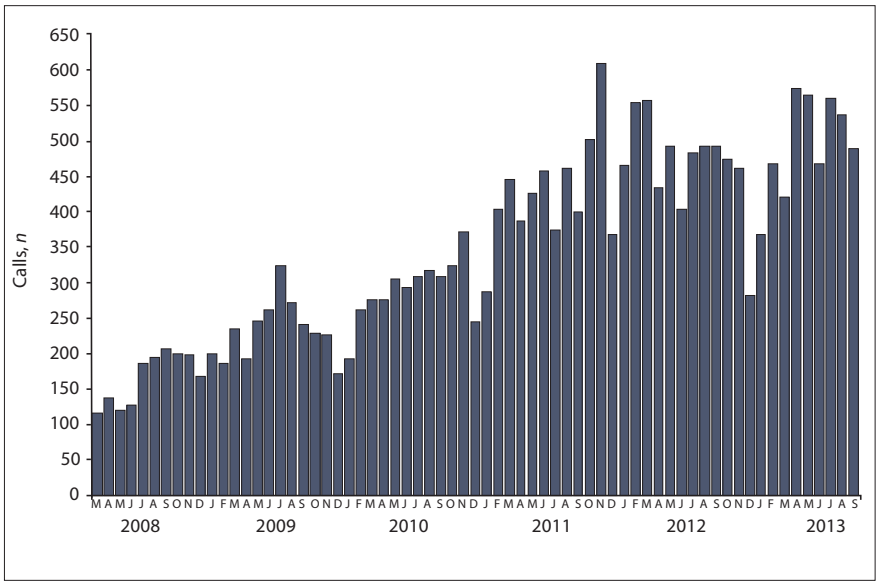

Fig. 1. Total number of calls per month to the hotline (all healthcare workers).

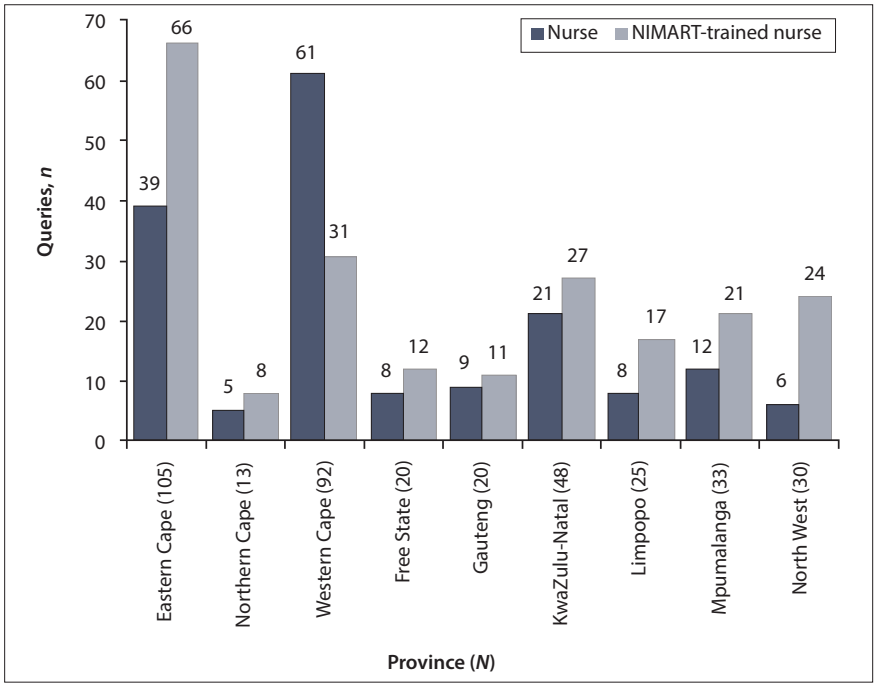

Fig. 2. Nurse calls by province. (NIMART = nurse-initiated management of antiretroviral therapy).

hotline from all healthcare professionals. Of these, 386 were received from nurses (26%), including 254 (66%) from nurses with NIMART training. The proportion of nurses who reported NIMART training differed significantly between provinces, with <60% reporting NIMART training in Gauteng (55%), Western Cape (34%) and KwaZulu-Natal (56%).

Fig. 2 illustrates the breakdown of the calls received per province by NIMART-trained and non-NIMART-trained nurses. During the three-month study period, most of the calls from nurses were received from the Eastern Cape (27.2%), followed by the Western Cape (23.8%). Only 13 calls were received from the Northern Cape.

Of the 386 queries received, 278 (72%) were answered immediately. Eighty-two queries (21%) were answered within 30 min, 10 queries (3%) were answered between 30 min and 1 hour after receipt and 12 queries (3%) took 1 - 4 hours to answer. Only three queries (1%) were not answered on the day that they were received.

The median time a call lasted when answered immediately was 5 min (range 0 - 18). There was no significant difference in the median time a call lasted between NIMART-trained nurses (median 4; interquartile range (IQR) 3 - 7) and non-NIMART-trained nurses (median 5; IQR 3 - 8, rank-sum p=0.69).

Subtopic(s) of questions

The 386 queries were subcategorised into one or more of 25 subject areas (Table 1), with a total of 529 allocated subtopics. The two most common subtopics were initiating therapy (20%) and adverse drug reactions (ADRs) (18%). There was no significant difference between frequency of topic occurrence when comparing NIMART-trained with non-NIMART-trained nurses (χ^2 p=0.79).

The frequency of query subtopics differed significantly between regions (χ^2 p=0.003). Initiating therapy accounted for the highest proportion of query subtopics in KwaZulu-Natal (37%) and the lowest in the Western Cape (6%). ADRs accounted for the highest proportion of query subtopics in the Western Cape (23%) and the lowest in the Eastern Cape (5%).

Knowledge gaps for further training

An experienced information pharmacist manually reviewed all the questions during the study period to identify specific gaps in the medical knowledge of nurses making use of the hotline.

For 182/386 queries (47%), no specific knowledge gap was identified. For the remaining 204 queries (53%), 22 different knowledge gaps were identified (Table 2). The most common question (37 queries) was how to interpret laboratory results before initiating patients on ART.

Number of calls and per nurse

During the study period, 214 nurses called 386 times (range 1 - 19 calls per nurse). Sixty-five (30%) nurses called more than once, and 23 (11%) called more than three times.

Queries requiring a specialist consultant

Of the 386 queries received, 59 (15%) required the input of a medical doctor experienced in HIV medicine and could not be answered directly by the medicine information pharmacist who took the initial call.

Discussion

With about 1.8 million people receiving antiretroviral therapy (ART), SA has the world's largest public sector ART programme.[4] Initially nurses were responsible for counselling, testing and preparing HIV-positive patients for ART. Since 2010, primary care nurses have also taken on the responsibility of initiating and maintaining patients receiving ART. This has resulted in increased access and reduced time to starting ART, reduced patient waiting times, improved patient satisfaction and comparable long-term outcomes.[5-7] This task-shifting is supported by the SA National Department of Health and the World Health Organization, as well as the majority of health professionals both locally and internationally.

In general, NIMART-trained nurses phoned the hotline more than non-NIMART-trained nurses. This is probably due to the fact that nurses are made aware of the hotline during NIMART training.

The four most common subtopics were initiating therapy (20%), ADRs (18%), TB (7%) and switching therapy (7%). Further training of nurses in these areas may be necessary.

Seventy-two per cent of queries were answered immediately. Except for three queries which were not answered on the day that they were received, the remainder were answered within four hours of receipt. This indicates that, in most cases, the nurse can attend to the patient's needs immediately, which is critical in resource-poor, busy clinic environments.

Fifteen per cent of the queries received from nurses required the input of an infectious disease specialist and could not be answered directly by the medicine information pharmacist who took the initial call.

For 204/386 queries, an experienced drug information pharmacist identified important knowledge gaps that could guide the future training of nurses. The most common knowledge gap identified was a lack of understanding of how to interpret laboratory results before initiating patients on ART. Thirty-seven queries were identified with this specific problem. This has important ramifications for common ART prescribing areas and patient safety, e.g. administering tenofovir to patients with an estimated glomerular filtration rate (eGFR) <50 ml/min and patients with liver function derangement.

The method of determining whether or not the nurse was NIMART-trained was limited by self report, i.e. it relied on the pharmacists

Table 1. Subtopic(s) of question

Subtopic	*n* (%)*
Initiating therapy	108 (20)
ADR	94 (18)
TB	37 (7)
Switching therapy	36 (7)
Other	34 (6)
Dosage	33 (6)
Paediatrics	32 (6)
Pregnancy	27 (5)
Interactions	24 (5)
Failure	20 (4)
Adherence	15 (3)
Second-line regimen	13 (2)
OIs other than TB	12 (2)
PEP	12 (2)
PMTCT	11 (2)
Availability/supply	5 (1)
Lactation	5 (1)
Renal failure while receiving TDF	4 (1)
IRIS	3 (1)
Resistance	2 (<1)
Complementary medicines	1 (<1)
Poisoning/overdose	1 (<1)

ADR = adverse drug reaction; TB = tuberculosis; OIs = opportunistic infections; PEP = post-exposure prophylaxis; PMTCT = prevention of mother-to-child transmission of HIV; TDF = tenofovir; IRIS = immune reconstitution inflammatory syndrome.

* Percentage of total subtopics allocated (N=529).

Table 2. Knowledge gaps identified

Knowledge gap identified	*n* (%) NIMART-trained nurse	Nurse	Total
Unable to interpret laboratory results before initiating ART	24 (12)	13 (6)	37 (18)
What ARVs to start in patients who have defaulted	7 (3)	6 (3)	13 (6)
Use of EFV during pregnancy	7 (3)	6 (3)	13 (6)
Initiating ART in children	7 (3)	5 (2)	12 (6)
Initiating ART in patients with renal dysfunction (eGFR <50 ml/min)	8 (4)	4 (2)	12 (6)
What ARV to change to when patients develop renal dysfunction while receiving TDF	6 (3)	5 (2)	11 (5)
Paediatric dosing	4 (2)	7 (3)	11 (5)
What to do when patients fail second-line ART	7 (3)	3 (1)	10 (5)
How to deal with NVP rash or hepatitis	6 (3)	3 (1)	9 (4)
Unable to calculate eGFR when serum creatinine value is available	7 (3)	2 (1)	9 (4)
How to deal with patients who develop ADRs while receiving d4T	5 (2)	3 (1)	8 (4)
Duration of NVP treatment in babies (both breast- and formula-fed) on a PMTCT programme (including those who have defaulted)	2 (1)	6 (3)	8 (4)
Dosage adjustment of ARVs in patients with an eGFR <50 ml/min	6 (3)	2 (1)	8 (4)
Keeping patients on failing first-line ART for prolonged periods	5 (2)	2 (1)	7 (3)
How to deal with drug stock-outs	5 (2)	2 (1)	7 (3)
What to start in patients who are HBsAg-positive and/or have abnormal LFTs	1 (<1)	5 (2)	6 (3)
Changing to non-interacting anticonvulsants before initiating or while receiving ART	5 (2)	1 (<1)	6 (3)
Understanding the difference between serum creatinine and eGFR	5 (2)	0 (0)	5 (2)
Indications for INH prophylaxis	3 (1)	2 (1)	5 (2)
Preferred NNRTI in patients receiving TB treatment	3 (1)	1 (<1)	4 (2)
Understanding why $CD4^+$ counts do not increase in some patients who are receiving ART	1 (<1)	1 (<1)	2 (1)
Age at which children can use TDF	1 (<1)	0 (0)	1 (<1)

NIMART = nurse-initiated management of ART; ART = antiretroviral therapy; ARVs = antiretrovirals; EFV = efavirenz; eGFR = estimated glomerular filtration rate; TDF = tenofovir; ADR = adverse drug reaction; NVP = nevirapine; d4T = stavudine; PMTCT = prevention of mother-to-child transmission of HIV; HBsAg = hepatitis B surface antigen; LFTs - liver function tests; INH = isoniazid; NNRTI = non-nucleoside reverse transcriptase inhibitor; TB = tuberculosis.

asking the nurses during each call whether or not they were NIMART-trained. In cases where this was not done, the nurse was classified as not NIMART-trained. We did not collect information on other training that nurses had received outside of the NIMART initiative.

Conclusion

The number of nurses contacting the hotline has increased significantly since its inception. This shows that the hotline is increasingly providing support to nurses throughout SA who are initiating and managing HIV and TB patients.

Author contributions. A Swart designed the study and managed the overall project. B Chisholm was responsible for the manuscript. D Cameron provided intellectual input and reviewed the manuscript. L Workman designed the database and performed statistical analysis. K Cohen performed statistical analysis and reviewed the manuscript. M Blockman reviewed the manuscript.

Acknowledgement. Sadly, Joe Talmud, who worked at the MIC since 1983, passed away in April 2013. He made many significant contributions to the safe and rational use of medicines during his career, while remaining humble and service-oriented. Improving the quality of life of the individual patient remained his ultimate goal. He stood for integrity, honesty and compassion. We will miss him dearly as a friend and colleague and acknowledge the contribution that he made to this article and to the hotline.

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REVIEW

Human papillomavirus infection and disease in men: Impact of HIV

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There is growing evidence of a significant burden of human papillomavirus (HPV) infection and associated disease in men. High rates of HPV infection have been observed in men from sub-Saharan Africa where HIV prevalence is high. HIV infection increases HPV prevalence, incidence and persistence and is strongly associated with the development of anogenital warts and anal, penile and head and neck cancers in men. Despite increasing access to antiretroviral therapy, there appears to be little benefit in preventing the development of these cancers in HIV-positive men, making prevention of infection a priority. New prevention options that are being introduced in many African countries include male circumcision and HPV vaccination. However, more data are needed on the burden of HPV disease in men before boys are included in HPV vaccination programmes.

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Human papillomavirus (HPV) is a common sexually transmitted infection (STI) affecting both men and women.[1] HPV infections can be classified as either low- (LR) or high-risk (HR).[2] HR-HPV infections have been associated with cancer of the anogenital and oropharyngeal tissues. While the majority of HPV infections are transient and clear spontaneously, persistent infection with HR-HPV is associated with the development of pre-neoplastic and neoplastic lesions in these areas (Fig. 1). While much is known about the natural history of HPV infection in cervical cancer in women, less is known about the development of HPV-associated disease in men. Emerging evidence points to a significant role for HIV infection in promoting HPV prevalence, incidence and persistence. This review provides an update on current evidence regarding the epidemiology of HPV infection and disease in men, the effects of HIV on HPV infection and disease in men in sub-Saharan Africa (SSA), and the prospects for prevention in this setting.

Global burden of HPV

HPV infection is ubiquitous in men. A systematic review of 62 studies using reliable methods of HPV DNA detection and conducted prior to 2009, representing 14 800 men in 23 countries, showed that anogenital HPV DNA prevalence is generally high in sexually active men. The review highlighted considerable variation in estimates by region, from 1% to 84% in LR men, to 2% to 93% in HR men.[3] Compared with studies in women, peak prevalence spanned a wide range of ages, suggesting that men have the potential for longer-term persistence of infection or higher rates of re-infection.[3] Type-specific HPV seroprevalence studies are better indicators of lifetime exposure to HPV infection, although they may underestimate cumulative HPV exposure, given that not all infections lead to seroconversion.[4] Recent population-based studies have estimated the prevalence of antibodies to vaccine-preventable HPV types 6, 11, 16 and 18. Among men aged 14 - 59 years in the USA, 12.2% of men were seropositive for any vaccine type, with a peak prevalence of 18% among men aged 50 - 59 years.[5] In a similar population-based study in Australia, peak prevalence of any vaccine type was 31.5% among men aged 40 - 49 years;[6] and a study from the Netherlands estimated that the seroprevalence of any HR-HPV in men aged ≥14 years was 20%.[7] There is some evidence that seroprevalence appears to be rising as a result of changes in sexual behaviour and earlier age of sexual debut. In a related study from the Netherlands comparing serosurveillance rates of HR-HPV in the periods 1995 - 1996 and 2006 - 2007, overall HR-HPV seroprevalence rates were significantly higher in the later survey, compared with the earlier survey across all age groups.[8]

Burden of infection in SSA

A recent global review of 117 studies worldwide suggests that the seroprevalence of HPV is even higher in SSA, although data on men in SSA are sparse.[4] In a small study of Tanzanian genital ulcer disease (GUD) patients, pregnant women and male blood donors, the prevalence of antibodies to HR-HPV ranged from 77% in male GUD patients to 15% in male blood donors. In this study, the prevalence of antibodies to HPV types 16, 18, 51 and 52 was considerably higher in HIV-positive patients with GUD.[9]

Although data on anogenital HPV DNA prevalence in men in SSA are also limited,[3] overall reported prevalences in men are high, ranging from 19% to 78%.[10-15] In most, but not all studies, the most prevalent type was HPV-16.[15] The observed heterogeneity in estimates can be attributed to differences in age distribution, sexual behaviour and HIV prevalence within the different populations. Emerging data

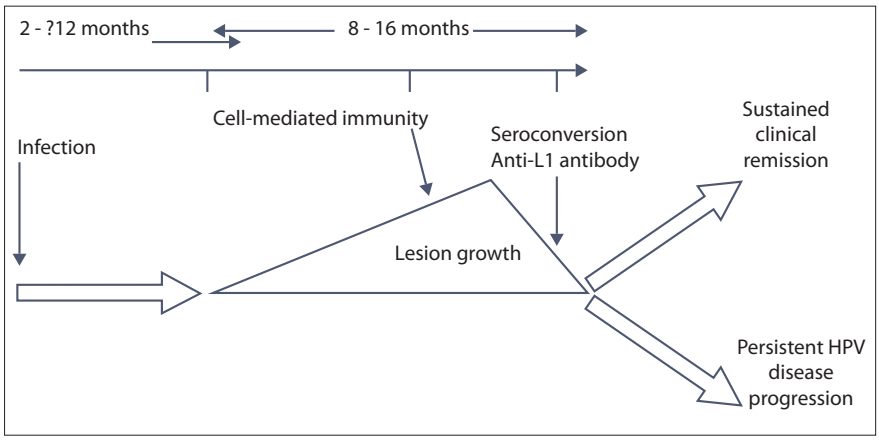

Fig. 1. Natural course of genital HR-HPV infection (source: Stanley[82]).

suggest that the incidence of HR anogenital HPV infection in men is also high, ranging from 35.7/100 person years in South African men to 40/100 person-years in East African men participating in male circumcision (MC) trials.[16-18] In both settings, the risk of HPV acquisition was doubled in HIV-positive men. These incidence rates are much higher than those previously observed elsewhere.[19,20]

Factors associated with HPV infection

HPV seroprevalence rates are consistently lower in men than in women,[6,21,22] with men also producing lower antibody titres than women.[23] There are several plausible biological explanations for differences in antibody responses between men and women. Men may experience a higher frequency of transient infections, a lower viral load, or produce less robust immunological responses than women.[24] It has been argued that the site of infection and/or type of epithelium influence antibody responses, with men experiencing a higher proportion of infections in more keratinised tissues (e.g. penile shaft) than women (e.g. anal canal or cervix). Thicker, more keratinised epithelium may present a barrier to infection, and if infected, may be less likely than mucosal surfaces to induce an immune response, given the relative distance from draining lymphatics and lymph nodes.[23,25] Recent data from a study comparing type-specific HPV antibody prevalence with the corresponding prevalence of HPV DNA detected in the external genitalia and anal canal in heterosexual men and men who have sex with men (MSM) support this notion. Higher HPV-6 and -16 seroprevalence rates were observed in men that had a same HPV-type infection in the anal canal, than in those with the same HPV-type infection in the external genitalia only. Higher seroprevalence rates were also observed in MSM compared with heterosexual men.[26]

The association between HPV infection and age is somewhat inconsistent, with fairly flat prevalence curves reported in populations where HIV prevalence is relatively low.[3,27] Data emerging from Africa, present a similarly mixed picture. A study among Kenyan fishermen showed a lower risk for HPV infection in older age groups,[10] while data from Kenyan men participating in an MC trial showed little variation in prevalence with age.[28] A more recent study in men from Tanzania demonstrated an association between increasing age and HPV prevalence, but that this association was driven by HIV-positive men.[15] Two recent incidence studies confirmed that increasing age is associated with a lower risk for HPV infection.[16,17] Combined, these data tend to suggest that the association between HPV infection and age in men in SSA is related to patterns of sexual activity, but confounded by HIV status, which may promote the persistence of HPV infection.

Sexual behaviour is an important risk factor for anogenital HPV infection. More recent publications have highlighted the importance of age of sexual debut,[8] marital status,[29] high number of lifetime sexual partners,[5,30,31] number of recent sexual partners,[30] longer history of sexual activity,[30] route of exposure,[26,30,32] and having sex with men[32-34] as risk factors for anogenital HPV infection. Similar observations about sexual risk behaviour and an association with HPV have been made in studies of men in SSA.[10,17,28] While the data on the protective effects of condoms are somewhat mixed,[35] evidence from African studies in men show a reduced risk of genital HPV infection associated with condom use.[10,28,36,37] Evidence from randomised controlled trials (RCTs) of MC has conclusively demonstrated the protective benefits of MC in reducing the risk of HPV prevalence and incidence.[17,36,38,39] Related findings from the trial in Kenya have highlighted less frequent bathing as a risk factor for HPV infection, which may be associated with poor genital hygiene in uncircumcised men.[18,28]

STIs are independently associated with the risk of HPV infection, particularly chlamydia,[19,30] herpes simplex virus (HSV)-2,[34] and hepatitis B.[40] While they may share a common mode of transmission, STIs are thought to increase the risk of HPV infection by facilitating access to the basal epithelium through micro-abrasions in the skin.[35] Recent reports on male populations in Africa point to a higher risk of penile HPV in men co-infected with laboratory-diagnosed *Chlamydia trachomatis* or *Neisseria gonorrhoeae,* and those who are HSV-2-seropositive.[28] Interestingly, HR-HPV clearance was recently shown to shown to be higher in HIV-negative men co-infected with syphilis or HSV-2, suggesting that other genital tract infections may also create an inflammatory cytokine milieu that may facilitate the clearance of HPV.[17]

HIV is a strong risk factor for HPV infection in men. While studies of anal HPV infection in MSM from Europe and the Americas first identified an increased risk for infection in HIV-positive men,[24] there is now a growing body of evidence from studies of men in SSA that shows that prevalent and incident anogenital HPV infection is more common in HIV-positive men.[15,16,37] Multiple infections, particularly with HR-HPV, are more common in HIV-positive men.[13,41] Prevalence of infection increases with declining $CD4^+$ count.[42] Partner HIV status has also been shown to increase the risk of HPV detection in men.[14,43]

Anogenital warts

Anogenital warts (AGWs) are the most common clinical manifestation of HPV infection.[44] Caused mainly by infection with HPV-6 and -11,[45] they are highly infectious. An estimated 65% of people whose sexual partner has genital warts will develop warts themselves.[46] The estimated incubation period from HPV infection to genital wart development is 2 weeks - 8 months.[47] While approximately 20 - 30% of genital warts will spontaneously regress,[48] recurrence is common, resulting in significant psychological morbidity and high medical costs for repeated treatment. These costs are not insignificant when compared

with costs for treatment of cervical cancer in women.[49] Two recent reviews estimated the prevalence and incidence of AGWs in the general adult population worldwide[45] and in SSA,[50] respectively. Worldwide, the overall prevalence of AGWs, based on genital examinations, ranged from 0.2% to 5.1%, with higher prevalence rates observed in males. Data suggest that prevalence has increased in recent decades, possibly as a result of changes in sexual behaviour.

Studies in male populations in SSA suggest much higher prevalence rates than in high-income countries, possibly as a result of higher HIV prevalence rates. Highest rates of 4.8 - 12.2% have been observed in HR men from Central and South Africa, a region of high HIV prevalence. Lack of circumcision and HIV infection have been identified as risk factors for AGWs in men.[12] Importantly, HIV-positive men with AGWs may also be at risk for infection with HR-HPV. In a small study in Johannesburg among HIV-positive men with penile warts, 85% were found to have HR-HPV as well. HPV-16 and -18 were most frequently detected.[41] These high rates of HR-HPV detection in men with HIV suggest that they are at significant risk for the future development of pre-neoplastic and neoplastic lesions, emphasising the importance of targeting screening programmes for HIV-positive men with AGWs.

Anal cancer

While relatively uncommon, the incidence of anal cancer in men appears to be rising.[51] A systematic review examined these trends, and found that age-adjusted incidence rates for anal cancer have increased in several high-income countries, with HPV infection identified as the most important associated aetiological factor.[52] Besides increasing age, smoking, receptive anal intercourse and HIV infection were the most important risk factors for anal cancer, with the highest incidence rates observed in HIV-positive MSM. While anal cancer incidence is highest in HIV-positive MSM, it should be noted that receptive anal intercourse is not a prerequisite for anal HPV infection, pre-cancer lesions or anal cancer. Piketty *et al.*[53] demonstrated high rates of anal infection and squamous intraepithelial lesions in HIV-positive men with no previous history of anal intercourse – an observation made subsequently in other studies.[54] In such instances, anal HPV infection is thought be transferred to the anal canal through transiently infected fingers or toys, as well as by shedding from other infected genital sites.

Anal cancer is considered to be biologically similar to cervical cancer. Like cervical cancer, it is thought to be preceded by a spectrum of intraepithelial changes and anal intraepithelial neoplasia (AIN), which can be graded similarly to cervical cancer. While there is strong supportive evidence that high-grade AIN is a precursor to invasive cancer, there is no consensus regarding the prevalence or significance of AIN, nor on the rate of AIN progression to cancer. Almost all of the natural history data come from studies in MSM, with few data on heterosexual, HIV-negative or African populations. A recent meta-analysis of anal HPV and associated lesions in MSM found that HIV-positive men were consistently more likely to be infected with HPV, to have associated lesions, and to have higher rates of anal cancer, although the excess in HIV-positive men was smallest for high-grade AIN, and was not statistically significant for that category. While there were no data on progression rates of AIN to cancer, estimates from this analysis suggest that rates of progression are significantly lower than those observed in cervical cancer.[55] Despite significant heterogeneity in the data, and a lack of prospective data, it remains plausible that high-grade AIN lesions regress more frequently than high-grade cervical lesions.[56] While the prevention of anal cancers in high-risk HIV-positive men is a priority, these findings raise doubts about the utility of anal cancer screening programmes at present. Until further evidence of benefit for screening in terms of reductions in anal cancer incidence and mortality become available, anal cancer screening programmes for men are likely to be controversial.

Despite immune reconstitution associated with highly active antiretroviral therapy (HAART), there appears to be little evidence that this therapy has a preventive effect on the development of anal cancer. The recent meta-analysis and other analyses of temporal trends in anal cancer incidence have highlighted the continuing high incidence of anal cancer, despite the widespread introduction of HAART.[55,57,58] These data suggest that prolonged survival afforded by HAART initiation may allow more time for AIN to progress to cancer, thus leading to higher anal cancer rates.

Penile cancer

Penile cancers are relatively rare. In 2008, of the estimated 22 000 new penile cancer cases, half were attributable to HPV, with much higher rates observed in regions with a low human development index.[59] Data from Zimbabwe suggest that southern Africa has higher incidence rates,[60] and a recently published report of HPV detection in cancerous and pre-cancerous penile lesions from men in South Africa demonstrated multiple HPV infections, with high rates of HPV-16.[61] Risk factors for penile cancer include: a lack of MC; phimosis and/or poor genital hygiene; AGWs; and HIV infection. HIV-positive men have an eight-fold increased risk of penile cancer, which may be associated with higher HPV infection rates.[62] Other risk factors for penile cancer that have been reported include current smoking, early age of first sexual intercourse, high lifetime number of female sexual partners, lack of condom use, chronic inflammatory conditions including balanitis and lichen sclerosus, and treatment with ultraviolet photochemotherapy for psoriasis.[63]

Head and neck squamous cell carcinomas

Head and neck cancer commonly refers to squamous cell carcinomas (SCCs) arising in the upper aerodigestive tract (oral cavity, nasopharynx, hypopharynx and larynx). Traditionally, most head and neck cancers were associated with tobacco and alcohol exposures and presented after the age of 60 years. More recently, a shift in the epidemiology of oropharyngeal SCC has been observed, with a rising incidence, particularly in the palatine tonsils and base of the tongue, occurring in younger age groups and in people who have never smoked.[64] Like the cervix and anus, there is an epithelial transition zone within the oropharynx which is prone to HPV infection, dysplasia and the development of SCCs. In a systematic review of studies involving histological specimens of head and neck SCCs, in 36% HPV DNA was detected, and HPV-16 was the most common HPV type associated with head and neck SCC.[65] HIV-infected individuals have a 1.5 - four-fold higher risk of oropharyngeal or tonsillar cancer than the general population. Although the proportion of oropharyngeal cancers is unknown, HIV-positive individuals appear to be at moderately increased risk of HPV-associated head and neck SCC compared with the general population.[66] D'Souza *et al.*[67] showed convincing evidence that oral cavity HPV DNA infection was related to sexual behaviour, including oral sex. There is

evidence that HIV-positive individuals have a higher prevalence of oral HR-HPV, even after controlling for sexual behaviour,[68] and that the risk for infection appears to be higher among those with a declining CD4+ count.[69] While there are limited data on the natural history of oral HPV infection, the majority of infections clear within two years,[70] although persistence appears to be associated with a CD4+ count <500 cells/μl.[71] There do not appear to be benefits for HAART on either the persistence of HPV infection or the clearance of oral lesions, but more evidence is needed in this regard.[66] Data on oral HPV and HPV-associated head and neck SCC in African populations is currently scarce, although one study from Senegal,[72] which included 117 invasive head and neck cancer histology specimens, mainly from men with a mean age of 52 years, found only four cases to be positive for HPV DNA. The authors remarked that larger studies are needed to confirm these findings and explore other potential risk factors specific to the region.[72]

Prevention of HPV-associated infection and disease in men

Evidence for the benefit of several strategies to prevent HPV infection and subsequent disease in men has emerged in recent years. Studies have shown a greater protective effect of condoms in the prevention of HPV acquisition in men. Analysis of data from a multi-national cohort study in men showed a two-fold lower risk of HPV acquisition in men with no steady partner and who always used condoms. In addition, the probability of clearing an oncogenic infection was 30% higher in men who consistently used condoms with non-steady partners.[73] Consistent condom use has also been associated with the regression of penile lesions in men.[74] Recent RCTs in Africa provide strong evidence that MC is protective against HPV infection. In these trials, MC has been associated with reductions in the incidence, prevalence and persistence of HPV infection in men. In HIV-negative men, MC has also been shown to reduce HR-HPV transmission to female partners.[75] Recent data suggests that decreased penile shedding of HR-HPV observed in HPV-infected circumcised men may help to explain the protective effects observed for female partners.[38] MC has also been associated with a lower prevalence of flat penile lesions in men.[39]

Vaccines are the ideal form of primary prevention for infectious diseases, and have been successful in the control of many other infectious diseases. Having been shown to be efficacious in women, HPV vaccine studies have now demonstrated evidence of benefit in men. An RCT involving 4 065 men from 18 countries aged 16 - 26 years showed that the quadrivalent vaccine was 90% effective in preventing infection with vaccine-specific types in the per protocol analysis, and 89% effective in preventing AGWs in the same population.[76] In 602 MSM aged 16 - 26 years, the quadrivalent vaccine was 77.5% effective in preventing HPV-6-, -11-, -16- and -18-associated AIN.[77] The bivalent vaccine is not currently registered for use in men. HPV vaccination has been shown to be safe and highly immunogenic in HIV-1 infected men.[78] Modelling studies predict benefits of vaccination for boys, when high levels of vaccine coverage are achieved in girls,[79] and data emerging from countries where national vaccination programmes have been introduced confirm this. Even though vaccination was restricted to girls, in Australia, there has been an 82% decline in AGWs in men aged <21 years since the introduction of the vaccine.[80] In Denmark, a 50% decline in AGWs in young men aged <19 years was observed only three years post vaccine introduction.[81] However, these benefits may not translate to all men, particularly MSM who may not benefit from herd immunity. Australia is the first country to extend vaccination to men. While several countries in Africa have recently introduced HPV vaccination programmes, these school-based programmes do not include boys. Further evidence is needed of the HPV-associated burden of disease in men, and the potential effects of HIV on HPV-associated disease in men before the vaccination of boys can be considered in lower-resource settings.

Conclusion

HPV infection and associated disease are common in men in SSA. While data on the burden of disease are limited, studies suggest that infection with HPV is common, particularly in the context of HIV. There is also growing evidence to suggest that HIV infection enhances HPV persistence – a precursor for the development of cancer. Given expanding access to HAART in Africa, there is now potential for significant morbidity and mortality from HPV-related cancers in men in the future. While MC and HPV vaccination programmes are being rolled out in many African countries where the burden of HIV is high, more data are needed on the natural history and burden of HPV-associated disease in men in Africa to inform the development of prevention programmes.

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CPD QUESTIONNAIRE

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Regarding the effect of antiretroviral therapy (ART) on pregnancy outcomes:

1. Studies from Europe and North America have suggested that *in utero* exposure to ART may be associated with prematurity, and this association appears particularly likely with nucleoside reverse transcriptase inhibitors (NRTIs).
2. Women initiating ART during pregnancy consistently appear to have lower birth weight infants than women who conceive after ART initiation.

Regarding patients failing second-line ART:

3. For ART to be effective, adherence rates must be at least 70%.
4. Studies show that the vast majority of cases of confirmed viraemia on second-line ART regimens are the result of antiretroviral resistance.
5. For patients receiving second-line regimens who have evidence of viraemia, further adherence counselling is unlikely to be helpful, and referral for genotypic testing and/or third-line ART is the only option.
6. A targeted adherence counselling intervention can lead to resuppression in individuals who appear to be failing second-line regimens.

Regarding human papillomavirus (HPV) infection in men:

7. HIV is a strong risk factor for HPV acquisition in men.
8. Anogenital HPV in men is not associated with significant pathology.
9. Compared with women, men have shorter-term persistence of infection and lower rates of re-infection of HPV.
10. The new HPV vaccine being rolled out in South Africa (SA) is not necessary for HIV-positive men.

Regarding queries from nurses working in ART services:

11. In many parts of SA, nurse-initiated management of antiretroviral therapy (NIMART) underpins public sector ART services.
12. The interpretation of laboratory results before initiating patients on ART is a common knowledge gap among NIMART nurses.

Regarding HIV self-testing in children:

13. Self-testing for HIV infection is being seen as a new way of reaching under-tested populations.
14. In line with key legal norms, children above the age of 12 years could consent to such a self-test.
15. There are already relatively high rates of health-facility-based HIV testing among children.

Regarding mental illness in HIV-positive individuals:

16. 'Common' mental disorders such as depression or anxiety occur less commonly in HIV-positive individuals than in the general population.
17. A primary care practitioner can often identify significant mental illness with a few simple screening questions.
18. In starting antidepressants, the governing principle is to start at low doses and escalate dosing gradually over time.
19. Efavirenz has psychotropic properties and is absolutely contraindicated in individuals with serious mental disorders such as schizophrenia.
20. The approach to medication to treat anxiety disorders (such as post-traumatic stress disorder) parallels that of depressive disorders, and serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine are the first-line treatment in most circumstances.

INSTRUCTIONS

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

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