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- HIV resistance testing guidelines
- Art for all HIV-infected pregnant women?
- Discordant immune responses on ART
- Psychotropic prescribing in HIV

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MESSAGE
From the Editor

This edition of the *Southern African Journal of HIV Medicine* is coming out slightly earlier than scheduled, timed to coincide with the first Southern African HIV Clinicians Society Conference in Cape Town. The conference features an exciting line-up of leading local researchers, as well as international experts. During 2013, the Journal will carry some of the reports and papers from the meeting; therefore, if you can't attend the conference, you will still be able to keep up to date on the latest trends and developments in HIV medicine and clinical care.

In this issue we feature a number of pieces related to the management of HIV-infected pregnant women. Some researchers, clinicians and policy makers see the prevention of mother-to-child transmission (PMTCT) of HIV as rather straightforward, and I've sat in on more than a few meetings where PMTCT is described by colleagues (both South African and international) as important yet 'boring'. Quite to the contrary, PMTCT interventions and policies are currently a hotbed of debate at the intersection of science, service delivery and policy-making. Along with other pieces in the Journal over the last few months, several of the contributions in this edition help to demonstrate why this is so. Firstly, Martin and Black[1] discuss the role of isoniazid preventive therapy (IPT) for tuberculosis in HIV-infected pregnant women. They suggest that given the relative health of HIV-infected pregnant women, even with low CD4 cell counts, routine use of IPT during pregnancy may not be the best use of resources to promote the health of HIV-infected mothers and their children. In addition, the choice of antiretrovirals (ARVs) during pregnancy can be controversial, with particular local concern surrounding ARV-related toxicities in pregnancy. Usually these concerns focus on fetal development and potential teratogenicity, but the choice of non-nucleoside reverse transcriptase inhibitors (NNRTIs) also has implications for maternal health. In this issue, Bera *et al.*[2] report two cases of apparent nevirapine (NVP) toxicities in pregnant women initiating ART. While case reports are rarely suitable evidence for making clinical or policy decisions, the authors point out that the evidence against the use of efavirenz in pregnancy comes mostly from case reports of teratogenicity – so perhaps these cases of NVP toxicity help to balance the scales somewhat.

Arguably the most contentious issue in PMTCT today regards the choice of prophylactic regimens for women with higher CD4 cell counts (e.g. >350 cells/mm^3). There is little debate that pregnant women with advanced HIV disease require rapid initiation of lifelong antiretroviral treatment (ART). However, the best ARV intervention for women with higher CD4 cell counts is unclear. Currently, South Africa and many other countries implement zidovudine prophylaxis during pregnancy for women with high CD4 cell counts (referred to as PMTCT 'Option A' in the World Health Organization (WHO) 2009 guidelines), while in Europe, Brazil and North America, triple-drug prophylaxis during pregnancy (WHO 'Option B') is commonplace. To date, these prophylactic strategies appear roughly equivalent in their effectiveness for PMTCT, and a randomised controlled trial comparing them is underway, with several sites in South Africa.

Recently there has been a call for universal initiation of lifelong ART for *all* HIV-infected pregnant women, regardless of CD4 cell count or WHO stage. This approach (sometimes referred to as WHO 'Optional B+') is the focus of a commentary in this issue by Besada and colleagues[3] from Médecins Sans Frontières (MSF). The WHO 'Optional B+' approach is being promoted heavily by WHO, the United States President's Emergency Plan for AIDS Relief (PEPFAR), and a range of international agencies, and – as presented here – there are strong hypothetical arguments for the idea of universal ART for pregnant women. On the other hand, there are also significant concerns raised by any strategy that calls for universal ART for all HIV-infected individuals. Yet, throughout these discussions about 'Optional B+', there is a striking absence of substantive evidence, and the knowledge base that could help inform a policy decision to implement universal initiation of lifelong ART for all HIV-infected pregnant women is astonishingly thin. In particular, there is as yet no meaningful evaluation of a programme that attempts to provide lifelong ART to all HIV-infected pregnant women. Without such evidence, national policy decisions regarding patient management can be leveraged by individual opinions, institutional agendas and donor priorities. In this context, we eagerly anticipate a decision by the National Department of Health on the future strategies for PMTCT in South Africa. Hopefully, along with the other PMTCT-related contributions in this issue, this debate helps to demonstrate that this is a topic that is anything but boring.

Happy reading.

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MESSAGE
From the Executive

'The times they are a-changing.' The South African National AIDS Council (SANAC) reconvened at an impressive inaugural meeting in Pietermaritzburg on 4 October 2012, attended by the Minister of Health, Dr Aaron Motsaeledi, and Deputy President Kgalema Motlanthe. SANAC announced that the incidence of mother-to-child transmission of HIV was down and life expectancy was up – all very good news. However, in my opinion, the most important development is that fixed-dose combinations are now going to be part of the national tender. While I think that this will improve adherence, more importantly, we will not be faced with stock-out of a single drug. The impact of patients having received two out of three of their drugs will be felt in the years to come.

The Southern African HIV Clinicians Society has been invited to be a plenary member of SANAC, so we will continue our role as the voice of reason to the Department of Health, to ensure that the goals of the National Strategic Plan are achieved. This is not the time to let up in any way – an AIDS-free generation is within our grasp.

Lastly, if you have not yet made travel arrangements to attend the conference of the Southern African HIV Clinicians Society in Cape Town from 25 to 28 November 2012, you should get onto it as soon as possible. Register for the conference as soon as you can. The line-up of speakers is impressive, and we have very interesting debates planned. Skills building will be provided in many areas, and conference attendees will have the chance to rub shoulders with the academics. More than that, the conference will present an opportunity to meet a number of brave and hardworking healthcare providers from the region. I encourage you to share your experiences and learn.

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GUIDELINES

The 2012 southern African ARV drug resistance testing guidelines

by the Southern African HIV Clinicians Society

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Disclaimer: Specific recommendations provided here 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.

Following the rapid scale-up of the programme for universal access to antiretroviral therapy (ART) in southern Africa, resistance to antiretroviral medications will occur. A detectable viral load must be treated as an emergency and should trigger intensive patient tracking and adherence counselling. In contrast to the developed world, the incidence of transmitted resistance is still low in most areas in the region. Therefore, in this consensus statement we do not recommend resistance testing in HIV-infected adults upon diagnosis or ART initiation. However, baseline resistance testing is recommended for children who have been exposed to ART for prevention of mother-to-child-transmission therapy and subsequently become HIV-infected. Resistance testing is also recommended after virological failure of first- and second-line ART regimens.

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1. Opening statement

Antiretroviral therapy (ART) has converted HIV infection from an almost universally fatal illness to a chronic manageable disease. Adherence to therapy is essential for full viral suppression and optimal immune reconstitution. If antiretroviral (ARV) drug levels are suboptimal, the risk of developing ARV drug resistance is high due to the high rate of HIV replication and the lack of proofreading capacity in the viral reverse transcriptase enzyme. Continuation of a failing ART regimen can affect both the treated individual and the community, as resistant viral strains can be transmitted to other persons.

Resistance can be minimised by uninterrupted supply of medication, scientifically sound prescribing practices, long-term adherence support, viral load (VL) monitoring, and rapid responses to demonstrated virological failure with timeous changes of therapy.[1]

We developed consensus guidelines for HIV resistance testing that consider international best practice and the financial constraints encountered in southern Africa. The guidelines, presented here, are based on the levels of resistance in the community as reported in the 2012 World Health Organization (WHO) HIV drug resistance report.[2] The North American and British resistance testing guidelines,[3-5] although ideal, are not affordable nor applicable in most southern African situations. These guidelines are aimed at southern African clinicians who manage individuals with HIV infection in both the private and public sectors in our region.

Appropriate, affordable resistance testing needs to be incorporated strategically into national guidelines relevant to southern Africa. In late 2012, the South African National Department of Health sanctioned the formalisation of a National HIV Drug Resistance Working Group. All relevant stakeholders were identified and a steering committee was formed. The working group has 4 clear pillars: *(i)* a clinical stream; *(ii)* a national database development team; *(iii)* a laboratory team (National Health Laboratory Service (NHLS) and National Institute for Communicable Disease (NICD)); and *(iv)* an epidemiology stream.

The presence of a VL >1 000 copies/ml in an individual who has been receiving ART for >6 months constitutes an adherence emergency, and should trigger a vigorous response from the healthcare provider, including increased adherence support, before the VL measurement is repeated.

2. Recommendations for ARV drug resistance testing

2.1 The diagnosis of HIV in children aged <2 years

Genotyping at baseline to detect resistance mutations should be performed for all HIV-infected infants who have been exposed to any form of ART taken by the mother or infant for the prevention of mother-to-child transmission (PMTCT) of HIV, or who have unknown exposure to PMTCT. Infants and children are a challenging group to treat with ART, especially in resource-constrained healthcare settings. Children and their mothers are likely to have been exposed to ARV medications in PMTCT

programmes. Approximately 52.6% (95% confidence interval (CI) 37.7 - 67.0) of children who fail PMTCT therapy have at least one non-nucleoside reverse transcriptase inhibitor (NNRTI) mutation after single-dose nevirapine (sdNVP), and about 16.5% (CI 8.9 - 28.3) after sdNVP combined with antepartum, postpartum or postnatal zidovudine (AZT) with or without lamivudine (3TC).[6] These mutations will generally have disappeared, or may not be detectable by routine resistance testing, 2 years after the last dose of prophylactic ART. Children aged <3 years are treated with a boosted protease inhibitor (PI) regimen, but it is important to document NNRTI resistance, as this will have implications in the choice of second-line regimens.[7] Resistance mutations in children failing ART seem to be more common than in adults.[8] Results from baseline resistance testing will ensure the most appropriate selection of ARV drugs. Further research on appropriate drug regimens in paediatric and adolescent populations is, critically, an unmet need.

2.2 Failure of ARV regimens

Resistance testing is recommended for all patients (children and adults) failing first-line NNRTI-based ARV regimens, with failure defined as two VL measurements >1 000 RNA copies/ml, with adherence and other issues addressed in the interval (see section 5). The accumulation of resistance mutations can be minimised by repeating the VL measurement within 3 months.[9-11] If the first-line regimen is fully effective, then the VL should have fallen by 1.0 $\log_{10}$ copies/ml within 4 weeks or be undetectable by 3 months (or <1 000 RNA copies/ml in patients whose initial VL was very high).[4]

Resistance tests serve two purposes: *(i)* a fully sensitive pattern may imply that the patient is not adhering to treatment or has completely interrupted ART; and *(ii)* if resistance mutations are present, then the clinician, preferably together with an expert, can decide on the most appropriate second-line regimen. In patients on a stavudine (d4T)- or AZT-containing NNRTI-regimen, or on a tenofovir (TDF)-containing regimen, the importance of excluding resistance to TDF is crucial. TDF may be required as part of the nucleoside reverse transcriptase inhibitor (NRTI) backbone in second-line ART, or for treatment of hepatitis B virus (HBV)/HIV co-infection in combination with 3TC.[12]

Resistance testing is recommended for all patients (children and adults) failing a PI-based ARV regimen. Failure is defined as two VL measurements >1 000 RNA copies/ml, with measurements taken 3 - 6 months apart and with adherence and other issues addressed in the interval. An absence of PI mutations during PI-based therapy strongly suggests non-adherence to treatment.[13] Children on any PI regimen are at high risk for PI resistance if co-treated with rifampicin (for tuberculosis). Repeated VL measurements and resistance testing are recommended for patients failing long-term PI regimens with a concurrent decline in CD4 count.

2.3 Acute infection

Recent HIV infection in adults is rarely documented; however, viral genotyping at this time may give valuable public health insights into currently circulating strains. Resistance testing recommendations for specific acute infection scenarios are shown in Table 1.

3. Scenarios where ARV resistance testing is not recommended

3.1 HIV diagnosis in adults and adolescents

At the current level of transmitted resistance in the community, performing resistance testing in all individuals who are diagnosed with HIV infection is not cost-effective.

For pregnant women, although we do not recommend routine resistance testing, we do recommend HIV VL testing 3 months after initiating triple ARV therapy (for CD4 counts <350 cells/mm^3) or at the time that pregnancy is confirmed in women already receiving ART. A VL >1 000 RNA copies/ml at this point should be regarded as an emergency, and should lead to intensive adherence support and screening for drug interactions or other reasons for failure (section 5), to minimise fetal transmission risk. The VL measurement should be repeated after 4 weeks, and, if >1 000 copies/ml, HIV resistance testing and an immediate switch to a second-line ART regimen must be performed.

3.2 ARV initiation in adults and children aged >2 years

Children aged >2 years who stopped taking prophylactic NVP during breastfeeding more than 2 years previously do not need a resistance test prior to ARV initiation. In such cases, resistance, if present, is very unlikely to be detected by genotyping. While super-infection with a resistant viral strain is a theoretical possibility, it is considered to be so rare that performing resistance tests would not be cost-effective.

3.3 Treatment interruptions without documented failure

Patients who have interrupted therapy for reasons other than proven virological failure should not have HIV genotype testing performed upon presentation for subsequent ART.[14] Rather, the previous ART regimen should be re-started, and VL should be measured after 3 months. Resistance mutations generally disappear rapidly in the absence of drug pressure and a reliable resistance test result may not be obtained during treatment interruptions. If the VL is not suppressed after adherence intervention, a resistance test can be obtained to document resistance, and an appropriate second-line regimen can be selected.[15]

4. National integration of public sector laboratories

In the public sector in South Africa, the NHLS has five centralised facilities capable of conducting sequence-based resistance testing. Currently, only two of these facilities perform routine genotyping for patient care on a large scale (Tygerberg and Johannesburg). Laboratories focus on genotyping assays, most using in-house assays, with backup from commercial assays such as Viroseq or TruGene. National surveillance is conducted at the NICD. As the ARV programme expands and patients receive treatment for longer periods of time, the capacity for resistance testing will need to be expanded. Currently, phenotyping capabilities for resistance are available, largely for research purposes, at several academic centres. Numerous research projects are underway to develop and assess more affordable and accessible approaches to resistance testing (e.g. sequencing short regions of the reverse transcriptase gene).

The Southern Africa Treatment and Resistance Network (SATuRN) has integrated the efforts of laboratories, researchers and clinicians to monitor HIV resistance patterns and advise on the clinical management of patients failing ART. The SATuRN drug resistance database systems are freely available and include two of the best public drug resistance databases in the world: the Stanford HIV Drug Resistance database and the RegaDB Clinical Management Database. SATuRN databases are used to deliver an approach to virological failure, delivering resistance genotyping, interpretation and clinical management to remote primary healthcare clinics without elaborate computer systems or infectious diseases specialists at each clinic.

Table 1. Recommendations for HIV resistance testing

Patient group	Recommendation	Comments
Recent infection		
Infected infants aged <2 years exposed to PMTCT or infected children aged >2 years who stopped taking daily NVP less than 2 years previously	Recommended	As soon as HIV infection is diagnosed
Infants aged <2 years where exposure to PMTCT is uncertain	Recommended	As soon as HIV infection is diagnosed
Documented acute infection* (seroconversion)	Recommended	Possible public health surveillance function
HIV diagnosis		
Patients without documented seroconversion presenting for routine clinical care	Not recommended	Background prevalence of transmitted resistance is low and time since infection is likely to be long, decreasing the likelihood of detecting resistance mutations
ARV initiation		
Children aged >2 years about to start first-line ART	Not recommended	Unless within 2 years of stopping daily NVP
Pregnant women about to start first-line ART	Not recommended	Pregnant women should have a VL measurement 3 months after ART initiation. Detectable viraemia >1 000 RNA copies/ml should be treated as an adherence emergency.
Adults about to start first-line ART	Not recommended	Background prevalence resistance is very low and the time since infection is likely to be long, decreasing the likelihood of detecting resistance mutations.
Failure of NNRTI-based ART		
Adults and children with two VL measurements >1 000 RNA copies/ml† and/or at least a <2 $\log_{10}$ drop in VL while on NNRTI-based ART (measurements at least 4 weeks, preferably 3 months, apart)	Recommended	Adherence‡ issues should be addressed comprehensively between the 2 measurements. Resistance testing should be performed while the patient is on the failing regimen or within 4 weeks of discontinuation.
Failure of a boosted PI-based regimen		
Adults and children with two VL measurements >1 000 RNA copies/ml† and/or a <2 $\log_{10}$ drop in VL while on PI-based ART (measurements 3 - 6 months apart)	Recommended	Failure on PI regimens is almost always due to poor adherence. Adherence‡ issues should be addressed comprehensively between the 2 measurements. Resistance testing should be performed while the patient is on the failing regimen or within 4 weeks of discontinuation.

PMTCT = prevention of mother-to-child transmission; NVP = nevirapine; ART = antiretroviral therapy; RNA = ribonucleic acid; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; VL = viral load.

*Some or all of the following features: high fever, generalised lymphadenopathy, oral ulcers, pharyngitis, maculopapular rash, lymphopenia, thrombocytopenia, and transaminases, in combination with a history suggestive of HIV exposure.

†Definition of virological failure may vary between southern African countries. A persisting VL of 500 - 1 000 copies/ml could be considered for resistance testing, with access to sensitive in-house assays.

‡See section on ARV adherence (section 5).

For each case, all laboratories (non-governmental, public and private) generate a report that includes clinical and resistance data. This report is sent to HIV specialists for review and feedback, to advise management at the primary clinic.

Meaningful interpretation of the results of genotypic resistance tests requires a detailed knowledge of the patient's full ARV history, including drug regimens used, VL and CD4 test results, any previous resistance test results, co-occurrence of other infections, and timelines. This information needs to be provided by the clinician/nurse upon submitting the resistance test.

4.1 Surveillance of ARV drug resistance

The ongoing monitoring of ARV drug resistance is a critical public health activity, particularly in settings where individualised ARV drug resistance testing (genotyping) is not routinely performed prior to ART initiation. The success of empiric ART regimens depends on the regular and timely knowledge and review of the epidemiology of ARV drug resistance. Recommended systems for surveillance include prevalence monitoring of HIV genotype results at sentinel sites among populations who have recently acquired infection: e.g. recent seroconverters, HIV-infected pregnant women aged ≤21 years, infants infected despite ARV exposure and those with acute HIV infection. There may also be additional value in prevalence monitoring at sentinel sites of ARV drug resistance among those newly initiating therapy.

4.2 Monitoring and evaluation

The proportion of ART-treated patients on first-line, second-line and subsequent therapy should be monitored routinely. Because a

detectable plasma VL while on ART requires immediate intervention, national monitoring of the proportion of patients with detectable plasma VLs is recommended. Thresholds for response should be determined at the public health level. For example, a facility or geographic area with >20% detectable plasma viraemia in patients on ARV who were previously undetectable, should urgently be investigated. Analyses should be performed according to demographic and geographic characteristics, and reported quarterly to national HIV treatment programmes.

The evaluation of the effect of HIV genotype testing on the selection of ARV regimens and clinical outcomes should be supported through networks of clinical programmes. Indicators to monitor the use of HIV genotype resistance assays should include: the number of assays per specified time period; the proportion of assays performed in adults, children and pregnant women; and the prevalence and type of resistance (including class of resistance and specific mutations). As the surveillance of ARV resistance and clinical use of HIV genotyping increases, additional monitoring and evaluation activities may be required.

Most settings require increased capacity for monitoring and evaluation. Resources to sustain adequate data management and interpretation are a public health priority. The net cost of incorporating resistance testing, for surveillance as well as patient management, needs to be evaluated carefully in ARV programmes in southern Africa.[16]

5. Non-adherence: Causes and interventions

The adherence requirements of ART are onerous, necessitating adherence rates >90% for first-line NNRTI-based regimens. The best biological marker of adherence is an undetectable VL in patients on ART. The regularity of pharmacy pick-ups is also a good marker of adherence. Other strategies, including pill counts, have limited practical utility in busy clinics, and are often inaccurate.[17] Pill boxes and treatment supporters may be useful in selected individuals.[18]

A detectable VL in patients on ART should be treated as a medical emergency, with immediate intervention, prompt evaluation by an experienced clinician and appropriate support staff (e.g. social workers, psychologists, and counsellors), and frequent follow-up. In the case of first-line virological failure, up to 50% of patients can re-suppress their VL,[7,8] if virological failure is identified timeously, and if adherence can be improved.

In patients failing second-line therapies, and where expensive third-line options are being evaluated, newer measures such as the use of electronic pill boxes (e.g. Medication Event Monitoring System (MEMS) caps) and hair PI levels may be used, if available.

In a significant minority of cases, patients will have no resistance on resistance testing. Data from South Africa reveal that this can be as high as 15 - 20% where patients have been genotyped.[19,20] This means the patient is missing a large number of doses, consequently resulting in insufficient drug pressure to induce or select out existing resistance. These patients have a poorer prognosis, paradoxically, than patients with established resistance,[21,22] as their poor adherence is often difficult to remedy, and may persist into subsequent regimen choices. Such patients often require the intervention of a psychologist or experienced counsellor.

Common causes of poor adherence (sections 5.1 - 5.12) are often complex and linked to social issues.

5.1 Inadequate treatment literacy

Most HIV programmes have extraordinary adherence rates when compared with other chronic diseases – largely due to efforts by clinic staff to ensure that patients understand HIV infection and ART. If a patient fails therapy, then some examination of the pre-ART counselling may be merited.

5.2 Side-effects

Side-effects are a very common reason for patients to default therapy. A careful history of often subtle but distressing side-effects (bad dreams, sleepiness, poor concentration, nausea, loss of appetite), in conjunction with a work history (shift work in particular) may allow for drug substitutions. Subtle signs of lipo-atrophy due to NRTIs are often not taken seriously by healthcare providers. Regular enquiry and immediate drug substitutions should form part of every healthcare worker encounter. Single drug substitutions should only be performed if the VL is undetectable.

5.3 Depression and mental illness

Undiagnosed or under-treated depression and other mental illnesses are often overlooked. The frequency of major depression is twice as high in HIV-infected patients as in matched HIV-negative patients.[23] Patients with depression usually respond well to treatement with an antidepressant in combination with other non-pharmaceutical interventions. Patients who respond to antidepressant medication should be treated accordingly for at least 6 months.

5.4 Poverty and food insecurity

Both poverty and food insecurity have been related to poor adherence and an increased frequency of missed clinic visits. Patients often lose their jobs due to ill health in the period leading up to ART initiation. Patients should be encouraged to return to the job market as soon as is feasible, or to seek support. The need to seek work may cause patients to move away from the current clinic; therefore, referral must be facilitated. Access to available grants, social support and employment NGOs may provide additional support.

5.5 Work-related issues

Work-related issues, including shift work and an inability to attend clinic visits on weekdays, are a major cause of poor adherence. Long clinic waiting times and monthly medication pick-ups, may make holding down a job untenable, especially with an unsympathetic employer.

5.6 Substance use

Alcohol use may cause significant problems with adherence. In addition, other recreational drugs may cause problems in certain parts of the country. Use may fluctuate according to availability and peer pressure.

5.7 Social problems

Social problems that affect adherence include stigma, both external and internal, and poor social support networks. Perceived stigma is correlated with poor adherence. This may manifest in: a fear of tablets being found; an inability to solicit family or partner support; fear around visiting the clinic or pharmacy; or anxiety regarding an employer, neighbours or a community. Social support groups may assist in this regard.

5.8 Denial

ART initiation in ambivalent, conflicted patients is unlikely to have a successful outcome. The involvement of family members and partners may be an effective mechanism for addressing denial.

5.9 Pill burden

Pill burden is less of an issue with current regimens, but must be considered in patients who are failing treatment. Pill burden due to treatment for other

conditions, such as hypertension or diabetes, should also be addressed. Dosing simplification, such as provision of fixed-dose combination regimens, where possible, should be a major part of advocacy within public programmes.

5.10 Altered fertility intentions

HIV-discordant or -concordant couples may spontaneously decide to cease their ART regimen with the intent to begin a family. Empathetic fertility counselling during ART initiation should prevent this from occurring.

5.11 Conflict of opinions

Conflict of opinions on the use of ARVs occurs frequently between healthcare providers, certain alternative health providers and churches. This is best addressed with an honest and non-judgmental conversation.

5.12 Other

Drug doses should be checked, especially in patients referred from the private sector or inexperienced sites. Drug interactions (e.g. rifampicin with a PI), absorption issues and primary acquisition of resistant virus may also result in failure.

6. Laboratory objectives

6.1 Recommendations and requirements

A meaningful interpretation of genotypic resistance test results requires detailed knowledge of the patient's full ARV history, including drug regimens used, VL and CD4 test results, any previous resistance test results, and timelines.

It is desirable that national databases be built, using unique patient identifiers (e.g. ID numbers), to allow the easy retrieval of information for patients who have been cared for at different clinics and tested by different laboratories. Besides improving patient care and easing clinical workload, this approach is cost-effective, as it prevents unnecessary repeat testing.

All resistance test results (including clinical information and sequences obtained) should be entered into a central database, such as the one maintained by SATuRN, to enable research and surveillance.

6.2 Genotypic ARV resistance testing: Practical issues

Testing requires ethylenediaminetetra-acetic acid (EDTA) whole blood or EDTA plasma (purple-top tubes). Alternatively, where established, dried blood spots (DBSs) may be used. To ensure sample integrity, whole-blood and plasma samples must be maintained and shipped cooled (4°C – fridge temperature) and reach the laboratory within 48 hours. For longer delays, whole-blood specimens must be centrifuged and the plasma stored at -20°C (frozen). Repeat freeze-thaw cycles must be avoided. DBSs can be maintained at room temperature for up to 4 weeks, and must be frozen at -20°C if the delay is longer than 4 weeks.

Current commercial tests have been licensed for specimens with a VL value of at least 1 000 RNA copies/ml. If DBSs are used, then the minimum usable VL is 2 000 - 5 000 RNA copies/ml. Nevertheless, many in-house assays can detect VLs of 500 - 1 000 RNA copies/ml. The probability of harbouring resistance in the VL range of 500 - 1 000 RNA copies/ml is only marginally less than in the 1 000 - 10 000 copies/ml range.[24] The acquisition of additional mutations is not necessarily associated with incremental increases in VL.[25]

Once a failing ART regimen has been discontinued, most resistant viral variants quickly become undetectable. Samples must therefore be obtained while the patient is still on the failing regimen or very shortly after discontinuation (to a maximum of 4 weeks).

Current test methods do not detect minority resistant viral variants (quasi-species present at less than approximately 20% of the total population) or archived resistance.[26]

Even in the best hands, the rate of failure to amplify virus is 5 - 10%, so not all samples submitted to the laboratory will have a genotype result.

6.3 Genotypic ARV resistance assays

Currently available genotype tests evaluate only the viral reverse transcriptase and protease genes. Mutations in the genes encoding these enzymes underlie resistance to the NRTIs, NNRTIs and PIs.

Raltegravir (RAL),[27,28] the first of the integrase strand-transfer inhibitors (ISTIs), is now registered in South Africa. Currently, no entry inhibitors – e.g. maraviroc (a CCR5 co-receptor inhibitor) or enfuvirtide (a fusion inhibitor) – have been registered. Future genotype tests will also need to incorporate these drug classes.

Current resistance testing is performed by means of polymerase chain reaction (PCR) amplification and sequencing/genotyping of the HIV-1 protease and reverse transcriptase genes, using commercial or validated in-house assays. The turnaround time of these assays is approximately 2 weeks. Current United States Food and Drug Administration (FDA)-approved commercial assays, including ViroSeq and Trugene, can be performed at a cost of approximately R5 000 per assay. In-house assays are about 50% cheaper. Results can provide data on the presence or absence of resistance mutations, with resistance mutations interpretable by drug resistance algorithms, many of which are available online.

7. Research priorities

7.1 Resistance assays

The main thrust of research activities remains the need to develop rapid, affordable, accessible resistance assays, including:

- advocacy to drive down current commercial assay costs
- the evaluation of innovative new testing approaches, e.g. the use of more cost-effective strategies such as allele-specific assays (e.g. M184V) to determine adherence
- improved logistics using creative approaches such as DBS technology
- national standardisation of technology and reporting across the country
- continual review to ensure the incorporation of new drug classes into assays
- integrase assays
- tropism assays for CCR5 inhibitors
- the constant evaluation of new testing platforms, e.g. ultra-deep sequencing strategies
- the suitability of assays for relevant local HIV subtypes.

7.2 Operational research activities

7.2.1 Laboratory-based activities

Laboratory-based activities should include:

- the upgrading and up-scaling of infrastructure, human resource skills, interpretation skills, and improved emergency reporting within and by the laboratory
- national data flow and reporting
- a monitoring and evaluation framework to evaluate the effect of the intervention
- ongoing cost-effectiveness modelling and analyses to assess cost-effectiveness
- ensured support for strengthened national surveillance activities (i.e. increased numbers processed in realtime).

7.2.2 Clinical activities

Clinical activities must include:

- strategies to develop a hierarchy of specialist support for interpretation, e.g. failure clinics
- resistance testing to support ongoing clinical research and guideline development
- strategising for the components of an appropriate standardised third-line regimen.

7.2.3 Basic research questions

Future work should address:

- the contribution of detecting minority variants and their effect on patient outcome (including ultra-deep sequencing)
- the significance and role of PI mutations in the local population
- the development of a national reference facility that conducts phenotyping and other sophisticated assays to support and develop a strong scientific agenda for resistance testing.

8. Closing comment

These guidelines reflect the current *status quo* in terms of levels of HIV resistance in southern Africa in late 2012, and will be reviewed every few years. Implementation of the recommendations herein will require a drastic expansion of the laboratory capacity in the region.

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ORIGINAL ARTICLE

Risk factors for discordant immune response among HIV-infected patients initiating antiretroviral therapy: A retrospective cohort study

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Background. The therapeutic goal of antiretroviral therapy (ART) is sustained immune recovery and viral suppression. However, some patients experience poor CD4 cell count responses despite achieving viral suppression. Such discordant immune responses have been associated with poor clinical outcomes.
Objective. We aimed to determine the prevalence of discordant immune response and explore associated factors in a retrospective cohort of patients attending 2 large public sector clinics, during the 6 months following ART initiation.
Methods. Data were analysed from 810 HIV-infected adults initiated on first-line HAART at 2 clinics in Johannesburg, between 1 November 2008 and 31 December 2009. Multivariate logistic regression models were used to estimate adjusted odds ratios (AORs) to determine associations between discordant immune response and clinical and demographic factors.
Results. At ART initiation, 65% (n=592) of participants were female, with a mean age of 38.5 years. Median baseline CD4 cell count was 155 cells/mm^3, 70% (n=645) of patients had a haemoglobin level >11 g/dl and 88% (n=803) were initiated on stavudine-lamivudine-efavirenz/nevirapine (D4T-3TC-EFV/NVP). Six months after ART initiation, 24% (n=220) of patients had a discordant immune response and 7% (n=67) a discordant virological response. On multivariate analysis, baseline CD cell count ≥200 cells/mm^3 (AOR 3.02; 95% confidence interval (CI) 2.08 - 4.38; p<0.001) and moderate anaemia (8.0 - 9.4 g/dl) at baseline (AOR 2.30; 95% CI 1.25 - 4.59; p=0.007) were independently associated with the development of discordant immune response, after adjustment for education level, World Health Organization (WHO) clinical stage and ART regimen.
Conclusions. Discordant immune response following ART initiation was common and associated with baseline anaemia and CD4 cell count in our cohort. Intensive monitoring of at-risk individuals may improve clinical outcomes.

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HIV infection is typically associated with progressive CD4 cell depletion and consequent immunodeficiency.[1-3] The introduction of antiretroviral therapy (ART) has seen a decline in the morbidity and mortality associated with HIV infection.[4] This is a consequence of the ability of ART to suppress HIV viraemia to undetectable levels and allow immune restoration, resulting in an increase in circulating CD4 cells.[5] In clinical practice, however, not all patients receiving ART

achieve the desired concordant response of viral suppression with CD4 cell count increase.[6] As many as 20 - 40% of patients on ART do not show a significant increase in CD4 cell count despite viral suppression.[6] This phenomenon is referred to as discordant immune response and is associated with an increased risk of developing an AIDS event or death.[6-9]

Discordant immune response may arise either as a result of failed immune reconstitution or the excessive destruction of CD4 cells.[10] The reconstitution of peripheral CD4 cells is a biphasic process with an initial rapid increase of memory CD4 cells, succeeded by a slow increase in naive CD4 cells.[11,12] The second rise in CD4 cells may be due to cellular expansion or sustained cell survival in the periphery, as well as the central regeneration of cells by the thymus.[10]

Despite the relative frequency of discordant immune response following ART initiation, data on the prevalence of this phenomenen and associated factors are still limited in South Africa (SA), as well as in other low- and middle-income countries, where treatment is primarily nucleoside reverse transcriptase inhibitor (NRTI)-based.[13] In these settings patients often initiate treatment at advanced stages of immunosuppression and have co-morbidities that compromise treatment response.[14] The lack of knowledge about this subgroup may contribute to inadequate clinical management, as current HIV treatment guidelines do not provide specific applicable guidance. In this retrospective study we describe the prevalence of, and factors associated with, discordant immune response in a cohort of patients from 2 large public sector clinics in SA in the first 6 months after ART initiation.

Methods

We retrospectively analysed data from 810 HIV-infected patients aged >16 years who initiated ART at 2 district comprehensive care management and treatment centres in Ekurhuleni, Gauteng Province, from 1 November 2008 to 31 December 2009. Ekurhuleni, the largest district in the province, has a population of nearly 3 million people, and an HIV prevalence of 31.5%.[15] Patients were included in the study if they were ART-naive at the time of treatment initiation, and were maintained on a standard first-line ART regimen[16] for at least 3 months following treatment initiation.

Ethical approval and study permission were obtained from the Human Research Ethics Committee of the University of the Witwatersrand and the Ekurhuleni Ethical Panel.

Data collection

Patient demographics and contact information were recorded at the commencement visit to the clinic. At ensuing visits, the patients' weight, reports of any symptoms and new diagnoses were recorded. Data were collated by trained data capturers after each visit. Results of CD4 cell count, plasma HIV viral load (PVL), full blood count and liver function tests (LFTs) were recorded upon receipt. All data were maintained in the patient health management database Therapy-Edge. STATA software (version 11) was used for data analysis.

Socio-demographic characteristics (age, gender, education level, occupation status and alcohol use/smoking), medical history including prior pulmonary tuberculosis (TB) and ART information were extracted from Therapy-Edge, as were physical examination findings such as body mass index (BMI), liver function and haemoglobin (Hb) values. Hb, LFTs and CD4 cell count were measured at ART initiation (i.e. baseline) and at 6 months post-ART initiation, with only PVL measured at 6 months.

Outcome assessment

Viral suppression was defined as a PVL <400 copies/ml at 6 months after ART initiation.[16] Immune reconstitution was defined as an absolute increase in the CD4 cell count value of 50 cells/mm^3 at an average of 6 months after ART initiation. A discordant immune response was defined as a failure of immune reconstitution (increase in CD4 cell count <50 cells/mm^3) within 3 - 6 months of ART initiation, in the presence of viral suppression (PVL <400 copies/ml). Measurements within 3 - 6 months of ART initiation were used, in accordance with the 6-month follow-up recommended in national guidelines.[16]

Statistical methods

Descriptive statistics, using means and standard deviations for continuous variables, and frequencies for categorical variables, were used to report sample characteristics. Associations between the main outcome and potential explanatory factors were assessed using variate logistic regression, using odds ratios (ORs) and 95% confidence intervals (CIs) to express the measure of association. Factors that were significant at $p \leq 0.2$ in univariate analysis were considered for inclusion in multivariate logistic regression models. Final models were derived using forward selection and backward elimination techniques. The final model was adjusted for education level, World Health Organization (WHO) clinical stage, baseline CD4 cell count, and ART regimen, and adjusted ORs (AORs) were presented. Baseline WHO clinical stage was included in the final model regardless of statistical significance in the univariate analysis because of the link between HIV clinical disease and outcome. These models were tested using the Hosmer-Lemeshow goodness-of-fit test. Interactions between all significant variables in the model were also investigated. Collinearity was tested in all the regression models. A sensitivity analysis to demonstrate the robustness of the study findings to variation in definition of CD4 cell count response was also conducted using a 30% increase from baseline CD4 cell count as the desired response.

Results

A total of 6 460 adults enrolled in the ART programme at the 2 clinics; 4 581 (80%) were excluded due to an absent baseline/6-month follow-up CD4 cell count and/or PVL, and a further 962 were excluded due to a lack of additional information (e.g. ART regimen or baseline laboratory values). Of the remaining 917 eligible, 810 were included for analysis. The remainder were excluded as they had discordant virological responses (i.e. immune reconstitution in the absence of viral suppression) or were non-responders (no change in CD4 cell count or PVL).

Prevalence of discordant immune response on ART

Within the cohort, 220 (24%) experienced a discordant immune response within 6 months of ART initiation. At baseline, the mean CD4 cell count in the discordant group was 218 cells/mm^3 (SD ±168), compared with 137 cells/mm^3 (SD ±85) in the group with a concordant response to treatment.

Factors associated with a discordant immune response

Baseline characteristics of discordant and concordant immune responders were

Table 1. Cohort characteristics with logistic regression analysis of factors associated with discordant v. concordant immune response

Characteristic	Total (*N*=810)	Discordant response *n* (%)*	OR (95% CI)	*p*-value‡	AOR (95% CI)	*p*-value‡
Age (years), mean (±SD)	220	39.5 (±8.9)	1.02 (1.00 - 1.04)	0.028	1.02 (1.00 - 1.04)	0.031
Gender						
Female	138	138 (63)	1			
Male	82	82 (37)	1.18 (0.85 - 1.66)	0.323		
ART						
D4T-3TC-NVP/EFV	188	188 (86)	1			
AZT-3TC-NVP/EFV	27	27 (12)	1.91 (1.14 - 3.20)	0.014		
TDF-3TC-NVP/EFV	5	5 (2)	0.78 (0.29 - 2.15)	0.639		
Baseline CD4 cell count (cells/mm^3)						
<200	122	122 (55)	1		1	
>200	98	98 (45)	2.90 (2.08 - 4.03)	0.0001	3.02 (2.08 - 4.38)	0.001
WHO clinical stage						
1	164	164 (75)	1			
2	4	4 (2)	2.12 (0.56 - 7.98)	0.268		
3	52	52 (23)	0.91 (0.63 - 1.31)	0.616		
Hb (g/dl)						
Normal (≥11)	162	162 (74)	1		1	
Mild anaemia (9.5 - 10.9)	31	31 (14)	0.76 (0.49 - 1.19)	0.230	0.88 (0.54 - 1.45)	0.629
Moderate anaemia (8 - 9.4)	23	23 (11)	1.55 (0.90 - 2.68)	0.117	2.30 (1.26 - 4.19)	0.007
Severe anaemia (≤7.9)	2	2 (1)†(2)	0.20 (0.05 - 0.88)	0.032	0.36 (0.08 - 1.63)	0.188
History of TB						
No	192	192 (87)	1			
Yes	28	28 (13)	1.26 (0.78 - 2.04)	0.335		
Smoking						
No	147	147 (79)	1			
Yes	38	38 (21)†(35)	0.99 (0.65 - 1.50)	0.948		
Alcohol						
No	139	139 (77)	1			
Yes	41	41 (23)†(40)	1.11 (0.73 - 1.67)	0.630		
BMI						
Normal (18.50 - 24.99)	93	93 (54)	1			
Underweight (<18.50)	15	15 (9)	0.94 (0.50 - 1.79)	0.854		
Overweight (25.00 - 29.99)	34	34 (20)	0.58 (0.37 - 0.91)	0.017		
Obese (≥30.00)	30	30 (17)†(48)	0.88 (0.54 - 1.41)	0.594		
Occupation status						
Unemployed	128	128 (64)	1			
Employed	71	71 (36)†(21)	1.25 (0.88 - 1.76)	0.210		
Education level						
Illiterate	9	9 (5)	1			
Primary	33	33 (17)	0.48 (0.18 - 1.24)	0.124		
Secondary	149	149 (78)	0.49 (0.20 - 1.19)	0.116		
Tertiary	1	1 (1)†(28)	0.10 (0.01 - 0.93)	0.043		
AST (IU/l)						
Normal	136	136 (64)	1			
Above normal	77	77 (36)†(7)	1.16 (0.83 - 1.61)	0.379		
ALT (IU/l)						
Normal	209	209 (95)	1			
Above normal	10	10 (5)†(1)	0.83 (0.40 - 1.71)	0.605		

ART = antiretroviral therapy; D4T = stavudine; 3TC = lamivudine; EFV/NVP = evafirenz/nevaripine; AZT = zidovudine; TDF = tenofovir; WHO = World Health Organization; Hb = haemoglobin; TB = tuberculosis; BMI = body mass index; ALT = alanine aminotransferase; AST = aspartate transaminase.

*Data are expressed as *n* (%) for categorical variables and mean (±SD) for continuous variables.

†Missing values.

‡*p*-values were obtained using χ^2 test and Student's *t*-test.

Table 2. Uni- and multivariate analysis for sensitivity of factors associated with discordant immune response at 6 months after ART initiation

	OR (CI)	*p*-value	AOR (CI)	*p*-value
Age (years)	1.02 (1.00 - 1.04)	0.0590	1.02 (1.00 - 1.04)	0.0300
Baseline CD4 cell count (cells/mm^3)				
<200	1		1	
>200	5.51 (3.91 - 7.77)	0.0001	5.31 (3.71 - 7.61)	0.0001

OR = odds ratio; AOR = adjusted odds ratio; CI = confidence interval.

compared (Table 1). Compared with concordant immune responders, patients with discordant immune responses were more likely to be older, to have initiated ART at a higher baseline CD4 cell count, to have been initiated onto zidovudine or tenofovir-containing ART regimens, and to have significantly different Hb levels and moderate anaemia at the start of ART. No significant differences were observed between the groups in terms of gender, occupational status, education level, history of tuberculosis, smoking or alcohol use, BMI, WHO clinical stage, or aspartate transaminase (AST) and alanine transaminase (ALT) levels.

In the final model, a discordant immune response was found to be associated with increasing age (AOR 1.02; CI 1.00 - 1.04; p=0.031), initiating treatment at a CD4 cell count >200 cells/mm^3 (AOR 3.02; CI 2.08 - 4.38; p<0.0001), and the presence of moderate anaemia (Hb 8.0 - 9.4 g/dl) (AOR 2.3; CI 1.26 - 4.19; p=0.007), after adjusting for baseline education, WHO clinical stage, CD4 cell count and ART regimen (Table 1). No significant interactions were found between the significant variables in the final model, which was deemed adequate using the Hosmer-Lemeshow goodness-of-fit test (p=0.416).

The results of the sensitivity analysis, conducted by considering a 30% increase from baseline CD4 cell count as the desired response, are summarised in Table 2. The univariate analysis produced similar findings to those in the primary analysis. Only baseline Hb level failed as a significant factor in the development of discordant response using the modified outcome definition.

Discussion

Despite an adequate virological response, 24% of patients did not achieve an adequate immune response at 6 months after ART initiation. Increasing age, initiating ART at a CD4 cell count >200 cells/mm^3, and initiating ART with moderate anaemia were associated with failure to achieve optimal immune restoration. No associations between discordant immune response and gender, BMI or ART regimen were observed, although these were identified as risk factors in other studies.[17,18]

The findings concerning age were consistent with findings from other studies, where increasing age was associated with poor immune recovery.[5] In the North American AIDS Cohort Collaboration on Research Design (NA-ACCORD) study, data from 19 cohorts and 12 196 participants showed that increasing age was associated with a lower chance of achieving an increase in CD4 cell count >100 cells/mm^3 at 24 months following ART initiation.[19] This has been linked to the observation that thymus activity, which is largely responsible for immune restoration, decreases with ageing.[10]

The literature is conflicting regarding the association of baseline CD4 cell count with discordant immune response outcome. Findings similar to ours emerged from a cohort of 4 810 patients initiating ART in the Antiretroviral Therapy in Low-Income Countries (ART-LINC) study.[20] The association between ART initiation with a baseline CD4 cell count >200 cells/mm^3 and the development of discordant immune response can be explained by the nonlinear nature of CD4 cell count increases after ART initiation across the different baseline CD4 cell count strata:[4] starting treatment at higher CD4 cell counts limits the scope for further increases.[21] These findings are important as treatment programmes increase the CD4 cell count threshold for ART initiation.

In contrast to our findings, several studies conducted in resource-rich settings have shown that low baseline CD4 cell count is associated with discordant immune response.[4] This is biologically plausible given that a low nadir pre-treatment CD4 cell count is thought to be suggestive of more extensive depletion of CD4 cells in the gut-associated lymphoid tissue during acute HIV infection, and may be delayed or refractory to reconstitution with ART.[22] Genetic variability has been investigated as a possible modulator of immunological recovery, and may explain the divergent associations in the existing literature.

These data suggest that moderate anaemia at baseline is associated with failure to achieve immune recovery at 6-month follow-up – an association that has not been documented previously. The aetiology of anaemia in HIV infection is multifactorial, but is commonly due to underproduction of erythrocytes by the bone marrow stem cells.[23] These stem cells are also responsible for the production of CD4 cells through the myeloid precursor cell.[24] Poor production of myeloid precursor cells can therefore result in decreased production of both CD4 cells and erythrocytes. In addition, the erythrocytes of HIV-infected individuals may experience membrane changes which result in decreased pliability and premature destruction.[25] The same applies to CD4 cells.[25] These mechanisms of reduced stem cell activity and membrane changes could explain the association between anaemia when starting ART and a subsequent discordant immune response. However, this finding should be interpreted with caution, as it was not significant in the sensitivity analysis when the definition of immune response was altered.

Study strengths and limitations

Although the sample size was relatively small, it was likely to be representative of patients in routine clinical care in Gauteng Province. The validity of the results may have been limited by the high proportion of missing data. Patterns in missing data could have resulted in non-differential misclassification of patients, as a consequence of inaccurate measuring of outcomes and subsequent bias. However, such errors could have been evenly distributed among the groups and data were noted to be missing at random (analysis not shown).

The outcomes were measured between 3 and 6 months after ART initiation; it is therefore possible that factors associated with discordant immune response may have varied with longer periods of treatment.

Conclusion

The findings of this study suggest that a significant proportion of patients initiating ART in SA do not achieve an optimal immune response after an average of 6 months on ART, despite virological suppression. Significant factors associated with the development of a discordant immune response were increasing age, baseline CD4 cell count >200 cells/mm^3, and an Hb level of 8.0 - 9.4 g/dl. While further studies are required in local populations to examine these associations, these data may assist in the early identification of patients that are likely to have discordant immune responses on ART.

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ORIGINAL ARTICLE

HIV and the urban homeless in Johannesburg

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Background. There are few data on HIV prevalence and risk factors among inner-city homeless and marginally housed individuals in South Africa.
Methods. We recruited 136 adults from a Johannesburg inner-city homeless clinic; mean age was 32.4 years, 129 (95%) were male, and 90 (66%) were of South African nationality. Participants were tested for HIV and answered a short demographic survey. Descriptive statistics and uni- and multivariate regression analyses were used for data analysis.
Results. The HIV prevalence in the cohort was 23.5%. Transactional sex, relationship status, number of concurrent sexual partners, condom usage and history of previously treated sexually transmitted infections (STIs), living on the street, the use of alcohol or drugs, and previous exposure to voluntary counselling and testing (VCT), were not significant risk factors for HIV-positivity. Statistically significant HIV risk factors on multivariate analysis included the presence of an STI (odds ratio (OR) 5.6; $p<0.01$) and unemployment (OR 6.7; $p<0.01$). South African nationality was a significant risk factor on univariate analysis (OR 2.99; $p<0.05$), but not on multivariate analysis (OR 2.2; $p=0.17$).
Conclusion. The HIV prevalence in the sample did not differ appreciably from HIV prevalence estimates in other at-risk populations in similar settings, suggesting that homelessness in a South African city alone may not be a significant risk factor for HIV infection. HIV prevention efforts cannot be restricted to behaviour change programmes, but must be more holistic, recognising the protective role that employment has on HIV incidence.

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South Africa (SA) bears a significant burden of the HIV epidemic, with an estimated 18.8% of the adult population (aged 15 - 49 years) infected.[1] However, the prevalence of HIV within an essentially homeless population, as found in the city centre of Johannesburg, is not known. Research performed predominantly in developed countries suggests a substantially higher HIV and sexually transmitted infection (STI) burden among the homeless and marginally housed.[2-4]

The relationship between HIV infection, employment status and homelessness is complex. It is well documented that HIV leads to neuropsychological impairment,[5] potentially leading to decreased job performance and unemployment, with up to 65% of HIV-infected individuals unemployed, even in developed countries.[6,7] Unemployment in turn leads to food insecurity, which has been associated with an increased risk of contracting HIV and lower CD4 counts.[8] The homeless are also at risk of psychiatric illness and have a decreased awareness of HIV,[3] both of which may affect uptake of prevention and/or treatment interventions.[9] In addition, the majority of the homeless in SA urban settings are male, and hence more difficult to reach with HIV interventions.[10] To gain a better understanding of these issues and to inform future HIV prevention strategies, we investigated the HIV prevalence and risk factors among urban homeless individuals in Johannesburg.

Methods

We performed a cross-sectional survey of 136 adults attending a Johannesburg inner-city centre soup kitchen and clinic, operated by a local non-governmental organisation. Participants were sampled conveniently and classified as homeless or marginally housed. Data were collected for 1 year commencing 1 April 2010. HIV testing was performed using 2 rapid finger prick tests from separate manufacturers. A third confirmatory test was used in the case of discordant results. We

also included 6 individuals who had proof of a previous HIV-positive test result. Exclusion criteria included: *(i)* earnings in excess of R5 000/month; and *(ii)* residing in a house defined on the grounds of a solid permanent structure with basic amenities (water, electricity, sewerage) and that is under the ownership or rental of the participant or family (excluding anything considered to be a form of shelter).

Ethics approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand. HIV risk factors were identified by uni- and multivariate logistic regression analysis. Data were represented as odds ratios (ORs) with 95% confidence intervals (CIs).

Results

Sample characteristics are summarised in Table 1. The HIV prevalence was 23.5% (95% CI 16.4% - 30.7%). Mean participant age was 32.4 years with 129 (95%) of the adults being male and 46 (35%) being foreigners.

Table 1. Sample characteristics

	N (%)		
	Total	**HIV-positive**	**HIV-negative**
Characteristic	**136 (100)**	**32 (100)**	**104 (100)**
HIV test result			
Positive	32 (24)	32 (100)	0 (0)
Negative	104 (76)	0 (0)	104 (100)
Gender			
Male	129 (95)	29 (91)	100 (96)
Female	7 (5)	3 (9)	4 (4)
Residence			
Street	68 (51)	21 (66)	47 (45)
Shelter	30 (22)	6 (19)	24 (23)
Informal settlement	8 (6)	2 (6)	6 (6)
House	28 (21)	3 (9)	25 (24)
Marital status			
Married	14 (11)	3 (10)	11 (11)
Single	91 (73)	21 (72)	70 (73)
Widowed	20 (16)	5 (17)	15 (16)
Nationality			
South African	87 (65)	26 (84)	61 (60)
Other	46 (35)	5 (16)	41 (40)
Employment status			
Employed	55 (42)	7 (22)	52 (50)
Unemployed	77 (58)	25 (78)	52 (50)
Education level			
<Grade 12	70 (62)	15 (54)	55 (56)
Grade 12	48 (38)	13 (46)	35 (35)
Tertiary	9 (7)	0 (0)	9 (9)
Reason for testing			
Multiple partners	6 (4)	3 (9)	3 (3)
Partner HIV-positive or advised by family/friends	5 (4)	0 (0)	5 (5)
Feeling unwell or advised by health worker	42 (31)	22 (68)	20 (19)
Retesting (confirming HIV-positive test)	3 (2)	3 (9)	0 (0)
Curious about status	96 (71)	15 (47)	81 (78)
Partner's behaviour or stopping condoms	14 (10)	1 (3)	13 (13)
Other	8 (6)	1 (3)	7 (7)
Result of most recent HIV test			
Positive	12 (16)	11 (55)	1 (2)
Negative	61 (82)	8 (40)	52 (98)
Did not collect	1 (1)	1 (5)	0 (0)
Current exposures			
Current STI	23 (17)	11 (35)	12 (12)
Cough for >1 week	27 (20)	10 (32)	17 (17)
Alcohol on most days	40 (30)	10 (31)	30 (29)
Smoking on most days	65 (48)	19 (59)	46 (45)
Recreational drug use in preceding week	16 (12)	3 (9)	13 (13)
Condom use at last sexual encounter	91 (51)	21 (44)	70 (53)

Table 1. Sample characteristics (continued)

	N (%)		
	Total	**HIV-positive**	**HIV-negative**
Characteristic	**136 (100)**	**32 (100)**	**104 (100)**
VCT			
Previous HIV testing and counselling	65 (49)	15 (50)	50 (49)
Exposure in preceding 12 months			
Vaginal or anal intercourse	114 (84)	26 (81)	88 (85)
Blood transfusion or medical injection	45 (33)	11 (34)	34 (33)
Intercourse after alcohol or illicit drugs	65 (48)	17 (50)	48 (46)
Transactional sexual intercourse	18 (13)	7 (22)	11 (11)
Had oral sex	28 (21)	6 (19)	22 (21)
Sexual intercourse without a condom	55 (40)	14 (44)	41 (39)
Symptoms of an STI	26 (19)	11 (34)	15 (14)
Diagnosed with an STI	16 (12)	7 (22)	9 (9)

STI = sexually transmitted infection; VCT = voluntary counselling and testing.

Table 2. Risk factors for HIV using logistic regression*

	Univariate		**Multivariate**	
Risk factor	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Unemployment	**3.7 (1.4 - 9.8)**	**0.009**	**6.7 (1.8 - 25.6)**	**0.006**
South African nationality	**2.99 (1.12 - 7.9)**	**0.028**	2.2 (0.7 - 7.0)	0.170
Current STI	**3.7 (1.4 - 9.8)**	**0.008**	**5.6 (1.5 - 20.7)**	**0.010**

STI = sexually transmitted infection.

*Statistically significant results are indicated in bold.

The mean monthly income for the HIV-positive and -negative groups was R 485 (95% CI R176 - R794) and R 863 (95% CI R540 - R1 186), respectively. There was no relationship between HIV-seropositivity and relationship status, educational level, number of sexual partners, smoking or use of alcohol, illicit drugs or condoms.

Previous exposure to voluntary counselling and testing (VCT) was not protective against HIV in this sample, as the number of previous tests was marginally higher in the HIV-positive group (1.6 v. 1.2; $p>0.05$). Of patients who tested HIV-positive, 36.3% had had a previous positive test result elsewhere, but had never been followed up in terms of CD4 count or antiretroviral therapy (ART) initiation. During post-test counselling, both HIV-positive and -negative groups reported unwillingness to disclose their status to others (59% and 50%, respectively).

The results of logistic regression modelling are shown in Table 2. There was a significant association between HIV-positive status and unemployment (OR 6.7; 95% CI 1.8 - 25.6; $p=0.006$), and current STI (OR 5.6; 95% CI 1.5 - 20.7; $p=0.010$). South African nationality was associated with HIV seropositivity on univariate analysis (OR 2.2; 95% CI 1.12 - 7.9; $p=0.028$), but not multivariate analysis (OR 2.2; 95% CI 0.7 - 7.0; $p=0.17$).

Discussion

The associations between homelessness and HIV in this study contrast markedly with international literature, in terms of absolute risk and behaviour patterns. The HIV prevalence in our study was high by international standards, but not substantially greater than that of a general SA population of similar age and gender.[12,13] Furthermore, no association was found between drug use and HIV in our sample, although this is a well-documented HIV risk factor in homeless populations in Europe and North America.[2-4]

HIV incidence in SA has only recently begun to plateau, with no consensus on the reason for this. It is unclear whether the successes of education and prevention programmes are finally being felt, or if increased access to ART and STI treatment are at play. Evidence suggests that HIV education and prevention programmes may not have had a significant effect on HIV status in our sample. For example, previous exposure to VCT did not appear to be protective against HIV, and the patterns of risk behaviour were similar between HIV-positive and -negative individuals. However, the association between HIV status and unemployment was significant, because it linked unemployment to HIV risk, rather than the more simplistic factor of homelessness.

Overall, the results of our study suggest that the dynamics of HIV among the urban homeless in SA may be different from other settings. High levels of inequality and unemployment, especially in an urban environment, lead to a unique set of risk factors which differ from that of the developed world. In SA, simply being homeless or marginally housed may not put individuals at increased risk of HIV compared with the general population. However, unemployment needs to be addressed to mitigate the effect of the HIV epidemic in this setting.

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FORUM

The case for Option B and Optional B+: Ensuring that South Africa's commitment to eliminating mother-to-child transmission of HIV becomes a reality

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In a previous issue of the *Southern African Journal of HIV Medicine*, Pillay and Black summarised the trade-offs of the safety of efavirenz use in pregnancy (Pillay P, Black V. Safety, strength and simplicity of efavirenz in pregnancy. *Southern African Journal of HIV Medicine* 2012;13(1):28-33.). Highlighting the benefits of the World Health Organization's proposed options for the prevention of mother-to-child transmission (PMTCT) of HIV, the authors argued that the South African government should adopt Option B as national PMTCT policy and pilot projects implementing Option B+ as a means of assessing the individual- and population-level effect of the intervention. We echo this call and further propose that the option to remain on lifelong antiretroviral therapy, effectively adopting PMTCT Option B+, be offered to pregnant women following the cessation of breastfeeding, for their own health, following the provision of counselling on associated benefits and risks. Here we highlight the benefits of Options B and B+.

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In a recent issue of the *Southern African Journal of HIV Medicine*, Pillay and Black[1] summarised the trade-offs surrounding the safety of efavirenz (EFV) use in pregnancy. Highlighting the benefits of each option for the prevention of mother-to-child transmission (PMTCT) of HIV proposed by the World Health Organization (WHO), the authors argued that the South African (SA) government should consider the adoption of Option B as national PMTCT policy, and pilot projects implementing Option B+ as a means of assessing the individual- and population-level effect of the intervention. We echo this call and further recommend that '*optional B+*' (i.e. the option to stay on lifelong antiretroviral therapy (ART), effectively adopting PMTCT Option B+) be offered to pregnant women for their own health after the cessation of breastfeeding, following counselling on the benefits and risks of the intervention. In this article we highlight the benefits of Options B and B+.

In April 2012, WHO released a programmatic update to the use of antiretrovirals (ARVs) for PMTCT and the treatment of HIV-positive pregnant women.[2] The key findings indicate that Options B and B+ are likely to prove preferable to Option A for operational, programmatic and strategic reasons. While all options recommend initiating triple ARV therapy in HIV-positive pregnant women with a CD4 count <350 cells/mm^3,

their recommendations differ for CD4 counts >350 cells/mm^3. For the latter, Option A promotes: the use of zidovudine (AZT) from 14 weeks' gestation, single-dose nevirapine (NVP) at birth, and 7 days of AZT/lamivudine (3TC) postpartum for the mother; and daily NVP for the infant until the cessation of breastfeeding or until 4 - 6 weeks of age if the mother is receiving antiretroviral therapy (ART) or is not breastfeeding. Option B recommends ART for the mother from 14 weeks' gestation until birth or the cessation of breastfeeding, and the use of NVP for the infant until 4 - 6 weeks of age. Option B+ advocates lifelong ART, and NVP for the infant as for Option B. The rationale behind these recommendations stems from increasing evidence at clinical and programme levels highlighting the benefits of a single, standardised regimen to serve PMTCT and the treatment of HIV-positive pregnant women. The WHO update reflects earlier recommendations from major donors such as the United States President's Emergency Plan for AIDS Relief (PEPFAR),[3] and has led to the adoption of Option B+ by other high-burden African countries including Malawi, Kenya, Uganda, Swaziland and Rwanda, with pilots underway in several others.[4] Further support for PMTCT Options B and B+ are echoed in a newly released report by the United Nations Children's Fund (UNICEF), the Business Leadership Council and the Clinton Health Access Initiative.[5] WHO further highlights that this suggested approach would strengthen the effectiveness of the PMTCT programme through improved linkages with ART programmes.

Options B and B+ are simpler, probably safer, and less resource-intense than Option A

Numerous challenges have been experienced with the implementation of Option A. In addition to requiring drug changes across the continuum of care (antenatal, delivery and postpartum care),[1,6] the option necessitates the use of different ARVs depending on CD4 count. Option A also involves a long period of AZT monotherapy with associated potential for developing thymidine analogue (TAM) mutations, and it complicates clinical management and delays treatment initiation, mostly where access to CD4 count measurement is scarce.

The provision of effective care in SA is challenged by congested health facilities and a lack of human resources. Appropriately, Options B and B+ reduce the burden on healthcare workers. Option B simplifies the delivery of care by ensuring that the same regimen offered to pregnant women is the first-line regimen for all adults, with the WHO recommendation of EFV for all stages of pregnancy.[7] A standardised fixed-dose ARV combination throughout antenatal, delivery and postpartum care would not only improve continuity of care, but also simplify drug forecasting, procurement, supply chain management, and stock-out monitoring. The current first-line regimen in SA is tenofovir (TDF)/lamivudine (3TC)/efavirenz (EFV); generic single-pill fixed-dose combinations are registered and most likely to be included in SA's ARV tender for 2013. Despite reassurance from the 2010 Medical Research Council (MRC) survey showing a reduction of mother-to-child transmission of HIV in SA to 2.7%,[8] there are concerns regarding the feasibility and acceptability of the daily administration of nevirapine (NVP) syrup, including multiple reports of associated delivery problems. With the hasty cessation of the provision of free formula in the public sector, there may be a future increase in breastfeeding transmission rates. Strangely enough, this seems to have been accepted as a fatality by the National Strategic Plan (NSP) 2012 - 2016 target of <2% at birth and <5% at the end of breastfeeding.

For even further programmatic simplification, Option B+ would altogether send one simple and strong message to patients: 'ART for life' – promoting good adherence and successful ART. Stopping ART after the cessation of breastfeeding is likely to lead to confusing messages for HIV-infected individuals, their communities and health workers. Moreover, there is a risk of developing non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance if ART is stopped without tail protection (i.e. continuing the 2 remaining ARV drugs for 7 days after withdrawal of an NNRTI). The possible field implications of this are not yet well understood. While Option B remains simpler than Option A, it requires that primary healthcare services: determine the HIV status of women at each pregnancy; determine the CD4 count/HIV clinical stage before ART initiation at each pregnancy; ensure timeous ART initiation at each pregnancy for HIV-positive women; identify intent to breastfeed and the duration thereof after each delivery (taking into consideration that women are known to breastfeed beyond the initially intended period); and ensure that ART is ceased safely after each pregnancy, with CD4 count follow-up. Each additional step in the treatment cascade increases the risk of patient attrition. A study in SA demonstrated a 33% retention rate from first CD4 count to ART initiation.[9] Option B also recommends ART initiation from 14 weeks' gestation – assuming that women present for care early in pregnancy. Programme data, however, show that the majority of women present much later in pregnancy. Many of these challenges would be overcome with Option B+.

Treatment interruptions may be harmful

The national fertility rate in SA is 2.5.[10] With multiple pregnancies, typical in developing countries, women identified as HIV-positive tend to be exposed to the potentially harmful repeated initiation and discontinuation of ARVs. This is particularly pertinent in other sub-Saharan countries with much higher fertility rates than SA (e.g. in Malawi, with 5 - 6 births per woman).[11] In a recent systematic review,[12] unstructured treatment interruptions were associated with a higher risk of death and opportunistic infection, a lower probability of increased CD4 cell counts, a higher prevalence of neurocognitive impairment, a lower health-related quality of life, and an increased risk of virological failure and drug resistance. Earlier trials demonstrated that structured treatment interruptions were harmful to patients.[13,14] Consequently, many experts endorse continuous ART for pregnant women, rather than stopping and starting therapy with each pregnancy.[6]

Early initiation on ART may improve outcomes for mothers

Following increasing supporting evidence and expert opinion, initiation of ART at a CD4 count >350 cells/mm^3 to reduce morbidity and mortality (outside the context of pregnancy) is now recommended in US and European guidelines.[15,16] However, there is ongoing controversy in this regard. While the debate remains open about the individual benefits of ART initiation above a CD4 count of 500 cells/mm^3, a special case could be made for women of childbearing age in an African context. Multiple pregnancies and increased infectious risks serve to predispose these women to a rapid decline in CD4 count; hence, there is a relatively short time period within which the women's CD4 counts are high enough for the benefits of ARV initiation to be questionable. In a study from Zimbabwe, the peri-partum mortality of women with CD4 counts of 400 - 600 cells/mm^3 was 5.4 times higher than for their HIV-negative counterparts.[17] Furthermore, continual increases in maternal mortality in SA have been attributed to the AIDS epidemic.[18]

Option B+ could reduce early *in utero* HIV transmission

Option B+ ensures that women are already receiving ART for subsequent pregnancies, covering the initial weeks and maintaining a higher CD4 count. Several studies have demonstrated that the lowest risk of transmission is among women who have initiated ART before conception in comparison with those who initiate ART during pregnancy. The reduced risk of transmission is believed to be as a result of reducing the risk of early *in utero* transmission.[19,20]

Horizontal transmission to HIV-negative partners

The HIV prevalence among women during their reproductive years is particularly high in SA. A study among couples across eastern and southern Africa demonstrated a prevalence of stable HIV-discordant partnerships of 8 - 31%, with 49% serodiscordance among couples with at least one HIV-infected partner.[21] In a meta-analysis in sub-Saharan Africa, the proportion of HIV-positive women in stable HIV-serodiscordant relationships was 47%, demonstrating that women are just as likely as men to be the index partner.[22] As demonstrated in the HPTN 052 trial,[23] ART decreases transmission in HIV-serodiscordant couples by 96%. Continuing ART in women between pregnancies during their reproductive years would also serve to protect their HIV-negative partners. This is in line with the new WHO recommendations that HIV-positive individuals in serodiscordant partnerships be given ART regardless of CD4 count.[24]

Cost-effectiveness of treatment scale-up

The expected reductions in the number of infections, morbidity and mortality, both in children and adults, through the provision of Option B+, will contribute to a decline in overall treatment cost after initial funding.[25]

Challenges and arguments against Option B+

Several arguments against the adoption of Option B+ must be discussed when considering the roll-out of this intervention.

Adherence

Adherence among HIV-infected pregnant women is probably the most challenging issue, for short-course (Option A/B) and lifelong therapy.[26-29] In a recent meta-analysis of ART adherence during and after pregnancy, ART adherence was well below what was recommended for adequate virological suppression, especially during the postpartum period.[30] This has significant implications for the success of lifelong treatment, as recommended with Option B+. Loss to follow-up among pregnant women initiating ART across SA was found to be the greatest in the first 3 months after ART initiation, with differences diminishing over time.[31] This highlights where adherence support is most required. New innovative strategies need to be identified and piloted to address this, including: simpler and more tolerable ART regimens (TDF – fixed dose and combination); a reduced number of clinic visits and time associated with such visits; and adherence support clubs to optimise peer support.

We suggest an 'opt-out' option at the end of the breastfeeding period for women with a CD4 count >350 cells/mm^3 who do not want to remain on ART, allowing structured ART cessation with tail protection.

Cost

ARV drug cost was a major determinant in the decision of many sub-Saharan countries to implement PMTCT Option A. In 2009, the average drug cost for implementing Option B was 3 - 5 times higher than that of Option A. However, by the end of 2011, the cost was only twice as high.[2] The annual cost of the TDF/3TC/EFV first-line regimen in SA is R1 361.45 (approximately US$162) per patient. A single-pill fixed-dose regimen costs only marginally more: R1 424.88 (approximately US$172) per patient.[32] The lowest international price is R828 (US$100) per patient, and further reductions are expected. With the opening of the SA ARV tender in October 2012, fixed-dose combination drugs are likely to become available in the public sector. Further studies by the United States Centre for Disease Control (CDC) show that Option B+ would cost marginally more than Option B (incremental cost of $270 at 5 years) in the case of multiple pregnancies.[33]

Risk of renal toxicity from TDF

TDF has the potential for renal toxicity. While pregnancy-related conditions such as hypertension, pre-eclampsia and diabetes increase the risk of renal impairment,[34] this is offset by the young age of pregnant women. Furthermore, Option B+ policy ensures that most women start ART early in their HIV infection. Concerns remain surrounding the effect of TDF exposure on infant growth, with limited available data.[35]

Conclusion

Recently, SA's National Strategic Plan considered the evidence to be insufficient to warrant a change from the current PMTCT Option A protocol. The WHO programmatic update concludes that both Options B and B+ offer programmatic and operational advantages that would go towards the elimination of mother-to-child HIV transmission. The implementation of Option B+ would require increased adherence support mechanisms, funding, and scale-up at the primary healthcare level, including the adoption of task-shifting for ART initiation. However, this would result in the best protection for the health of pregnant women and infants, and contribute to reduced HIV transmission among sero-discordant couples according to the latest evidence.[23] In the medium term, this strategy is highly likely to be cost-effective.

Further research is required to address the challenges faced by PMTCT programmes while drawing on the latest scientific evidence to ensure that it is translated into policies reflecting the needs and realities of the millions of women living with HIV and their children. SA's PMTCT programme must ensure the delivery of the best care possible and move towards the elimination of paediatric HIV. A more aggressive PMTCT option such as B+ should be tested urgently, as it may be a necessary step to reach this goal.

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FORUM

Tuberculosis prevention in HIV-infected pregnant women in South Africa

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The high burden of HIV and tuberculosis (TB) among pregnant women in South Africa contributes to a high maternal mortality rate. Isoniazid preventive therapy (IPT) is recommended for the prevention of active TB in HIV-infected individuals, including pregnant women. However, there are few data regarding IPT use in the latter, with concern regarding the concurrent use of IPT with nevirapine in pregnancy, as both treatments are hepatotoxic. The benefit and safety of IPT in HIV-infected pregnant women has not been established. We recommend a simplification of HIV and TB interventions by providing triple antiretroviral therapy to all HIV-infected pregnant women.

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Maternal deaths in South Africa (SA) continue to rise, despite the target of the fifth Millennium Development Goal (MDG) of a 75% reduction in maternal mortality by 2015. This target cannot be addressed without an appreciation of the effect of HIV and tuberculosis (TB) on maternal mortality in the country: the antenatal HIV sero-prevalence stands at 29.4%,[1] and HIV is the most common contributory condition to maternal mortality.[2] A number of studies have confirmed the contribution of HIV in maternal mortality and morbidity.[3-5]

The prevalence of TB in HIV-infected pregnant women in SA is similar to that of the general population: approximately 795/100 000.[6] In 2009, the prevalence of active TB in HIV-infected women attending antenatal care in Soweto, Gauteng Province, was found to be 688/100 000; higher than the prevalence in HIV-uninfected women (201/100 000).[7] These findings were comparable with data from Durban, KwaZulu-Natal, where prevalence rates of active TB between 1996 and 1998 were 774/100 000 HIV-infected pregnant women; 10 times higher than the prevalence for HIV-uninfected pregnant women.[8]

It is well established that TB and HIV are closely linked. An estimated 70% of adults presenting with new cases of TB in SA are co-infected with HIV, with TB being the most common cause of morbidity and mortality in HIV-infected individuals.[9] TB is a leading cause of maternal mortality and morbidity, causing 15% of all maternal mortality in high HIV prevalence settings, and 15 - 34% of indirect obstetric maternal mortality.[10] In SA between 2008 and 2010, TB accounted for 27% of deaths in women who died of AIDS-related complications during pregnancy, childbirth or the puerperium.[2] The findings of a study in Durban revealed a 3-fold higher maternal mortality ratio (MMR) among HIV-infected women with TB (12 170/100 000 live births) compared with TB-infected HIV-uninfected women (3 850/100 000 live births) in the absence of antiretroviral therapy (ART).[11] Of the women diagnosed with TB, 79% were co-infected with HIV.[11] Similarly high MMRs in TB/HIV-co-infected women have been observed in a number of studies in sub-Saharan Africa.[4,12-14]

The challenge of TB diagnosis in HIV-infected pregnant women

Although diagnostic approaches to TB are similar for HIV-infected pregnant women as they are for HIV-uninfected and non-pregnant women, there are major challenges to the diagnosis of TB in the former. The symptoms of TB may be non-specific in pregnancy, or even absent, mimicking physiological changes. Weight loss associated with TB disease may be masked by normal weight gain in pregnancy.[15] The disease may only present post delivery in either the mother or infant.[16] Furthermore, clinical signs of HIV may overlap with those of TB and there may be a wide differential diagnosis.[16] HIV-infected adults may also have a high prevalence of subclinical TB disease,[17] with HIV-infected pregnant women also less likely to be sputum acid-fast bacilli smear-positive than HIV-uninfected pregnant women with TB disease.[7,18] Barriers to accessing care may contribute further to the under-diagnosis of TB in these women.[7]

TB prevention strategies in the context of HIV

TB prevention, diagnosis and treatment in HIV-infected pregnant women should be integrated into routine maternal healthcare services. Key strategies adopted by the World Health Organization (WHO) to decrease the effect of TB on people living with HIV include the 3 I's: intensified TB case finding,

isoniazid preventative therapy (IPT); and infection control for TB.[19]

It has been established that the use of IPT reduces the risk of active TB in HIV-infected individuals. However, this is more pronounced in those with a positive tuberculin skin test (TST).[20,21] The most recent meta-analysis of the treatment of latent TB infection (LTBI) in HIV-infected individuals encompassed 12 trials and 8 578 HIV-infected participants.[20] Overall, the treatment of LTBI reduced the risk of active TB by 32% (risk ratio (RR) 0.68; 95% confidence interval (CI) 0.54 - 0.85). This benefit was stronger in TST-positive individuals (RR 0.38; 95% CI 0.25 - 0.57) than in TST-negative individuals (RR 0.89; 95% CI 0.64 - 1.24). Isoniazid (INH) monotherapy was found to reduce mortality only in those who were TST-positive. However, overall, there was no evidence that preventive therapy reduced all-cause mortality.[20] A randomised controlled trial (RCT) of 6- v. 36-month IPT for TB in HIV-infected adults in Botswana also found a benefit of IPT in TST-positive individuals, but no benefit for those who were TST-negative.[21]

The use of ART in HIV-infected adults also reduces the incidence of TB. In a meta-analysis of 9 observational cohort studies, a 67% reduction in TB incidence across a range of CD4 cell counts and WHO disease stages was reported.[22] TB risk reductions with ART occur irrespective of TST reactions.[22,23] Although the greatest absolute risk reduction of TB is observed in individuals with the most advanced immunodeficiency at baseline,[22] patients starting ART earlier, at higher CD4 cell counts, have a 2-fold lower risk of TB compared with those initiating ART at lower CD4 cell counts.[23,24] HIV-infected individuals starting ART with low CD4 cell counts remain at high risk of TB until CD4 cell count recovery has occurred.[23]

Studies have suggested that there may be additional benefit to concurrent IPT and ART.[21,25,26] In a recent RCT in Khayelitsha, a 37% reduction in the risk of TB was evident in individuals receiving IPT and ART compared with patients receiving ART only (RR 0.63; 95% CI 0.41 - 0.94). However, the risk of stopping INH or placebo due to grade 3 or 4 elevation of alanine transaminase (ALT) was twice as high in the patients receiving IPT compared with those receiving placebo and, overall, there was no evidence of mortality benefit.[27] The effect of timing of IPT v. ART initiation has not been determined. Experts recommend not initiating IPT at the same time as ART, but rather delaying initiation until stabilisation on ART, at approximately 3 months.[22,28]

The safety of IPT in pregnant women

Current national and international guidelines recommend the use of IPT for 6 months for all HIV-infected adults asymptomatic for TB, including pregnant women.[9,29] WHO advises that, although not a requirement for IPT initiation in HIV-infected individuals, TSTs may identify those who would benefit most from IPT. The American Thoracic Society (ATS) recommends a TST for the diagnosis of LTBI in pregnant women with a specific risk factor for LTBI or who are at risk for progression to TB disease. This includes women who are HIV-infected or who have a recent TB case contact. Although ATS acknowledge that treatment for LTBI in pregnancy is controversial, they do recommend such treatment for cases of recent TB or HIV infection where there is an increased risk of haematogenous spread of organisms to the placenta, as well as in situations with a high risk of progression of LTBI to disease.[30] Guidelines do indicate that IPT can be administered during pregnancy, but it is unclear when and if IPT should be given if the pregnant woman is receiving ART.

There is little evidence available on IPT use in HIV-uninfected pregnant women in general. Furthermore, to our knowledge, there is no evidence available of the effectiveness of IPT in reducing TB risk in HIV-infected pregnant women.

In a study which modelled the cost-effectiveness and outcomes of different treatment strategies for LTBI in pregnancy, antepartum IPT was anticipated to result in the fewest cases of TB and be more cost-effective than no treatment or delaying treatment until postpartum.[31] Ante- and postpartum IPT was predicted to be less costly and result in a higher life expectancy than no treatment, despite a higher mortality rate due to hepatitis in the antepartum group.[31] However, HIV infection and the use of ART were not taken into account.

INH is not teratogenic, even if given during the first trimester,[32] but it has a number of known adverse effects which include neurological toxicity, skin rash and hepatotoxicity. Reported rates of INH-associated clinical and biochemical hepatitis range from 0% to 5%.[28] In a systematic review of the risk of age-related hepatotoxicity in LTBI treatment, a median hepatotoxicity rate of 1.8% was reported. Studies with close monitoring of hepatotoxicity reported lower rates of hepatotoxicity than those without monitoring. In studies with available information, there was only one reported case of hospitalisation and no reported cases of mortality.[33] A comparison of treatment with rifampicin for 4 months v. INH for 9 months found rates of hepatotoxicity of 1.4 - 5.2% in the latter.[34]

Although it is not conclusive whether the side-effects of INH are worsened by pregnancy, 2 studies have suggested that pregnant or postpartum women may be at higher risk of hepatotoxicity.[30] Pyridoxine supplementation is recommended in HIV-infected and pregnant individuals taking INH to prevent neurological toxicity.[30]

The rate of INH-associated hepatitis in HIV-infected individuals appears to be similar to that of the general population.[35] In a Brazilian study of HIV-infected patients receiving IPT (with or without ART), 1.2% of participants had adverse reactions leading to discontinuation of IPT.[36] In a study of 1 762 HIV-infected individuals receiving IPT in Botswana, 1.1% developed hepatitis, and one death was reported.[28] In Khayelitsha, a hepatitis risk of 2.9% was reported in patients receiving IPT and ART.[27]

Some antiretroviral drugs are known to be associated with significant adverse effects, including hepatotoxicity. A 4.4% prevalence of grade 3 - 4 hepatotoxicity and 7% prevalence of grade 1 - 2 hepatotoxicity have been associated with nevirapine (NVP) use in HIV-infected pregnant women. The rate of NVP side-effects is higher in women with CD4 counts >250 cells/mm^3.[37] NVP is part of the first-line regimens used to treat HIV-infected pregnant women with CD4 counts ≤350 cells/mm^3 or WHO clinical stage 3 or 4 conditions in SA.

Increased rates of INH-associated hepatitis have been reported in patients receiving NVP-containing ART regimens compared with those receiving efavirenz (EFV)-containing regimens. In a previous study, the use of ART by 480 patients was not associated with INH-hepatitis, although those receiving NVP had a higher rate of hepatitis (2%) than those receiving EFV (0.9%). Interestingly, a CD4 cell count <200 cells/mm^3 was associated with INH hepatitis (RR 2.80; 95% CI 1.13 - 6.84).[28]

Conclusion

There is a high burden of HIV and TB among pregnant women in SA, contributing to a high

MMR. Despite ART availability in the country, the recent maternal mortality survey showed that the majority of women who died from HIV did not access ART. If we are to progress towards the MDG targets, interventions need to be safe, easy to implement and simplified to maximise early nurse initiation of ART. IPT initiation after ART in pregnancy adds additional steps to antenatal care, which is currently under-resourced. This may further burden the programme and compromise other areas of care, for a benefit apparently limited to TST-positive individuals and that, to date, has no evidence of efficacy in pregnancy.

Screening all pregnant women for TB and HIV is imperative. Those with TB disease should be treated accordingly, with contact tracing and screening of household contacts. Although not currently stipulated in guidelines, all HIV-infected pregnant women should be considered for initiation onto combination ART. With this approach, IPT initiation may be better deferred until the postpartum period. Triple ART for all HIV-infected pregnant women will reduce mother-to-child HIV transmission, adverse pregnancy outcomes, maternal mortality, horizontal transmission to uninfected partners and, specifically, the incidence of TB disease.

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FORUM
Enabling HIV self-testing in South Africa

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In a South African context, we consider the implications of the United States Food and Drug Administration's recent approval of the OraQuick HIV self-testing kit. We argue that current law and policy inhibit the roll-out of accurate and well-regulated self-testing kits, and create a loophole for sale in supermarkets, but not pharmacies.

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In July 2012, the Food and Drug Administration (FDA) approved the OraQuick test (OraSure Technologies) as the first HIV self-testing kit in the USA.[1] This over-the-counter test, retailing at approximately US$35 - 40 (R245 - 280), uses saliva from a mouth swab and provides a result within 20 - 40 mins. OraSure has established a consumer support centre that provides telephonic support and referrals.[2] In a recent study of New York-based men who have sex with men (MSM) who were provided with the self-testing kit, few experienced problems performing the test.[3] Studies by the Integration of TB in Education and Care for HIV/AIDS (iTEACH) in rural KwaZulu-Natal, South Africa (SA), are showing equally promising results (K Dong, personal communication). It would seem that, with appropriate support, self-testing is poised to revolutionise HIV-testing.

SA has made immense strides in improving HIV testing coverage, at least partly owing to direct intervention by the Minister of Health.[4] However, average CD4 counts at initiation of HIV treatment remain low, suggesting that late diagnosis may still be a problem for a sizeable proportion of the population. New, more convenient ways to test for HIV may increase the proportion of individuals who know their HIV status, and help to identify infected individuals earlier in the course of disease. A recent *Lancet* editorial notes: 'Ironically, the lack of mandatory counselling with OraQuick may help decrease the stigma around testing'.[5]

Previously, we examined the arguments against self-testing and showed that critics' objections to its roll-out in SA were based largely on vague fears with little supporting evidence.[6] Similar conclusions in support of self-testing have been drawn by others.[7,8] There are a wide range of self-tests currently available in pharmacies and supermarkets in SA, including tests for pregnancy, prostate cancer, ovulation, recreational drugs and breathalysers for alcohol. Few objections have been raised against the availability of these tests, and their distribution is not regulated. We have argued that self-testing in SA may have an enormous positive effect on HIV testing uptake and early diagnosis. Self-testing could extend to groups that have been traditionally hard to reach with general public health campaigns, and would be in line with the spirit of the Patients' Rights Charter and the National Health Act, urging people to take responsibility for their own health.[6]

Yet, SA's legal and policy frameworks do not facilitate the dissemination of HIV self-tests. Self-tests are classified as 'medical devices' under the Medicines and Related Substances Control Act (Act no. 101 of 1965, as amended), but there is no regulatory system in place yet for medical devices. This means, for example, that the manufacturers of the OraQuick test would be able to market it in SA – as long as the kit, ironically, is not available in pharmacies. The only legally binding restriction on the distribution of self-testing HIV kits is provided by the Good Pharmacy Practice (GPP) standards issued by the South African Pharmacy Council.[9] The 4th edition of the GPP, last updated in 2010, prevents pharmacists from selling the test or administering it in a pharmacy. Section 2.13.5.5 of the GPP states that 'only rapid tests which use a blood sample may be performed in a pharmacy'. Section 2.13.5.8(h) adds that 'pharmacists must not sell HIV tests for patients to perform at home.' Interestingly, this restriction does not apply to any other tests. Nor does the GPP apply to general supermarkets or corner cafes, creating a loophole for distribution. While the

FDA stamp of approval means that the public need not be concerned about the accuracy of OraQuick if it were to become available locally, this would not necessarily hold true for other HIV self-tests that are currently obtainable at community pharmacies, and are left unregulated. Although implementing an effective regulatory system for medical devices is challenging, unjustified restrictions such as those in the GPP could easily be addressed.

A recent Civil Society Consensus Statement on strategies to improve HIV testing and counselling highlighted these and other challenges of HIV-testing policies, paradigms and legal frameworks in SA.[10] The Statement endorsed self-testing 'if accompanied by the same essential components of any HIV testing service, including easy access to accurate information' and linkages to care. These are indeed vital components of the goal to enable everyone in SA to test for HIV regularly, and to do so when and where they choose.

Useful websites:

- 'The first in-home oral HIV test': http://www.oraquick.com/home
- 'OraQuick In-Home HIV Test': http://www.cvs.com/shop/product-detail/OraQuick-in-home-HIV-test?skuId=896631

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FORUM

Psychotropic prescribing in HIV

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Disclaimer. Drug profiles, adverse effects and drug-drug interactions have been shortened to include the most common or serious, and are not intended to be exhaustive.

Psychiatric disorders frequently co-occur with HIV, as preceding conditions or consequent to HIV infection. This potentially compromises HIV diagnosis and antiretroviral (ARV) treatment adherence. We provide a brief guide to the diagnosis and treatment of common mental disorders in people living with HIV/AIDS, including: prescribing psychotropics in HIV; neuropsychiatric side-effects of ARVs and other medications commonly prescribed in HIV; and the diagnosis and treatment of depression, anxiety, psychosis, agitation, sleep disturbance, pain, and mania. Psychotropic treatments recommended were drawn primarily from those available in the public sector of South Africa.

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Psychiatric disorders frequently co-occur with HIV infection, as conditions preceding or consequent to infection. A high degree of adherence to highly active antiretroviral therapy (HAART) is required to prevent the development of resistant viral strains and to minimise the risk of medication failure. Psychiatric co-morbidities potentially compromise adherence to antiretroviral therapy (ART) and can complicate HIV diagnosis and treatment. Although close collaboration between physicians, psychiatrists and other members of the multidisciplinary team is the ideal, psychiatric support is not readily available in certain settings. This article is intended to guide the diagnosis and psychotropic treatment of common mental disorders in people living with HIV/AIDS (PLWHA).

Many psychotropics are taken for ≥6 months, and both psychotropics and antiretrovirals (ARVs) are metabolised by the cytochrome P450 enzyme system, necessitating consideration of pharmacokinetic interactions. There also needs to be awareness of the differences in medication responses and tolerability in this population. Here we summarise: prescribing psychotropics in HIV; neuropsychiatric side-effects of ARVs and other medications commonly prescribed in HIV; and the diagnosis and treatment of depression, anxiety, psychosis, agitation, sleep disturbance, pain, and mania. The psychotropic treatments recommended here were drawn primarily from those available in the public sector of South Africa (SA).

Psychotropics in HIV: basic principles

A few simple points should be kept in mind when considering the management of mental disorders in HIV-infected individuals. Firstly, patients with HIV infection are generally very sensitive to medication side-effects as they often metabolise drugs more slowly, have less lean body mass and have compromised blood-brain barrier functioning. Although most patients ultimately tolerate standard doses of most medications, it is advisable to start at low doses and escalate dosing slowly over time.[1,2] Furthermore, PLWHA often receive multiple medications (ARVs, antibiotics, tuberculosis (TB) medications, etc.). Consequently, healthcare providers need to avoid prescribing complex regimens (e.g. daily dose instead of twice daily, where possible), anticipate drug interactions, and consider possible mood, behavioural and cognitive effects of medications such as ARVs.

The fact that treating HIV infection and related conditions is essential for optimal psychiatric care is often under-appreciated. Close collaboration between psychiatrists, physicians, nursing staff and all members of the multi-disciplinary healthcare team is crucial. It is important to make the distinction between primary and secondary psychiatric symptoms (e.g.

those caused by other medications, delirium, central nervous system (CNS) infections, etc.), as results of standard psychiatric treatment may be inadequate if these are not addressed.[1]

ARV neuropsychiatric side-effects

The introduction of HAART has transformed HIV infection from a death sentence to a chronic treatable illness. Unfortunately, most ARVs have neuropsychiatric side-effects (Table 1),[2] most commonly insomnia and headache, with efavirenz (EFV) being the agent most often implicated. These symptoms usually emerge shortly (within 3 months) after commencing ARVs and abate on withdrawal thereof. Although EFV is not absolutely contra-indicated in patients with a history of severe mental illness, patients should be informed of potential side-effects and closely monitored for any emergence or exacerbation of symptoms. Furthermore, where possible, alternative ARVs should be considered. The optimal HAART regimen for patients with CNS disease remains to be established. It is unclear whether ARV regimens with better CNS penetration are superior to others,[3] but there is consensus that optimal peripheral viral suppression is necessary.[4]

Depression

Depressive disorder is common in HIV-positive individuals, with a prevalence of 11.1% for major depressive disorder and 29.9% for mild depression in SA clinics.[5] It has been suggested that depression is often under-diagnosed[2] and insufficiently managed.[6] The following screening questions may prove helpful in identifying patients requiring further treatment or referral:

- 'During the past month, have you often been bothered by feeling down, depressed or hopeless?'
- 'During the past month, have you often been bothered by little interest or pleasure in doing things?'
- 'Is this something with which you would like help?'

It is also important to ask patients about suicidal thoughts, self-esteem, feelings of guilt or worthlessness, and outlook. Although the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (DSM-IV) includes problems with sleep, energy and appetite as diagnostic criteria for depression, these may be HIV-related.

If the patient answers 'yes' to one or more of the above questions, it is helpful to differentiate between mild-moderate and severe depression, to inform further management. In mild-moderate depression, patients usually experience transient or mild symptoms occasionally, have low levels of distress, and do not have suicidal thoughts or plans. Such symptoms can often be in relation to a recent diagnosis or the commencement of ARV treatment. These patients can be referred to a supportive adherence counsellor or can be considered for referral for psychotherapy where psychologists are available. In cases of severe depression, patients often have persistent, severe symptoms, high levels of distress and

Table 1. ARV side-effects

Class	Agent	Side-effects*
Nucleoside reverse transcriptase inhibitors (NRTIs)	Didanosine (ddI)	• Common: insomnia, mania
	Lamivudine (3TC)	• Rare: insomnia, mania, restlessness, agitation, delirium, depression, irritability
	Stavudine (d4T)	• Headache, insomnia, mania, abnormal dreams, anxiety, depression, somnolence, emotional lability
	Tenofovir (TDF)	• Common: aesthenia, depression, insomnia, anorexia (possibly related to co-use of EFV)
	Zidovudine (AZT)	• Common: insomnia, anorexia, dizziness • Rare: confusion, mania, convulsions, anxiety, somnolence
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz (EFV)	• Common: depression, dizziness, insomnia, somnolence, impaired concentration, vivid dreams, and anxiety • Rare: agitation, paranoia, delusions, euphoria, confusion, amnesia, depersonalisation, hallucinations, suicidal ideation, convulsions, false-positive cannabinoid test
Protease inhibitors (PIs)	Lopinavir/ritonavir (LPV/r)	• Rare: parasthaesia, insomnia, reduced libido, anxiety, abnormal dreams
	Ritonavir (RTV)	• Common: aesthenia, circumoral and peripheral paresthaesia, altered taste
	Atazanavir (ATV/r)	• Common: dizziness, insomnia • Rare: depression, confusion, amnesia, abnormal dreams, anxiety
Antibacterials	Co-trimoxazole	• Rare: insomnia, depression, anorexia, apathy
	Isoniazid (INH)	• Common: peripheral neuropathy • Rare: agitation, depression, hallucinations, paranoia, impaired memory
Other	Metronidazole	• Rare: CNS toxicity, agitation, depression, delirium, seizures
	Amphotericin B	• Common: headache • Rare: delirium, agitation, anorexia, lethargy, diplopia
	Steroids	• Euphoria, mania, depression, psychosis, confusion

CNS = central nervous system.

*Common: <10%; rare: <1%.

Table 2. Side-effects, drug interactions and advantages of concurrent SSRI use with ART

Agent	Dose	Side-effects	Drug interactions[8,9]	Notes
Fluoxetine	20 - 60 mg/day	Nausea, dyspepsia, abdominal pain, anxiety (especially in first 10 days), headache, tremor, sexual dysfunction, hyponatraemia, insomnia and agitation	• LPV/r: may increase fluoxetine levels – increased risk of serotonin syndrome	• Advantages: low cost, available at most centres • Agitation can be a big problem in the first few days: adequate explanation and reassurance can reduce impact • Safe in overdose
Citalopram	20 - 60 mg/day	As for fluoxetine	• Not a potent inhibitor of most cytochrome-P450 enzymes: few drug interactions • Use with caution with NSAIDs/ warfarin	• Advantage over fluoxetine: starting dose can be halved (10 mg), and fewer drug interactions • Safe in overdose

LPV/r = lopinavir/ritonavir; SSRI = serotonin selective re-uptake inhibitor; NSAIDs = non-steroidal anti-inflammatory drugs.

Table 3. Side-effects, drugs interactions and advantages of concurrent TCA use with ART

Agent	Dose	Side-effects	Drug interactions[8,9]	Notes
Amitriptyline	25 - 150 mg/day (usually taken at night)	• Dry mouth, blurred vision, constipation, urinary retention, sedation, arrhythmia • Contra-indicated if myocardial infarct in preceding 6 months, cardiac conduction abnormalities or prostatism	RTV: increases levels and thereby the antimuscarinic effects of amitriptyline (reduce the dose)	• Lethal in overdose: not suitable for patients at risk of suicide • Dry mouth can be a problem with oral candida • Usual dose of 25 mg for insomnia or pain is often **not** sufficient as an antidepressant – may need >3 tablets • Useful if sedation/analgesia is required
Imipramine	75 - 150 mg/day	As for amitriptyline, but less sedating		

TCA = tricyclic antidepressant; RTV = ritonavir.

suicidality. These patients should be referred to psychiatric services and/or treatment with antidepressant medication should be initiated.

Antidepressants

Using more than one antidepressant should be avoided, as the risk of serotonin syndrome may be increased in HIV-positive patients.[2] The syndrome, which constitues a medical emergency, presents with pyrexia, sweating, diarrhoea, hyperreflexia, myoclonus, loss of consciousness and seizures.

In general, the duration of treatment with antidepressant medication depends on whether or not the patient has experienced previous depressive episodes. For a first episode, medication should generally be continued for 6 - 12 months to prevent relapse. Treatment should be continued for 2 - 3 years in the event of a patient's second or third episode, and lifelong medication should be considered for >3 prior episodes.

St John's wort, a herbal product with antidepressant effects, may reduce the plasma concentrations and clinical effects of EFV, nevirapine (NVP) and lopinavir/ritonavir (LPV/r). Patients must therefore be informed that its concurrent use with these ARVs is contra-indicated.[7]

First-line agents include the serotonin selective re-uptake inhibitors (SSRIs), fluoxetine (for patients on first-line ART regimens) **or** citalopram (for patients on second-line regimens or receiving protease inhibitors (PIs)). In most public sector facilities, treatment with citalopram needs to be initiated by a psychiatrist. The side-effects, drug interactions and potential advantages of these SSRIs are outlined in Table 2.

If the patient has a co-morbid sleep disorder or chronic pain, tricyclic antidepressants (TCAs), such as amitriptyline or imipramine, should be considered (Table 3). These can be prescribed as monotherapy: 100 - 150 mg/day, or 25 - 50 mg/day as augmentation.

In patients with co-morbid anxiety and/or patients who have not responded to SSRIs, the use of venlafaxine (Efexor) – a serotonin and noradrenaline re-uptake inhibitor (SNRI) – could be considered. The drug is not available at all centres and needs to be initiated by a psychiatrist (at a dose of 37.5 mg/day, increased to a maximum of 225 mg/day). Treatment with venlafaxine should never be stopped abruptly, as discontinuation symptoms can occur. Potential side-effects include nausea, insomnia, dry mouth, somnolence, sweating, headache, nervousness, constipation, sexual dysfunction and elevation of blood pressure at higher doses. The drug should be avoided in patients at risk of arrhythmia.[2]

Anxiety

Anxiety is a normal human emotion and may be adaptive in many circumstances. However, when it is present for prolonged periods of time, is excessive in relation to the person's current life stressors, or interferes with daily functioning, an anxiety disorder may be present. Anxiety symptoms often mimic common mental conditions and may occur as part of depression, or alone. It is important to exclude and treat physical causes that can resemble the physical symptoms of anxiety, such as thyroid disease, cardiac disease and seizures. The DSM-IV

Table 4. Benzodiazepine use with ART

Benzodiazepines (short-term prescribing only)	
Long-acting (half-life >20 hours)	• Diazepam (Pax, Valium): 2 - 30 mg (oral or IV; never IM) up to 3 times daily • Clonazepam (Rivotril): 0.5 - 2 mg twice daily
Intermediate-acting (12 - 24 hours)	• Lorazepam (Ativan, Tranqipam): 1 - 12 mg (oral, IM or sublingual) up to 3 times daily • Alprazolam (Alzam, Xanor): 0.25 - 4 mg (see interactions below) twice daily
Short-acting (6 - 12 hours)	• Oxazepam 10 - 30 mg twice daily
Ultra-short-acting (<6 hours)	• Midazolam (Dormicum): 7.5 - 15 mg (see interactions below) usually stat dose, but may be used up to 3 times daily
Benzodiazepine interactions with ARVs[8,9]	
Diazepam	• Use with caution with EFV and LPV/r: may need dose adjustment because of increased sedation, confusion and respiratory depression
Clonazepam	• EFV: possible increase or decrease in clonazepam levels; avoid combination • NVP: possible decrease in clonazepam concentrations and symptoms of withdrawal • RTV: likely to increase levels of clonazepam – use with caution
Alprazolam	• EFV: may increase levels of alprazolam – avoid • RTV: increases alprazolam effect when RTV is started; after 10 days no significant interaction • NVP: may reduce alprazolam effect
Midazolam	• Do not co-administer with EFV, indinavir or LPV/r • Use with caution with NVP
Lorazepam/oxazepam	• No clinically significant interaction expected

IV = intravenous; IM = intramuscular; EFV = efavirenz; RTV = ritonavir; LPV/r = lopinavir/ritonavir; NVP = nevirapine.

Table 5. Approach to prescribing psychotropics for the agitated patient

Step	Agent	Dose	Notes
Oral (first step after non-pharmacological treatment)	Lorazepam	1 - 2 mg (maximum 12 mg/day)	Repeat after 45 min to a maximum of 12 mg/day
	Promethazine	20 - 25 mg	Daily
IM/IV (second step after oral measures have failed/are not possible)	Lorazepam	1 - 4 mg IM	Have flumazenil to hand in case of respiratory depression
	Haloperidol	5 mg IM	Should be the last drug considered as incidence of acute dystonia is high
	Diazepam	10 mg over 10 min IV (**never** IM)	Repeat after 10 min if insufficient effect (up to 3 times)

IVI = intraveous; IM = intramuscular.

distinguishes between the following anxiety disorders:

- generalised anxiety disorder (GAD): excessive and pervasive worry and tension about a variety of events and activities in daily life, associated with somatic symptoms
- panic disorder: recurrent, unexpected sudden attacks of overwhelming anxiety
- phobias: excessive fears of specific objects (e.g. spiders) or situations (e.g. flying or social situations)
- post-traumatic stress disorder (PTSD): distressing dreams or flashbacks, nervousness, poor sleep and avoiding reminders following a life-threatening or traumatic event
- obsessive-compulsive disorder (OCD): repetitive, uncontrollable thoughts or images that are disturbing; or an inability to cease performing rituals or repetitive actions.

If symptoms of the above disorders are present for ≥1 month, where possible, we advise considering pharmacotherapy and referral to a psychologist. SSRIs are considered first-line treatment. Importantly, people with anxiety disorders may be particularly prone to adverse effects and tolerate high initial doses poorly.[10] Patients with anxiety generally require higher doses of SSRIs than those with depression; however, medication should be titrated up cautiously to moderate side-effects. Antidepressants for anxiety may need to be taken for 12 months after the remission of symptoms, depending on the diagnosis.

Either fluoxetine (for patients on first-line ART regimens) or citalopram (for patients on second-line regimens or receiving PIs) could be commenced at half the usual starting dose. Citalopram needs to be psychiatrist-initiated, but has the advantage over fluoxetine of being a scored tablet, making it easier to start at half the usual dose (10 mg). Venlafaxine (psychiatrist-initiated) should be considered for patients who have not responded to SSRIs.

Benzodiazepines (Table 4) provide rapid symptomatic relief of anxiety, but because of their potential to cause physical dependence and withdrawal symptoms,[11] and the potential for abuse, these drugs should be used at the lowest effective dose for the shortest period of time (<3 weeks). Benzodiazepines should be used in conjunction with SSRIs during treatment initiation. Caution should be exercised because of serious interactions with ARVs, particularly ritonavir (RTV), and especially with alprazolam, midazolam and triazolam. Lorazepam and oxazepam have the least number of interactions with ARVs. Benzodiazepines also cause or exacerbate cognitive impairment and are sedating; therefore, patients must be advised not to drive, operate machinery or drink alcohol concurrently with their use.

Psychosis

Psychosis can occur at any time during the course of HIV disease. A psychotic syndrome includes at least 2 of the following symptoms:

- delusions (fixed false beliefs)
- hallucinations (auditory and other)
- disorganised speech or thought
- disorganised behaviour.

Psychotic disorders include schizophrenia, substance-induced psychosis, and psychosis secondary to a general medical condition such as HIV. Reported rates of new-onset psychosis in HIV-positive patients range from 0.5% to 15%.[12]

It is essential to differentiate psychotic symptoms caused by delirium or encephalopathy, to identify and treat the underlying cause; although short-term symptomatic treatment may include low-dose antipsychotics. In delirium, the psychotic symptoms may occur in the context of fluctuating attention, sleep/wake disturbance and poor orientation.

Anti-psychotics

Importantly, with regard to prescribing antipsychotics, HIV-positive patients may be more susceptible to extra-pyramidal side-effects (EPSEs), neuroleptic malignant syndrome and tardive dyskinesia. Antipsychotics should always be initiated at the lowest effective dose and for the shortest period of time necessary. Atypical or second-generation antipsychotics (SGAs), where available, are generally preferred over first-generation antipsychotics, because of the decreased risk of EPSEs. Risperidone is the most widely studied atypical antipsychotic (or SGA), and generally appears to be safe, although levels have been reported to increase with concurrent RTV use.[2,13] An overlap in metabolic side-effect profiles, e.g. weight gain, dyslipidaemia and impaired glucose tolerance of the SGAs and ARVs (PIs and nucleoside reverse transcriptase inhibitors (NRTIs) in particular), complicates the risk-to-benefit equation.[14,15]

Beside the interactions between risperidone and RTV, antipsychotics do not generally significantly inhibit or induce P-450 enzymes and can safely be added to HAART regimens without causing toxicity or HAART failure. Theoretically, RTV may increase the serum levels of haloperidol; therefore, close monitoring of adverse effects is advised.

The use of clozapine in HIV-positive patients is not routinely recommended, although it may be helpful in otherwise medically stable patients with higher CD4 cell counts.[2] It is not

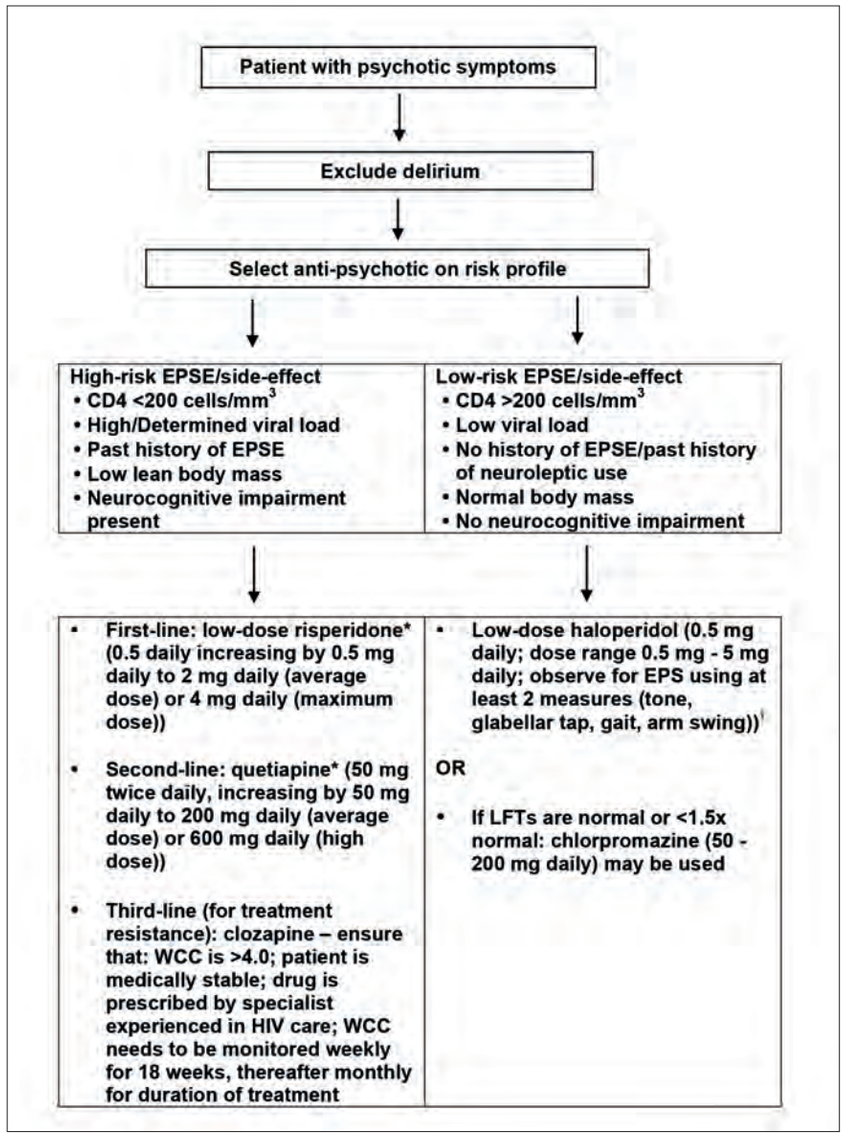

Fig. 1. Decision tree for initiating appropriate anti-psychotic treatment for psychosis in HIV-infected individuals. EPSE = extra-pyramidal side-effects; WCC = white cell count; LFTs = liver function tests.
**Risperidone and quetiapine may be initiated ONLY by a psychiatrist.*
†Depot medications are not contra-indicated. Consider a zuclopenthixol depot if clinically indicated; use a test dose of 50 - 100 mg, and repeat in 1 week. Thereafter, the depot can be administered monthly.

known whether HIV-positive patients receiving clozapine have a greater risk of agranulocytosis; therefore, extremely close monitoring of white cell count is recommended. Clozapine should only be initiated by a psychiatrist. The drug should be used with caution with LPV and RTV,[8,9] as this could increase clozapine plasma concentrations, resulting in an increased risk of arrhythmias, seizures and haematological effects.

A guide to initiating appropriate treatment is provided in Fig. 1. Benzodiazepines can be added in the initial stages for agitation or aggressive or disruptive behaviour. Following diagnosis, a depot preparation can be given if adherence is likely to be a problem (or if the patient chooses it). A test dose should be considered.

Agitation

Aggressive or disruptive behaviour can occur in the context of psychiatric illness, physical illness, substance abuse or personality disorder. This can put staff and patients at risk. In general, it is important to attempt to examine the patient as thoroughly as possible before sedation to establish the underlying aggravating factors. It is also crucial to gain help from nursing staff, doctors and security staff where possible. The safety of the clinician, other patients and staff must be ensured. Non-pharmacological methods should be attempted first, e.g. talking down, distracting, and reassuring the patient. The patient must not be threatened, as this often escalates the situation. Oral treatment must be offered first and biperiden must be available if neuroleptics are introduced. Drug interactions between benzodiazepines and ARVs, and the approach to prescribing psychotropics in the agitated patient are summarised in Tables 4 and 5, respectively.

Sleep disturbance

A patient with insomnia may have difficulty with falling asleep, early-morning wakening and/or frequent waking during the night. Before treating insomnia with drugs (Table 6), it is important to consider and address underlying reversible causes such as depression, mania, pain, medication side-effects, substance abuse, and poor sleep hygiene. It must be ascertained whether the patient has realistic expectations of sleep and whether other medications are being given at appropriate times, e.g. stimulating drugs in the morning and sedating drugs at night. If medication is prescribed, then the lowest effective dose for short-term use only must be used, and patients must be advised of interactions with alcohol.

Pain

Pain symptoms are common in HIV infection and may be caused by painful neuropathy, headaches, cancers and secondary infections. Pain disorders may be acute or chronic, with the latter often accompanied by depression, anxiety, and/or sleep disorders. In addition to analgesia use, psychotropics are frequently used to ameliorate pain symptoms:

- TCAs (e.g. amitriptyline at doses 25 - 75 mg at night): refer to the section on 'Depression' for further information. Other antidepressants should be considered if co-morbid depression is present. Duloxetine is an antidepressant registered for chronic pain but is not on State code in SA.
- Anti-convulsants: carbamazepine is not advised because of interactions with ARVs.[8,9] Gabapentin (Lyrica) is used in chronic pain, but is not freely available.

Bipolar affective disorder/mania

The essential characteristic of a bipolar mood disorder is one or more manic (or hypomanic) episodes with/without depressive episodes. Mania is a recognised presentation in HIV-infected individuals. A manic episode, which is severe enough to impair functioning or warrant hospitalisation, is characterised by abnormal and persistently elevated, expansive or irritable mood, with: grandiosity; decreased need for sleep; talkativeness; flight of ideas/accelerated thoughts; distractibility; and/or increased involvement in pleasurable activities with potentially negative consequences, e.g. excessive buying or sexual indiscretions.

Mood stabilisation

Management is described in Fig. 2. HIV-positive individuals may be more sensitive to the side-

Table 6. Available classes of psychotropics for insomnia*

Agent	Dose	Side-effects
Promethazine	10 - 25 mg	Can cause dry mouth and 'hangover' effect
Amitriptyline	10 - 25 mg	Useful in patients with peripheral neuropathy
Oxazepam	15 - 30 mg	Risk of dependency; prescribe no more than 14 days' supply, unless prescribed by a psychiatrist or neurologist

*Refer to the text for ARV drug interactions.

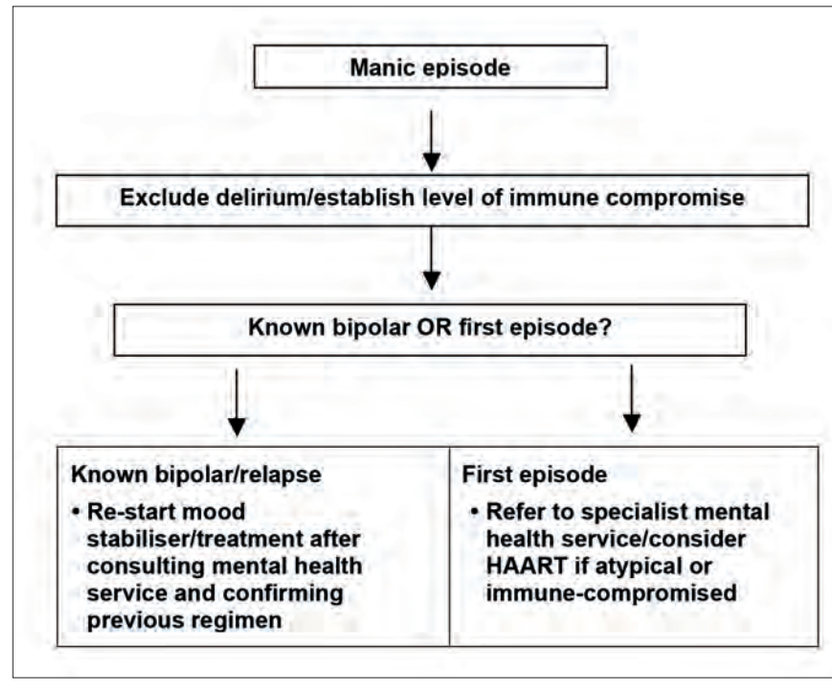

Fig. 2. An approach to the HIV-infected patient with mania. HAART = highly active antiretroviral therapy.

effects of mood-stabilisers, especially in the case of neurocognitive dysfunction. Agents such as valproate, lamotrigine and lithium may be used cautiously, but carbamazepine (Tegretol) should be avoided because of potential interactions with ARVs (RTV, NVP and EFV), and the risk of neutropenia.[2,8,9]

Valproate (Epilim) is generally considered the first-line treatment, but there is an additive risk of fatty liver with didanosine (ddI), abacavir (ABC), lamivudine (3TC), stavudine (d4T) and zidovudine (AZT). It is important to monitor the patient's liver function and adjust the dose accordingly, and it is advisable to test pre-treatment hepatic transaminases (AST/ALT) and platelet levels. The potential for teratogenesis in women of child-bearing age remains a concern. Some drug interactions do occur with LPV/r and LPV. Valproate levels may be decreased with co-administratiokn of RTV. An increase in the dose of valproate may be requried. No significant interaction occurs with tenofovir (TDF), NVP or EFV.[8,9]

Lithium should be avoided in patients with dehydration and renal function impairment. The agent is not always well tolerated, and it may be advisable to limit its use to individuals with higher CD4 cell counts.[2] Careful monitoring of lithium levels is needed, usually 5 days after any dose adjustment, then monthly and 3 - 6-monthly thereafter.

Lamotrigine (Lamictin) can also be considered and is mainly used for depression in bipolar disorder. In most State facilities its use needs to be initiated by a psychiatrist or neurologist and the dose needs to be increased gradually to avoid Stevens-Johnson syndrome. RTV decreases lamotrigine levels by about 50% due to induction of glucuronidation; therefore, an increased lamotrigine dosage may be required.

Additional treatments that can be used in manic episodes include antipsychotics (such as Risperidone and Quetiapine) and benzodiazepines.

Conclusion

Many patients with HIV/AIDS have co-occurring mental health conditions that affect ART adherence, quality of life, morbidity and mortality. Although close collaboration between physicians, psychiatrists and other members of the multidisciplinary healthcare team is the ideal, many clinicians work in settings where psychiatric support is not readily available. This article is intended to guide prescribing antipsychotics in these settings.

Additional resources

- Medicines Information Centre: http://www.mic.uct.ac.za; tel: +27 (0)21 406 6829
- HIV drug interactions: http://www.hiv-druginteractions.org
- Psychiatry services and resources in the Western Cape province: http://www.hivmentalhealth.co.za.

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CASE REPORT

Maternal deaths following nevirapine-based antiretroviral therapy

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We report 2 cases illustrating that it is too simplistic to link nevirapine (NVP) toxicity exclusively to individuals with immune preservation. Not enough is known about the mechanism of hepatotoxicity or cutaneous eruption to predict these events. This type of hypersensitivity reaction occurs rarely among HIV-exposed infants taking NVP prophylaxis or antiretroviral therapy (ART)-experienced adults with complete plasma viral load suppression. Conversely, HIV-uninfected adults and ART-naive pregnant women appear to be disproportionately affected by the adverse effects of NVP.

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Over the last decade, South Africa (SA) has made major progress in the prevention of mother-to-child transmission (PMTCT) of HIV. PMTCT uptake among women known to be HIV-infected increased from 65% in 2006 to >90% in 2010,[1,2] and the most recent national mother-to-child transmission rate at 6 weeks postpartum (2.7%) is the lowest recorded to date.[1]

At the same time, maternal mortality-related HIV has continued to increase despite the increasing availability of antiretroviral therapy (ART). Data from the National Confidential Enquiry into Maternal Deaths show that 28% of all maternal deaths in 2008 - 2010 were AIDS-related, compared with an estimated 20% in 2002 - 2004.[3] The most recent report included a new category of maternal deaths, attributed to ART-related toxicity. The majority of the 73 deaths in this category were attributed to acute liver failure and Stevens-Johnson Syndrome (SJS). Although relatively uncommon, the occurrence of ART-related toxicity deaths was twice as high during 2010 than in previous years. This increase coincided with the release of the 2010 SA PMTCT guidelines[4] that promoted nevirapine (NVP)-based ART for pregnant women with World Health Organization (WHO) clinical stage 3 or 4 disease, regardless of CD4 cell count, hepatitis B infection, the presence of abnormal liver transaminases, or the need for tuberculosis co-treatment.

Recently, WHO noted its support for the expanded use of efavirenz (EFV) in pregnancy, based on growing evidence for the lack of EFV teratogenicity in the first trimester.[5] Still, many health professionals remain at odds over the choice of non-nucleoside reverse transcriptase inhibitors (NNRTIs) – EFV and NVP – particularly for pregnant women in the case of advanced immune suppression or during the first trimester.

Case reports are of limited value to the practice of evidence-based medicine, but they can illustrate the potential effect of clinical decisions. Previous recommendations to avoid EFV use in pregnancy were based largely on 5 case reports of birth defects in humans, 3 of which (myelomeningocele) resembled those from animal studies.[6] A recent case report of cleft palate and micropthalmia following EFV use at conception[7] is likely to re-ignite the debate around the safety and wider use of the drug in pregnancy. Although the handful of cases of birth defects that may be associated with EFV use are widely discussed, much less attention has been given to reports of much more common toxicities associated with NVP use. We report 2 recent cases of maternal deaths at our institution, both from liver failure, following initiation of NVP-based ART.

Case 1

A 22-year-old HIV-infected woman in her second pregnancy was commenced on tenofovir (TDF), lamivudine (3TC) and NVP at 31 weeks' gestation. Her nadir CD4 cell count was 201 cells/μl and alanine transaminase (ALT) was 14 IU/l at baseline. She was assessed as WHO clinical stage 1. After 2 weeks, the dose of NVP was doubled to 200 mg 12-hourly. Apart from haematinics, she received no other medication. Six weeks following ART initiation, she presented in labour with restlessness, jaundice, confusion, and an intra-uterine fetal death. Her alanine transaminase (ALT) was 462 IU/l, aspartate transaminase (AST) 134 IU/l and international normalised ratio (INR) >10. She delivered a fresh stillborn weighing 2.7 kg. She bled profusely following delivery, during which time she experienced a convulsion. The patient's capillary glucose was 2.4 mmol/l. Although she was adequately resuscitated and scheduled for exploration under anaesthesia, she had a cardiorespiratory arrest *en route* to theatre. She was declared dead after an hour of resuscitation. The woman's family declined a postmortem examination.

Case 2

A 29-year-old woman with nadir CD4 count 119 cells/µl was commenced on TDF, 3TC and NVP (initially 200 mg daily) at a peripheral clinic. She was 26 weeks pregnant. No baseline ALT measurement was performed and no other medication was prescribed. The patient presented a month later with a generalised rash and fulminant liver failure. By the time of referral to our facility, she was jaundiced, hypotensive, breathless, oliguric and had an altered level of consciousness. Her haemoglobin was 9.2 g/dl, white cell count 32.9 x 10^9/l, platelets 207 x 10^9/l, urea 8.8 mmol/l, creatinine 202 µmol/l, AST 548 IU/l and INR 4.47. Results of screening for malaria and viral hepatitis were negative. The patient was ventilated and received inotropic support. Ultrasound examination confirmed an *in utero* fetal death. A computed tomography scan of her brain was normal. She delivered a fresh stillborn after induction of labour. Postpartum, she developed grade 4 hepatic encephalopathy, persistent hypotension non-responsive to inotropic support, and worsening liver dysfunction (AST 568 IU/l, ALT 412 IU/l and INR 5.53), and required continued ventilation. The patient demised the following day.

Discussion

These cases are typical of the maternal deaths due to ART-related toxicity that are occurring with increasing frequency across SA. While the cases are not definitive and key investigations of interest (e.g. liver biopsy) are lacking, they provide a useful counterpoint to the case reports regarding EFV teratogenicity that have had a strong influence on SA policy.

Not enough is known about the mechanism of hepatotoxicity or cutaneous eruption related to NNRTIs to enable a reliable prediction of these events in people taking NVP. This type of hypersensitivity reaction occurs rarely among HIV-exposed infants taking NVP prophylaxis, or ART-experienced adults with complete plasma viral load suppression.[8] Conversely, HIV-uninfected adults and ART-naive pregnant women appear to be disproportionately affected by the adverse effects of NVP.[9] Severe adverse events following NVP-based ART among pregnant women are relatively common. In a cohort of pregnant women from Kenya, severe hepatotoxicity and severe rash occurred in 8% and 6%, respectively.[10]

Although the pharmacogenetic basis of NVP hypersensitivity is not well understood, there is some support for *HLA-DRB*1* allele and HLA-Cw8 expression in its pathogenesis.[11,12] A group of investigators recently identified NVP-derived adducts (haptens) with the *N*-terminal valine of haemoglobin, in 12/13 individuals receiving NVP-based ART.[13] Drug bio-activation to reactive metabolites, capable of forming protein adducts and binding to self-proteins, is believed to be the trigger behind these idiosyncratic allergic reactions. The detection of this adduct may provide a clue to the molecular mechanisms underlying NVP hypersensitivity.

The current British HIV Association Guidelines recommend either EFV- or NVP-based ART for pregnant women with a CD4 count <250 cells/µl.[14] The SA National Confidential Enquiry into Maternal Deaths has recommended EFV to replace NVP when initiating ART in pregnancy from the second trimester onwards.[3] Although a Cochrane review suggested the equivalence of EFV and NVP for efficacy endpoints in the treatment of HIV disease, EFV may be safer, notably for the development of raised liver transaminases and neutropenia.[15] Given that the United States Food and Drug Administration assigned EFV to pregnancy category D (indicating evidence of human fetal risk), it is unsurprising that there are no trials comparing NVP and EFV in pregnant women.[6] However, in the absence of head-to-head data on the choice of NNRTI in pregnancy, decision-making on the basis of case reports and series has led to conclusions that may not be in the best interests of the public's health.

Our view is that EFV should be recommended to all pregnant women in need of ART for their own health. Apart from regimen simplicity across all CD4 cell counts, there are a number of conditions unique to pregnancy (including pre-eclampsia; the haemolysis, elevated liver enzymes and low platelet (HELLP) syndrome; and acute fatty liver) that may mimic NVP toxicity, leading to inappropriate withdrawal of ART. Conversely, these conditions may delay diagnosis of NVP toxicity, with progression to overt liver failure. Although the evidence for EFV teratogenicity is equivocal, given the labelling of EFV, ART should be delayed until around 12 weeks' gestation to enable neural tube closure and embryogenesis of the face to be completed.[16]

Generally, there is a clear and urgent need for more evidence to inform the choice of NNRTI during pregnancy. We support calls for the development of a register of ART exposure during pregnancy, with particular focus on the first trimester. Given that the background prevalence of neural tube defects in some regions of SA is as high as 3.55/1 000 live births,[17] approximately 3 000 - 4 000 first-trimester EFV exposures would be required to identify (or rule out) the teratogenicity of EFV with some confidence. Until more useful data are available on the safety of EFV use around conception, the drug's use in the first trimester will remain a vexing issue.

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CASE REPORT

Acute generalised exanthematous pustulosis secondary to cotrimoxazole or tenofovir

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Cutaneous adverse drug reactions are a common complication of antiretroviral therapy and of drugs used to treat opportunistic infections. We present a rare case of acute generalised exanthematous pustulosis secondary to cotrimoxazole or tenofovir.

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Cutaneous adverse drug reactions (CADRs) are a common complication of antiretroviral therapy (ART) and of drugs used to treat opportunistic infections.[1] The common clinical manifestations range from mild maculopapular eruptions to the more severe recognised spectrum of Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Occasionally, however, a rare manifestation of CADR occurs which presents a diagnostic dilemma.

Case report

A 24-year-old South African woman was newly diagnosed with disseminated culture-positive tuberculosis (TB) and HIV. Her CD4 count was 77 cells/mm^3 and she had no prior TB history (including contacts). The patient was initiated on Rifafour, and cotrimoxazole prophylaxis was started 9 days later. After a further 2 weeks, ART was initiated (tenofovir (TDF), lamivudine and efavirenz).

One month after ART initiation, the patient presented with sudden-onset generalised, pustular, itchy rash, associated with 1 week of fatigue, nausea, vomiting and painful feet. She had renal impairment (creatinine 521 µmol/l) and was anaemic (haemoglobin 6.1g/dl). Treatment with TDF, cotrimoxazole and rifampicin was ceased, and the patient was referred for further assessment.

On examination, she was tachycardic but apyrexial. She had a widespread pustular rash sparing the palms and soles (Fig. 1). Pustules were <5 mm in size and monomorphic on an erythematous background, with areas of desquamation on the lower limbs. She had no mucous membrane involvement, but had manifested angular cheilitis and oral candidiasis. Tender hepatomegaly and painful, peripheral sensory neuropathy were noted.

A pus swab from one of the lesions showed neutrophils, but Gram-stain and culture testing were both negative. Testing of a pustule aspirate for varicella zoster virus by polymerase chain reaction (PCR) was also negative. Blood, urine and sputum bacterial cultures were negative, as was syphilis serology, serum cryptococcal latex antigen test and hepatitis B serology. In addition to anaemia, the patient had a leucocytosis of 11.5 x 10^9/l (93% neutrophils), but her platelet count was normal. She was hypo-albuminaemic (19 g/l) with mild liver dysfunction (total bilirubin 23 µmol/l, alkaline phosphatase 171 U/l, gamma-glutamyl transferase 111 U/l, alanine transaminase 34 U/l and aspartate transaminase 58 U/l). A chest X-ray showed diffuse bi-basal nodularity. Necrotic lymph nodes and multiple splenic hypodensities, suggestive of abdominal TB, were evident on abdominal ultrasound.

Two days after admission, treatment with abacavir was started to replace TDF, and the patient was started on

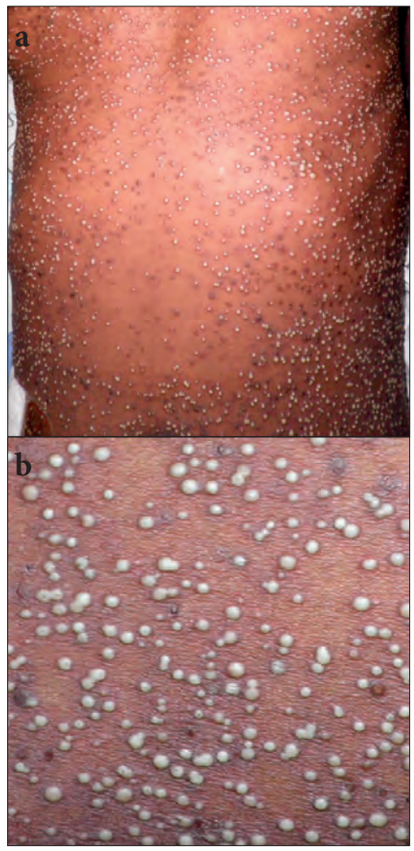

Fig. 1(a and b). Acute generalised exanthematous pustulosis.

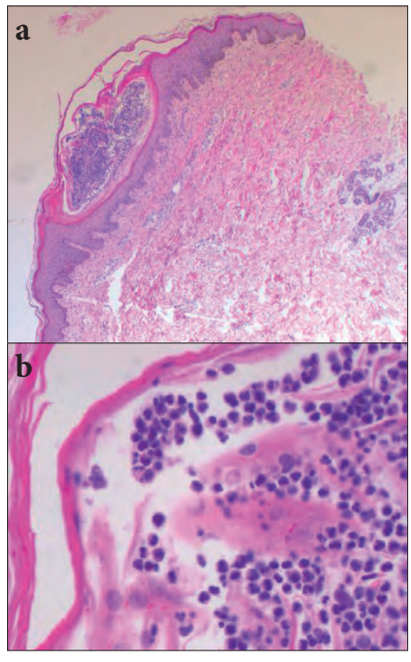

Fig. 2. (a) Intracorneal pustule (x20) containing (b) neutrophils and occasional lymphocytes (x200).

acyclovir, pending the results of investigations. Rifampicin was re-introduced on day 4. Her rash had considerably improved after 8 days and her creatinine level diminished to 303 µmol/l. Renal biopsy was delayed due to the overlying skin lesions.

Histopathology of a skin biopsy on admission showed basket-weave hyperkeratosis, spongiosis and an intracorneal pustule, containing neutrophils and occasional lymphocytes (Fig. 2). Small cocci were noted within the pustule and a mild superficial perivascular lymphocytic infiltrate was present. Superficial dermal vessels were mildly dilated and contained marginated neutrophils. Special stains for fungi and acid-fast bacilli were negative and no granulomas, dysplastic or malignant cells were found. A histopathological diagnosis of acute generalised exanthematous pustulosis (AGEP) was made.

Multi-drug resistant TB (MDR-TB) was subsequently diagnosed on the basis of a urine culture (sampled on admission) and her TB regimen was altered. She was discharged with a clinical diagnosis of acute kidney injury secondary to TDF, disseminated MDR-TB, and AGEP most likely secondary to cotrimoxazole or TDF. She has had a good clinical response and, at the time of writing, remains in care 7 months post discharge.

Discussion

AGEP is an uncommon severe cutaneous reaction associated with drug exposure in 90% of cases. The remaining 10% of cases have been attributed to viral infections, vaccines, spider bites, heavy metal exposure, chemotherapy and radiation.[2] The reaction has a mortality rate of 2%, typically occurring in the elderly with co-morbidities, and is related to septic complications.[2] A wide spectrum of pustular skin diseases forms the differential diagnosis, including pustular psoriasis, Sweet's syndrome (acute febrile neutrophilic dermatosis), pustular erythema multiforme, TEN, DRESS and bullous impetigo.[2,3] In our patient, disseminated varicella was also considered. The combination of clinical and histological features together with appropriate drug exposure is usually enough to make the diagnosis of AGEP.[2,3]

To date, a single case of AGEP has been described in an HIV-infected patient with a CD4 count of 220 cells/mm^3, attributed to boosted darunavir, which recurred on atazanavir re-challenge.[5] Protease inhibitors (indinavir and boosted lopinavir) have also been implicated in AGEP in patients receiving post-exposure prophylaxis.[6,7] Nucleoside/nucleotide reverse transcriptase inhibitors have not been implicated as causal agents. However, there are case reports of AGEP following cotrimoxazole treatment in HIV-negative patients.[8,9]

The pathophysiology of AGEP involves drug-specific T cell activation by dendritic cells followed by T cell expansion and migration to the dermis and epidermis. The T cells are activated to produce high levels of neutrophil-attracting chemokine (CXCL8) and express a type 1 T-helper (Th-1) cytokine profile (granulocyte-macrophage colony-stimulating factor, interferon gamma and tumour necrosis factor-alpha). Stimulated keratinocytes recruit T cells and neutrophils to the inflamed skin. Drug-specific cytotoxic CD8 T cells are responsible for killing keratinocytes and for vesicle formation, while neutrophils migrate along the CXCL8 gradient into the vesicles to form pustules.[2] In the case described here, the delayed presentation following initiation of cotrimoxazole, the most likely causative agent, may have been attributed to reduced drug-specific T cell activation in advanced HIV disease.

Characteristic features of AGEP include an acute generalised cutaneous eruption of whitish non-follicular, sterile pustules <5 mm in size and on a background of erythema, which may be accompanied by a burning sensation. Lesions often start on the face or intertrigenous areas, moving to the trunk and limbs within a few hours. The reaction rarely affects the palms and soles and has mucous membrane involvement in only 20% of cases. Half of affected patients may report other skin symptoms. The rash lasts for a mean of 9.4 days (range 4 - 10), followed by desquamation. The rash is accompanied by a fever >38°C that lasts for approximately 1 week.[3] The onset of rash follows 2 distinct patterns: *(i)* a rapid onset after drug ingestion (a few hours to 2 - 3 days) which is most commonly associated with antibiotics and may signify previous sensitisation; and *(ii)* an onset after 1 - 3 weeks (mean 11 days), which may result from primary sensitisation.[3,4]

A neutrophilia occurs in 90% of cases, while up to 30% have mild eosinophilia. Renal dysfunction (predominantly pre-renal) occurs in one-third of cases. Rarely, hypocalcaemia and a mild elevation in amino-transferases have been observed.[2,3] The skin biopsy is characterised by spongiform subcorneal or intradermal pustules, papillary oedema and neutrophilic perivascular infiltrates.[2,3]

When there is doubt over the causal agent, and there are no alternative therapeutic agents,

confirmatory tests may be performed under specialist supervision:

- Drug provocation testing: although the gold standard for CADR, this is contra-indicated in AGEP.[10]
- Patch testing: although this has only a 50% sensitivity and 85% specificity, it is the best available test for practical reasons.[2]
- The lymphocyte transformation test (LTT): requires a specialised laboratory, but has an improved sensitivity of 78% with varying specificity.[2]

Treatment of AGEP is symptomatic, with withdrawal of treatment with the offending drug. Antibiotics are not indicated unless secondary infection occurs. Corticosteroid treatment has been used, but is not required in the majority of cases.[3]

Conclusion

This case highlights a rare adverse drug reaction that can occur in HIV-infected patients and is an important differential diagnosis of a pustular eruption. Antibiotics are the most common causative agents, and protease inhibitors are the most commonly implicated ART drugs. Early recognition and drug withdrawal are vital. If drug re-challenge is required, this should be done under specialist supervision.

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CASE REPORT

Varicella zoster virus infection causing urinary retention in a child with HIV infection

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An 11-year-old boy receiving antiretroviral therapy for HIV infection and antibacterial therapy for pulmonary tuberculosis presented with urinary retention due to varicella zoster virus infection involving the sacral nerves, confirmed on serological testing. The perineum over dermatomes S2 - S4 on the left was involved with a vesicular and superficially erosive rash. A transurethral catheter was inserted and the patient was treated with acyclovir (300 mg 6-hourly for 5 days). At follow-up 4 weeks later, the perineal skin lesions had healed, the catheter was removed and the patient was able to pass urine.

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Varicella zoster virus (VZV) of the human herpes virus family causes childhood chickenpox, becomes latent in sensory ganglia and re-activates years later in immunocompromised and elderly persons to produce shingles (herpes zoster). The annual incidence of herpes zoster in children aged <10 years is reported to be 0.74 per 1 000 children per year.[1] The association of VZV infection and neurogenic bladder dysfunction is rare and mostly seen in adults, with only one reported case in a child.[2]

Severe and debilitating zoster-associated dermatological, ophthalmological and neurological complications may occur in patients with HIV infection.[3] We describe the case of an HIV-positive child who presented with acute urinary retention secondary to VZV infection.

Case description

An 11-year-old boy was referred with urinary retention. He complained of difficulty passing urine, lower abdominal discomfort, and a painful rash over the perineum for 5 days. His mother had noticed that he had lower abdominal swelling.

The patient was HIV-positive and receiving treatment accordingly (300 mg zidovudine twice daily, 250 mg didanosine daily and 200 mg/50 mg lopinavir/ritonavir twice daily). He was also receiving treatment for pulmonary tuberculosis, diagnosed 6 months prior (300 mg rifampicin and 150 mg isoniazid daily). The boy had no previous history of chickenpox.

On examination, the patient was pyrexial (temperature 39°C) and appeared acutely ill. His bladder was distended, easily palpable and mildly tender. His penis, scrotum and perineum over dermatomes S2 - S4 on the left were involved with a vesicular and superficially erosive rash. Severe swelling of the prepuce caused the appearance of phimosis (Fig. 1). On digital rectal examination, his anal tone was normal. The bulbocarvernosus reflex was not tested due to severe tenderness in the perineal area. No abnormalities were found on neurological examination of his lower limbs.

Fig. 1. Blistering and superficially erosive skin lesions due to varicella zoster virus infection involving the sacral nerves (S2 - S4) on the left side.

An 8F Foley catheter was inserted transurethrally and 1 500 ml of clear urine was drained. The boy was admitted to hospital and treated with 300 mg acyclovir 6-hourly (intravenous), 4 drops of oral tilidine 6-hourly and 1 000 mg paracetamol 8-hourly.

Urine dipstick testing showed a trace of blood. Urine microscopy showed leukocytes <1 000 cells/mm^3 and erythrocytes <1 000 cells/mm^3, and was negative for bacterial cultures. The patient's absolute CD4 count was 159×10^6/l with a CD4% of lymphocytes of 9.42% and CD45 positive white cell count of 6.18×10^9/l. Blood tests revealed 136 mmol/l sodium, 4.3 mmol/l potassium, 2.8 mmol/l urea, 32 µmol/l creatinine, a 5.9×10^9/l white cell count, 11.5 g/dl haemoglobin and 303×10^9/l platelets.

Serological tests were IgG-positive and IgM-negative for human simplex virus (HSV) types 1 and 2, and IgG-positive and IgM-positive for VZV. Smears for viral culture were negative for HSV 1 and 2 and negative for VZV; however, the smears were taken after the blisters had ruptured and there was already scab formation. Due to the clinical picture and the serology results, treatment for herpes zoster was continued.

The boy was discharged after 7 days with the transurethral catheter *in situ*. At follow-up one week later, the preputial swelling had resolved but phimosis was present due to scarring. Circumcision was performed under general anaesthesia. A trial without catheter was attempted. After 3 hours the bladder was palpable, but he had no urge to urinate. A 12F Foley catheter was re-inserted and 600 ml of urine was drained. At follow-up 2 weeks later, the perineal skin had healed and a trial without catheter was repeated. He was able to urinate 250 ml with a post-void residual volume of 124 ml urine on ultrasound. He appeared well and was urinating without difficulty at last follow-up 2 months later.

Discussion

The prevalence of HIV infection in children aged 2 - 14 years in South Africa is approximately 2.5%.[4] The incidence of herpes zoster in children aged <10 years is approximately 0.74 per 1 000 per year.[1] This incidence is higher in HIV-positive children (164 per 1 000 per year) and possibly even higher in children with a low CD4 count.[5] Bladder dysfunction secondary to herpes zoster is uncommon, affecting 3.5 - 4.2% of people with VZV infection, but occurs more often when the lumbosacral dermatomes are involved (28.6%).[5]

Voiding dysfunction caused by herpes zoster may be classified as cystitis-associated, neuritis-associated or myelitis-associated.[5] Neuritis-associated dysfunction leads to an acontractile bladder and hypoesthesia. In cystitis-associated bladder dysfunction, the neurological examination is normal, whereas overflow incontinence and neurological abnormalities occur with myelitis-associated dysfunction, according to the level of spinal involvement. It is important not to ascribe urinary retention to the pain of genital ulceration.[5]

The prognosis is favourable with acyclovir therapy and intermittent or indwelling catheterisation. The usual time to recovery of voiding function is 8 weeks. Antiviral therapy decreases the duration and number of vesicles, but there is no evidence that it reduces the duration of neuropathic bladder dysfunction.[6,7] It is uncertain whether starting acyclovir therapy after the vesicles have formed alters the outcome.

Viruses associated with neurological complications that affect bladder function are HSV types 1 and 2 (most common), VZV, cytomegalovirus and Epstein-Barr virus. Radiculomyelitis causing transient urinary retention and sensory lumbosacral symptoms is known as Elsberg syndrome.[8]

The most common diagnostic pitfall with VZV is its confusion with HSV infection. HSV lesions may appear in a dermatomal pattern, especially when involving the thighs or buttocks. The major difference between the two diseases (when HSV occurs in belt-like patterns) is the significantly higher re-activation frequency of HSV.

Laboratory tests may be required to differentiate HSV from VZV. A definitive diagnosis is made by isolation of the virus in cell cultures inoculated with body fluids. Polymerase chain reaction techniques may be used to detect viral DNA in the cerebrospinal fluid. Heterologous antibody responses to HSV and VZV may occur in some patients because the two viruses share common antigens.

In our patient, the clinical picture was in keeping with VZV rather than HSV infection, and the serological tests were compatible with a diagnosis of acute VZV infection.

Acknowledgement. Written informed consent was obtained from the patient's mother to take clinical photographs of the perineal skin lesions at presentation and follow-up.

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TRUE (A) or FALSE (B) – click on the correct answer:

Regarding the urinary tract manifestations of varicella zoster virus

1. The mechanism through which varicella zoster virus causes urinary retention is almost always related to pain of genital ulceration.

Regarding tuberculosis (TB) prevention in pregnant women

2. The sensitivity of typical TB symptoms (e.g. weight loss) in diagnosing TB in HIV-infected pregnant women is similar to other HIV-infected adults.

3. Isoniazid is not known to be teratogenic.

Regarding HIV in homeless populations in South Africa

4. In settings of low HIV prevalence, homelessness is a well-established socioeconomic risk factor for HIV infection.

Regarding cutaneous reactions to cotrimoxazole

5. Acute generalised exanthematous pustulosis is the second most common cutaneous adverse drug reaction caused by Bactrim.

Regarding immunological responses after ART initiation

6. Less than 5% of individuals initiating ART will have poor immunological responses as measured by CD4 cell count.

7. Poor immunological responses on ART occur more commonly in older adult patients.

Regarding self-testing for HIV infection

8. Although self-testing kits are available from chemists, there is, as yet, no FDA-approved testing kit.

Regarding resistance testing in HIV infection

9. According to the new South African ART resistance testing guidelines, all infants newly diagnosed with HIV infection should have HIV genotyping, with particular concern related to non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistant mutations.

10. According to the new South African ART resistance testing guidelines, all adults newly diagnosed with HIV infection should have HIV genotyping, with particular concern related to protease inhibitor (PI)-resistant mutations.

11. In any patient on first-line therapy with first-time detectable viraemia (>1 000 copies/ml), non-adherence is the most likely explanation, and intensive adherence counselling and support are required before repeating viral load testing.

12. In adults, resistance testing is recommended for any patient failing first-line therapy; the nucleoside reverse transcriptase inhibitor (NRTI) of greatest interest here is lamivudine (3TC).

13. Genotypic testing is required following any treatment interruption before re-starting therapy.

14. Failure to achieve viral suppression on a PI-containing regimen is almost always due to resistance.

Regarding the prescribing of psychotropic medication in individuals on ART

15. Although not commonplace, several NRTIs can have central nervous systems manifestations that warrant consideration in patients with known mental illness.

16. After excluding organic causes and delirium, HIV-infected adults who require antipsychotics should ideally be started on haloperidol, as extrapyramidal side-effects are less common in HIV-infected patients than in uninfected patients.

17. Promethazine and amitriptyline are suitable choices for patients on ART who report sleep disturbances.

18. Commonly used antipsychotic medications (such as haloperidol) do not interact with most antiretroviral drugs.

19. Commonly used mood-stabilising medications, such as carbamazepine and valproate, do not typically interact with most antiretroviral drugs.

Regarding nevirapine toxicity in pregnancy

20. In the context of pregnancy, nevirapine toxicity occurs more commonly at low CD4 cell counts.

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