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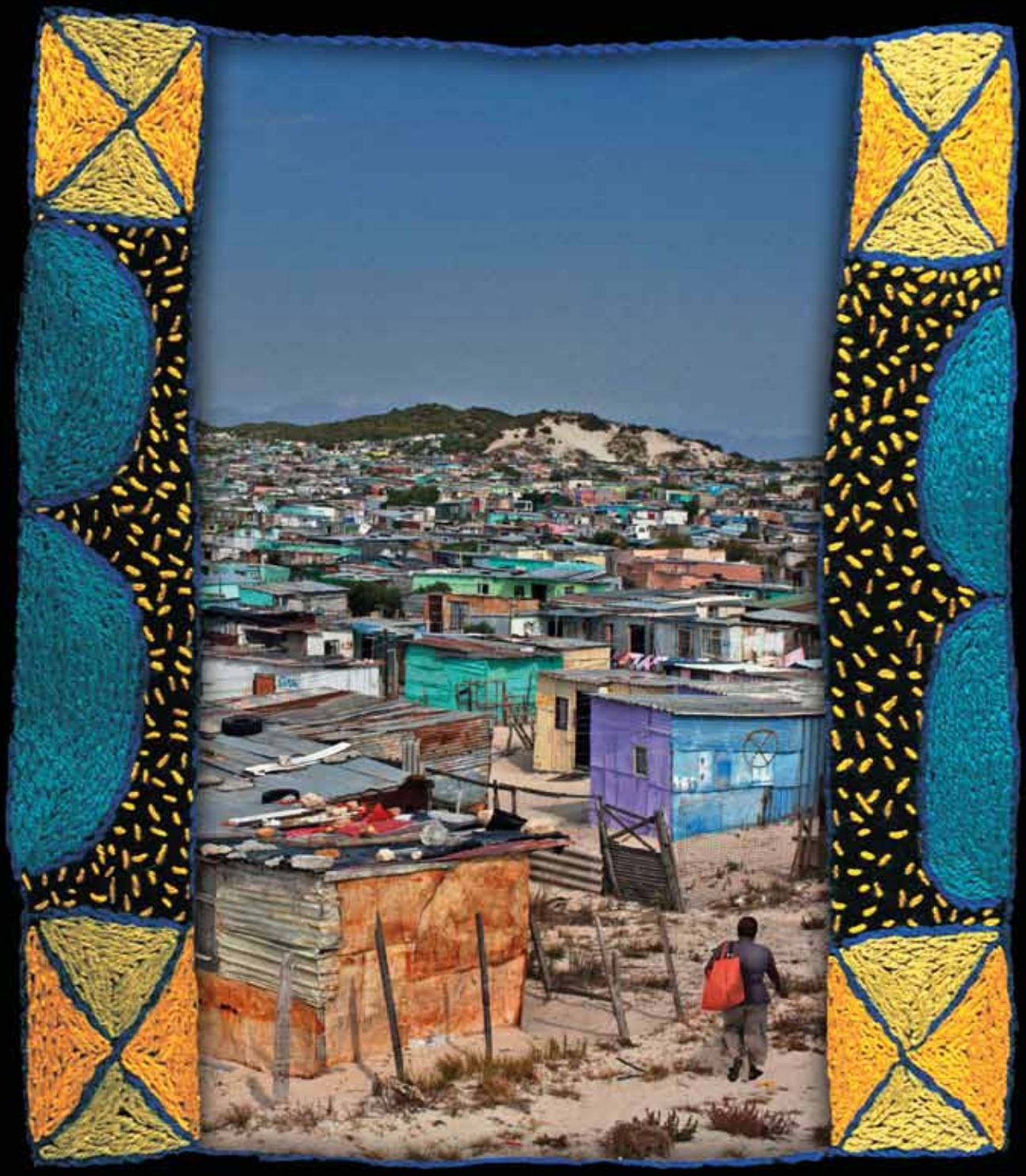

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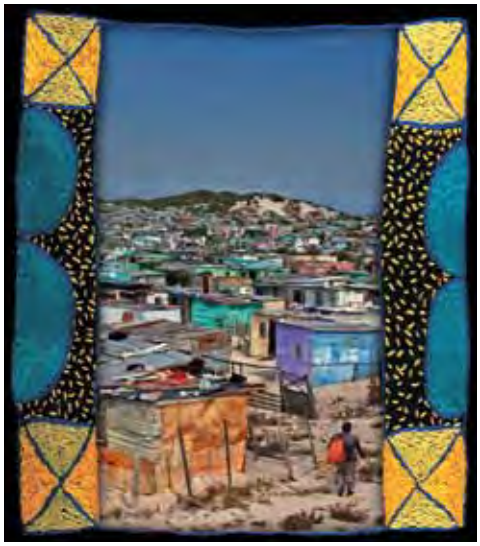

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Cover: *The cover photograph, taken by Jose Cendon of Médecins Sans Frontières, shows part of Khayelitsha, Cape Town. Khayelitsha has been the focus of more than 10 years of innovative programmes around HIV prevention, antiretroviral therapy and TB services, led by MSF.*

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FROM THE EDITOR

FEEDING HIV-EXPOSED INFANTS

The most appropriate strategies for feeding HIV-exposed infants have been a source of great debate in South Africa for years. During this time policy makers, healthcare providers and (most importantly) mothers living with HIV infection have been concerned and sometimes confused about what is best for the HIV-exposed but uninfected infant.

Over the past few months, the announcement of a new national policy promoting breastfeeding with daily nevirapine prophylaxis for infants has presented a single, unified policy for services across the country. This is leading to the rapid cessation of replacement feeding provided through the public sector to HIV-infected mothers and their infants. But far from ending the debate on infant feeding, these new policies have refreshed the discussion. There have been a number of newspaper editorials and media releases presenting strong voices in support of, and cautioning against, the wholesale withdrawal of replacement feeding.

A recent debate in Johannesburg held by the SA HIV Clinicians Society provided a valuable summary of the key issues and a sense of the complexity in any attempt to develop a nationwide infant feeding strategy (for those who missed it, the presentations from the debate are available on the Society's website, http://sahivsoc.org). In this issue of the *Journal*, Haroon Saloojee and colleagues present one viewpoint on the new national policies. Dr Saloojee was one of the participants in the Johannesburg debate, and I hope that this opinion piece will help generate productive discussions on a topic that clearly remains unresolved. (Note that opinion pieces that include other perspectives on the new infant feeding policies were solicited, but unavailable at the time of going to press – we hope these will be available for the next issue.)

Looking forward, the HIV Clinicians Society has been a leader, nationally and internationally, in developing evidence-based guidelines to address various issues in HIV treatment and prevention. Given the ongoing debate, there is certainly scope for rational guidelines to address the safest infant feeding choices across a range of scenarios. We hope the Society will take up the challenge of developing guidelines on infant feeding in the coming months, as this is an important time to present a balanced voice on a topic that remains contentious.

Also in this issue, Dramowski and colleagues describe the 'missed opportunities' for reducing HIV-related paediatric admissions at Baragwanath Hospital in Soweto. Among the missed opportunities they document are the failure to deliver effective prevention of mother-to-child transmission (PMTCT) services, including antenatal counselling and testing and antiretroviral interventions, leading to preventable paediatric infections. This research took place in a period when use of replacement feeding was common in Soweto, but presumably this will change radically during 2012 under the new feeding policies. Reading the articles by Dramowski and Saloojee together, the future seems unusually opaque. Will we look back 10 years from now to view the removal of replacement feeding for HIV-exposed infants as a critical opportunity rightly taken to promote child health, or yet another opportunity missed in our efforts to eliminate paediatric HIV?

This edition has many other exciting contributions. Innes and colleagues ask important questions about stavudine dosing, and provide an intriguing proposal for future research into a neglected issue with major implications given the number of patients on stavudine. Boyles discusses the ideal package of care for individuals who do not yet require antiretroviral therapy (ART), an aspect of services that may be sorely neglected in many parts of the country. An original article from Peltzer suggests a very high prevalence of depression among new HIV-infected mothers in KwaZulu-Natal, raising an important issue in thinking about PMTCT interventions in the postpartum period. Cullen presents a case report on an unusual case of optic neuritis in an HIV-infected patient, and in a review article Garone and colleagues discuss the progress to date and lessons learned from 10 years of programmes delivered through Médecins Sans Frontières in Khayelitsha, Cape Town. MSF's projects in Khayelitsha have been a vanguard for the development of models to deliver ART as well as integrated HIV/TB care, and as we approach the 10-year anniversary of public sector ART services in South Africa, this review provides an important reminder of how far things have come.

Happy reading.

LANDON MYER
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MESSAGE FROM THE EXECUTIVE

By the time you read this, there will be a new Board for the Society, a new President and a new Memorandum of Association (legal speak for a constitution) for the Society in place. We hope that there will be a new CEO as well, from the beginning of next year. The prior Executive and interim Board have created a strong, well-run organisation, and the new Board will be responsible for making it even better. It has been a pleasure working with this Executive, as well as with the office staff and a host of unpaid helpers. We look forward to 2012 being a very good year!

FRANCOIS VENTER

OPINION

HIV AND INFANT FEEDING – ONE STEP FORWARD, TWO STEPS BACK

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The recent decision by the South African Department of Health to withdraw the provision of free replacement (formula) feeds to HIV-exposed infants has hardly evoked any response from clinicians, health professionals or civil society groups. This paper argues that the decision is short-sighted, lacks an adequate evidence base, and is retrogressive and unconstitutional. Nine supporting arguments are presented and an alternative policy proposed.

The recent 'Tshwane Declaration of Support for Breastfeeding in South Africa' championed by the national Department of Health seeks to promote breastfeeding and halt practices deterring optimal breastfeeding in South Africa (SA).[1] The Declaration's intentions are most welcome, including greater support for the Baby Friendly Hospital Initiative which facilitates breastfeeding soon after birth, increasing numbers of community health promoters who will visit homes and support mothers with breastfeeding, workplace support for breastfeeding mothers, and stricter monitoring of the milk industry's compliance with the code of marketing of breastmilk substitutes.

However, one decision stands out as short-sighted, poorly evidenced and retrogressive. The plan to remove the provision of free replacement (formula) feeding to infants of HIV-positive women is frankly bewildering. HIV accounts for over 50% of child mortality in SA,[2] and is primarily responsible for the loss of hard-earned gains in child health in South Africa over the past two decades. Postnatal transmission of HIV through breastfeeding is now the commonest form of mother-to-child transmission (MTCT), and its contribution is increasing as programmes introduce more effective antenatal and perinatal ARV regimens. Annually, more than half a million infants globally acquire HIV through breastfeeding, highlighting the failure of previous strategies, including those promoting exclusive breastfeeding.

There are currently only two recognised postnatal preventive strategies – antiretroviral prophylaxis provided to mother or infant, and avoiding HIV exposure through replacement feeding. To deliberately discard one of these two strategies is a luxury that the country can ill afford and requires substantial evidence that the strategy is either ineffective or results in major harm. Evidence to support either of these contentions in the South African setting is simply lacking.

REPLACEMENT (FORMULA) FEEDING REMAINS A LEGITIMATE HIV PREVENTION STRATEGY

Multiple strategies are currently available to prevent HIV transmission in adults. Despite good evidence about the benefit of condoms, microbicides, circumcision and pre- and post-exposure prophylaxis, among others, the search continues for different and more effective prevention options such as an HIV vaccine. Clearly, a single strategy could never meet the needs of all. If the Department of Health were to summarily withdraw the provision of any one of the established HIV prevention strategies, the HIV community would be toyi-toying in the streets.

Yet the government's decision to remove a well-evidenced child HIV prevention strategy – replacement feeding – has hardly elicited a whisper from HIV activists, clinicians or civil society. Is it that they have been cowed into inaction because supporting replacement feeding is somehow automatically viewed as being anti-breast? Certainly, this was the fate of the authors of this piece when we recently wrote an opinion piece in the *Mail & Guardian* questioning the validity of the Department's decision.[3] Supporters of the Department's proposal lambasted the newspaper's irresponsible behaviour in publishing the piece. They went on to describe us as ill-informed and 'dissidents'.[4] Such malicious name-calling demonstrates a degree of intolerance unbecoming of fellow scientists on a decision that has great scientific and public health importance and deserves rigorous debate.

Indeed, at an open public debate hosted by the SA HIV Clinicians Society in Johannesburg in October 2011, over 70% of the more than 120 attendees (who included doctors, nurses, policy makers and nutritionists) voted against the Department's proposed change. A similar percentage of attendees agreed that provinces should be free to determine their own policy rather than being

forced to offer a single option. Clearly the views of many important stakeholders have not been considered in the Department's decision, and there appear to be many dissidents lurking out there. The most silent voice has been that of HIV-positive women.

NO EVIDENCE THAT THE NEW PROPOSAL WILL MAXIMISE HIV-FREE CHILD SURVIVAL IN SA

Supporters of the withdrawal of replacement feeding will quickly point out that it is not just the acquisition of HIV infection but overall child survival (HIV-exposed children staying alive) that matters. That is correct. The pertinent question then is whether replacement feeding inevitably results in increased child mortality in SA. The primary author of the *Mail & Guardian* piece attacking our stance readily acknowledged in a paper published in the *Bulletin of the World Health Organization* in 2011 that '… no determination has been made about which feeding practice will maximize HIV-free survival nationally'.[5]

Much of the evidence arguing that HIV-free survival (being alive and HIV uninfected) is similar for formula-fed and exclusively breastfed infants originates from countries such as Zambia, Malawi and rural Botswana. However, the extremely high background mortality in the study children (e.g. 21% in Zambia)[6] because of the high burden of infectious disease, poor hygiene and sanitation, and limited access to quality health care, easily masks any possible benefits of replacement feeding (since so many children die). These dismal conditions are much less likely in South African settings. In rural KwaZulu-Natal, for instance, the probability of HIV-free survival at 18 months was marginally higher in HIV-exposed infants who had never been breastfed compared with infants who had ever been exclusively breastfed (80% v. 75%, p=0.05), the difference being mostly attributed to acquisition of infection through breastfeeding.[7] A second confounder present in most studies is that since few trials randomised feeding choice, higher-risk women (with lower CD4 counts) were directed to, or selected, replacement feeding. This obviously attenuates possible benefits of replacement feeding.

Evidence from diverse African cities such as Nairobi[8] and Abidjan[9] convincingly indicates that replacement feeding can be safely supported in these settings and can reduce HIV infection rates, without jeopardising child survival. With safe replacement feeding, the vertical HIV transmission rate can be reduced to less than 2%, even in a resource-limited setting such as rural Rwanda.[10] The high HIV-free survival rate reported in the Rwandan cohort of infants whose caregivers were supported with exclusive replacement feeding is remarkable and among the highest reported for a cohort of HIV-exposed infants.[10]

SOUTH AFRICA IS NOT A SINGLE HOMOGENEOUS COUNTRY

Using data from poorer southern African countries to argue that replacement (formula) feeding cannot be undertaken safely in SA is inappropriate. Over half of South African children are urbanised.[11] Many have good access to safe water (62%), sanitation (63%) and electricity, and these statistics exceed 87% in Gauteng and the Western Cape, including their townships and informal settlements.[12] Under-5 mortality rates (U5MR) vary substantially among provinces and districts; for example, in 2008 the U5MR in Western Cape was 31/1 000 live births, while it was almost fourfold higher in the Free State (117/1 000).[13] District-level data are unavailable.

At least a third to one-half of SA caregivers should therefore be able to safely replacement feed their children. SA data from peri-urban and rural settings such as Paarl, Umlazi and Rietvlei confirm that formula feeding halved HIV transmission or death among children living in households with piped water. Among those who had piped water and fuel and who disclosed their HIV status, the protective effect of formula was greater (68% reduction).[14] Furthermore, the increasing availability of rotavirus and pneumococcal vaccine in SA is rapidly reducing the incidence and severity of diarrhoea and pneumonia, two major morbidities associated with replacement feeding.

This does not mean that that choosing to formula feed an infant in some rural parts of the country, or in an under-serviced informal settlement, could ever be considered an appropriate choice. However, denying individual choice and failing to support a legitimate HIV prevention strategy in circumstances where this can be safely done violates caregivers' and infants' rights to basic health care and may be unconstitutional.

A SINGLE INFANT FEEDING OPTION IS INAPPROPRIATE FOR ALL HIV-POSITIVE WOMEN IN SA

A 'one-size-fits-all policy' is certainly simpler to promote, and the notion that 'mixed messages lead to mixed feeding' makes sense. However, the simplest policy is not necessarily the best. Until recently infant feeding policy in SA was made at the provincial level. This makes sense because SA is heterogeneous in so many respects – the rural-urban mix, the availability of water and sanitation, the background infant mortality and the provincial variation in the percentage of mothers with HIV. The newly proposed policy demands that the whole country assume the same position – no free formula provision. This position is contrary even to the 2010 WHO HIV and infant feeding policy, on which the South African policy is based, which recommended that decisions be made by 'national or sub-national health authorities' in recognition of in-country variances.[15]

THE NEW PROPOSAL IS RETROGRESSIVE IN TERMS OF SUPPORTING WOMEN'S CHOICE AND ANTI-POOR

Arguing that parents can pay for formula from their own pockets if they choose this option may seem reasonable, but this denies access to an estimated 25 000 infants in whom formula feeding may be safely undertaken, but is unaffordable. Data from Rietvlei, Paarl and Umlazi confirmed that as many as a third of women living in these peri-urban and rural settings met the adequacy for replacement feeding criteria, dubbed AFASS

(affordable, feasible, acceptable, sustainable, safe), despite being poor.[14] Disallowing middle- and upper-class women access to free state-sponsored formula may be justifiable, since access to many health services for this class of citizens require them to bear the costs themselves. However, insisting that a poor woman (who qualifies for a child support grant, for instance) who meets the AFASS criteria be denied the opportunity to have an HIV-uninfected child, simply because she is poor, is discriminatory.

THE NEW PROPOSAL IS BASED ON EXTRAPOLATION RATHER THAN FIRM EVIDENCE

Much of the enthusiasm for the proposal to withdraw support for replacement feeding stems from research suggesting that extended nevirapine provision to infants for 6 months, or triple antiretroviral therapy provision to their mothers, can reduce HIV transmission rates to less than 2% at 6 months in exclusively breastfed populations. Whether the benefits of antiretroviral prophylaxis continue to 12 months (the suggested duration in SA), and whether the intervention is equally beneficial in mixed-fed infants (the likely situation in SA), is unknown. Similarly, the consequences of antiretroviral interruption while breastfeeding are unclear. There are further unanswered questions. How serious are the long-term effects of exposure to multiple antiretroviral drugs *in utero* and during breastfeeding? Can adequate adherence be achieved to avoid emergence of drug resistance? Will there be negative effects on discontinuation of antiretroviral therapy (ART) after stopping breastfeeding in women who do not require it for their own health?

THE ABILITY OF THE HEALTH SYSTEM TO SUPPORT THE NEW PROPOSAL IS NOT GUARANTEED – FAILURE TO DELIVER WILL HAVE DRASTIC CONSEQUENCES

The new proposal is a huge public health experiment and could even be considered a high-stake gamble. While nevirapine toxicity does not seem cumulative, the adherence and programmatic challenges of long-term prophylaxis are untested. Extrapolating data from highly controlled experimental settings to real-world situations is risky, particularly in the absence of a single local pilot project demonstrating successful implementation. At present, not one province has any monitoring or evaluation plan to establish effectiveness.

Perhaps the most pertinent question is whether many South African settings that are still battling to provide single-dose nevirapine or dual therapy are capable of offering this new standard of care. What should not be under-estimated are the demands on the health system of the new proposal. It is anticipated that of the approximately 300 000 HIV-positive pregnant women each year, about half will qualify for ART (for life) for their own health. For these mothers ensuring adherence is the major issue, since their infants will not be receiving nevirapine, and if the mother stops taking ART her infant will be left with no prophylaxis. Mothers not qualifying for ART need to be convinced to exclusively breastfeed for 6 months, and to provide their healthy uninfected infants with a daily dose of a drug (nevirapine) for up to one year. The health service will need to monitor these children at least monthly and ensure that drug supplies do not falter. The benefit of extended nevirapine if a mother starts mixed feeding or forgets to provide the drug for any period is unknown.

A failure to meet any of these requirements will mean that transmission rates of infant HIV could start escalating again. All the problems of ensuring an adequate formula supply that have plagued the PMTCT programme will be replicated with extended nevirapine or ART provision, except that the consequences of a failed supply line will be far worse; while mothers still had to feed their infants and make alternative plans when formula was scarce, it is less likely that they will do so when nevirapine or ARTs runs out at a clinic.

Little consideration seems to have been taken in the new proposal of the myriad of situations where initiation or continuation of breastfeeding of HIV-exposed infants will not be possible, such as mothers returning to work or school, grannies caring for grandchildren, and abandoned or orphaned children.

SOUTH AFRICAN DATA INDICATE REPLACEMENT FEEDING AS AN HIV-PREVENTION STRATEGY IS COST EFFECTIVE DEPENDING ON MORTALITY RATES

During this time of fiscal restraint where healthcare resources are finite, information about both effectiveness and costs is important for policy makers as evidence-based decisions are made. When the issue of costs was raised during the recent breastfeeding consultation, the comment that 'a back of the envelope calculation shows that breastfeeding is much cheaper and more cost-effective than formula and could save R200 million a year' was met with wild applause. This type of feeble evidence to support a major policy shift is unfortunate. Cost, logistics and cultural preferences should be considered in policy decisions.

A new, unpublished modelling exercise using SA data indicates that extended nevirapine is a cost-saving intervention in both typical urban and rural settings and results in improved HIV-free survival. Changing feeding practices to promote breastfeeding is cost-saving in typical rural settings, while promoting replacement feeding in typical urban settings is the most cost-effective feeding option (personal communication, Mandy Maredza, 1 November 2011).

AN HIV-FREE GENERATION CAN NEVER BE ACHIEVED WHILE BREASTFEEDING CONTINUES

The current call and challenge posed by the UNAIDS, and taken up in SA national policy, to eliminate MTCT by 2015 (i.e. zero new HIV infections) is unlikely to be achieved with a single strategy for infant feeding in SA, since at least 6 000 new infections annually can be expected in breastfeeding infants provided extended nevirapine. In reality there will be many more infected children, since implementation will hardly be perfect

because of imperfect behavioural compliance. In the rush to ensure that SA is on a path to decreasing child mortality from all causes it is critical to ensure that recent gains in the number of HIV-exposed children's lives saved through existing interventions, including replacement feeding, are not erased.

WHAT A NEW POLICY SHOULD SAY

A more appropriate infant feeding policy for the country would offer antiretroviral prophylaxis and breastfeeding as the national default option. However, provinces, and perhaps even districts, should be allowed the freedom to decide whether they wish to continue to support the provision of replacement feeding for poor women who meet the AFASS criteria, based on their own circumstances. Whatever choice women ultimately make, much more emphasis needs to be placed on a more supportive environment including adequate counselling, education and support through community health workers.

The availability of antiretroviral prophylaxis is a big step forward for HIV-positive women choosing to breastfeed their infants. It's a crying shame that in introducing this promising intervention, the Department of Health has chosen to take the low road (by insisting on a single option) rather than following the high one where the provision of safe water, sanitation and other resources, and employment would also have been prioritised for all citizens, so that any parents wanting to guarantee a HIV-free future for their child could do so knowing that the choice of replacement feeding could be safely supported too.

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OPINION

HOW SHOULD WE CARE FOR PATIENTS WHO ARE NOT YET ELIGIBLE FOR ART?

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In 2009, there were an estimated 5.6 million people living with HIV in South Africa.[1] Based on a threshold of CD4 <350 cells/µl, it is estimated that around 46% of patients are not yet eligible for antiretroviral therapy (ART).[2] The Department of Health guidelines from 2010[3] have limited recommendations for the care of patients not eligible for ART. There is no guidance on how to develop a package of care or how roles should be assigned between different cadres of staff. It is unclear whether pre-ART care services are currently being offered to large numbers of patients, and it is our opinion that comprehensive guidelines based on effective models of pre-ART care are urgently needed. We believe that this has the potential to reduce morbidity, mortality and transmission and increase long-term retention in care in South Africa.

Currently, rates of retention in pre-ART care are disappointing. A recent review of studies from sub-Saharan Africa found that the median proportion of patients lost to care was 59% between testing and receipt of CD4 counts, 46% between staging and ART eligibility, and 68% between ART eligibility and initiation.[4] Based on the information available, only about 18% of patients who are not yet eligible for ART when diagnosed with HIV remain continuously in care until ART eligibility. Although some patients may enter care elsewhere, others may only present again when unwell and some time after becoming eligible for ART. The median starting CD4 count of patients in South Africa remains well below the level at which patients become eligible for ART,[5-6] and loss to care of ineligible patients is likely to be an important contributor to this. Low CD4 nadir is associated with poor clinical outcomes[7] and increased costs.[8] In response, calls have been made for significantly improved adherence to pre-ART care and monitoring of patients not yet eligible for ART to achieve AIDS strategy goals and reduce the problem of late presentation and initiation of ART.[9]

One reason for low retention in care in the pre-ART period may be lack of availability of comprehensive HIV care services. Patients simply asked to return for repeat CD4 testing after 6 months may be less inclined to return than patients offered a comprehensive service package upon diagnosis. Another reason may be a perception among patients that ART is only necessary as a last resort when becoming sick despite other attempts to remain well while living with HIV. The 2003 World Health Organization (WHO) recommendations for ART in resource-limited settings were to start ART when the CD4 count dropped to ≤200 cells/µl or the patient developed WHO stage 4 illness.[10] This message was interpreted by many as ART only being necessary when one becomes sick. Many people's only experience of ART was seeing it prescribed to sick and late-presenting patients, which served to reinforce the misunderstanding. The 2010 WHO recommendations (adopted by South Africa in August 2011) that all patients with a CD4 ≤350 cells/µl initiate ART[11] were widely welcomed by campaigners. However, there was a word of caution from Vuyiseka Dubula, the General Secretary of the Treatment Action Campaign in South Africa, who explained: '... our communities were made to believe we only needed ART when we were sick, now we have a massive task ahead of us to change deeply entrenched community perceptions' (personal communication). It may take some time for communities to buy into the importance of accessing ART early, and engagement of patients not yet eligible for ART is an ideal forum to begin.

Our own service model in the rural Eastern Cape province of South Africa provides an example of how effective comprehensive HIV services including pre-ART care can be delivered.[12] Outcomes analysis of 1 803 patients initiating ART found that the 270 who had received >6 months pre-ART care started ART at higher CD4 counts than the cohort as a whole (192 v. 123). Notably, receiving >6 months pre-ART care was independently associated with clinically relevant outcomes including a 50% reduction in both mortality and loss to follow-up (LTFU) after starting ART. This was an observational study with some selection bias, as the pre-ART care group were included as a result of being adherent to the pre-ART care programme for at least 6 months. This is more likely to explain the differences in LTFU than those in starting CD4 count and mortality. Data from the private sector in South Africa also show that patients receiving pre-ART care incur lower overall direct costs.[13]

Our service model focuses on engaging patients in peer educator-led community care groups immediately upon testing positive, regardless of eligibility for ART. Groups are run on a weekly basis and are decentralised to local primary healthcare clinics with patients usually choosing

to attend the group nearest their home. Meetings begin with group education around a specific topic facilitated by a peer educator; examples include the importance of ART adherence and the long-term side-effects of ART. Each patient has a paper file held at the clinic, and at each attendance the peer educators record weight and replies to specific screening questions about tuberculosis and sexually transmitted infection (STI), and ask whether there are any other symptoms. Patients with weight loss or any symptoms are referred to the clinic nurse on the same day. Pre-ART patients are prescribed multivitamins or co-trimoxazole and counts of returned pills are used to assess readiness for ART. Peer educators also provide one-on-one counselling for patients preparing for ART.

Groups are fully integrated between those on ART and those who are not yet eligible. This approach has allowed groups to grow quickly and may have reduced HIV-related stigma in the community. Depression is common following a diagnosis of HIV and may be worse in areas with high levels of stigma.[14-15] Depression is associated with both reduced linkage to care and impaired adherence to ART,[16] but can be effectively treated with interpersonal support group therapy.[17] The formation of community support groups of patients who have disclosed their HIV status to the group may prevent depression and improve retention in care in newly diagnosed patients. Incentives to remain in long-term pre-ART care include the provision of prophylactic medication such as isoniazid preventive therapy (IPT), access to screening services such as Pap smears, and inclusion in the social activities associated with joining a community group.

Until universal ART coverage is achieved in South Africa it is likely that resources will predominantly be concentrated on ART delivery, and it is important that pre-ART services are delivered in the most resource-efficient way. In our service model the majority of tasks are performed by lay counsellors. Referrals to nurses are only made for specific clinical reasons (Fig. 1). While our care groups are run on clinic premises, it would be preferable to move them out of the clinic altogether and into the community. Innovative approaches to community-led pre-ART care could be adapted from successful community ART models, which have been shown to reduce the burden on healthcare facilities and achieve higher rates of retention in care.[18]

The WHO recommends at least 6 months of IPT for all HIV-positive adolescents and adults with latent tuberculosis, whether or not on ART.[19] By the end of 2009, only around 85 000 people with HIV had received IPT, representing <0.3% coverage worldwide.[20] ART-ineligible patients are a large group who could be targeted to increase IPT coverage. IPT is an ideal component of pre-ART care as it provides a tangible treatment option and allows monitoring of adherence issues. Distribution of free co-trimoxazole has been shown to decrease loss to follow-up in patients not yet eligible for ART,[21] and it is likely that IPT would have a similar effect. Prescribing IPT in the pre-ART period reduces the risk of overlapping drug toxicities and high pill burden once ART is commenced. Additional benefits are that active tuberculosis must be ruled out before prescribing IPT, which increases active case finding.

Proven HIV prevention interventions to be included in pre-ART care include treatment for sexually transmitted infections after symptom screening by lay counsellors,[22] condom promotion and distribution,[23] contraception[24] and pregnancy planning services.[25] Initiating ART at CD4 counts >350 cells/μl for patients in serodiscordant couples is a highly effective prevention strategy[26] that could be implemented more easily if patients were retained in active pre-ART care.

Improved patient preparation has been shown to improve retention in care rates on ART.[27] Patients who are ineligible for ART at the time of diagnosis may benefit from extended ART preparation, giving them extra time to adjust to the need for lifelong therapy and to attend multiple group education sessions. Early preparation and retention of ineligible patients also allows programmes to respond quickly to changes in eligibility criteria.

There are many challenges to providing comprehensive HIV services and more data are required to inform us of the cost and benefits. It is unlikely that a single model will be appropriate for all settings, and consultation with patients should guide local programme models.

Tasks of peer educators
1. ART adherence counselling
2. CD4 monitoring according to guidelines
3. TB & STI symptom screening
4. Refills of isoniazid & co-trimoxazole
5. Distribution and promotion of condoms
6. Weight monitoring
7. Prolonged psycho-social ART preparation and HIV education
8. Provide nutritional supplementation

Tasks of nurses
1. ART initiation
2. IPT initiation
3. Management of symptomatic patients or those losing weight
4. Pregnancy testing and care
5. Pap smears
6. Blood taking
7. Contraceptive services

Fig. 1. Service package delivered in pre-ART services by various cadres of staff.

Our experience suggests that important features in any setting will be delivering services close to people's homes or jobs, integrating services with those of patients already on ART, and task shifting to appropriate cadres of staff. Our opinion is that no time should be wasted in integrating active management of patients not yet eligible for ART into programme models. We believe this can have a major public health impact by reducing morbidity, mortality and transmission and by increasing long-term retention in care. Furthermore, this can be achieved without overburdening an already stretched healthcare service.

The authors declare no conflicts of interest.

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OPINION

WHY SHOULD WE STILL CARE ABOUT THE STAVUDINE DOSE?

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Current recommendations advise that stavudine be phased out of use. The logistics and cost of switching are significant, and the World Health Organization has forecast that 1.55 million people will still be on stavudine-based antiretroviral therapy by the end of 2012. Stavudine is co-formulated in many countries, is very cheap and effective, and is well tolerated in initial therapy. However, the 40 mg BD dose was associated with considerable long-term toxicity. Several studies suggest that half the original recommended dose has excellent antiviral efficacy with significantly reduced metabolic side-effects. Despite generic tenofovir now being cheaper than zidovudine, tenofovir consumes the majority of adult antiretroviral programme medication budgets in programmes in Africa, where it is used in first-line therapy. Abacavir is far more expensive than zidovudine or tenofovir, and is a major cost driver in paediatric programmes with access to abacavir-based first-line treatment. Low-dose stavudine may offer the only cheaper (and possibly as effective and safe) alternative to programmes grappling with limited financial resources.

The UNAIDS 2010 global report estimated that 20 million adults and 2.3 million children in sub-Saharan Africa are HIV-infected,[1] of whom 6.7 million and 518 000, respectively, are currently on antiretroviral therapy (ART).[2-3] In the late 1990s stavudine was selected as the first-line antiretroviral of choice for adults and children in the developed world because it is extremely safe in the short term, in contrast to the toxicity and intolerance associated with zidovudine. In fact, stavudine was regarded as so safe that the original recommended dose for adults was 40 mg twice daily (BD), even though a number of randomised clinical trials had shown that it was equally effective at a dose of 20 mg BD.[4-7] Forty milligrams BD was chosen fairly arbitrarily over 20 mg BD after the Stavudine 019 trial[8] chose to test 40 mg twice daily rather than a lower dose, and found that stavudine had minimal short-term toxicity at that dose. The children's dose was extrapolated from the adult dose using data from paediatric pharmacokinetic studies that showed that an oral dose of 1 mg/kg/dose twice daily in children weighing under 30 kg results in plasma exposure similar to that of an adult over 60 kg taking 40 mg twice daily, and that an oral dose of 0.5 mg/kg/dose twice daily in children results in plasma exposure similar to that of an adult over 60 kg taking 20 mg twice daily.[9-10] No virological outcomes were reported in those paediatric pharmacokinetic studies.

ART-associated lipoatrophy was first described in 1998,[11] 4 years after the introduction of stavudine as an antiretroviral agent. By 2002, lipoatrophy was recognised as a frequent delayed adverse effect of stavudine.[12] A large number of studies have since shown a causal link with nucleoside reverse transcriptase inhibitor exposure, particularly didanosine, stavudine and zidovudine, of which stavudine shows the strongest link. The effect of stavudine in causing lipoatrophy appears to be strongly dose-related, and in 2007 the World Health Organization advised that the recommended adult dose be lowered from 40 to 30 mg BD.[13-14] The children's dose was not lowered, however, because lipoatrophy was believed to be uncommon in children (although this assumption is currently being refuted). The lipoatrophy caused by stavudine typically does not manifest until 18 - 24 months of therapy, and even then may go unnoticed or may not be taken seriously by the health care provider for months or years as it slowly progresses. The typically long delay between drug initiation and manifestation of toxicity may have contributed to the delay in the global response in reducing the recommended dose from 40 to 30 mg BD. In the meantime, stavudine has gained a bad reputation due to the stigmatising effect of lipoatrophy, which resolves slowly and poorly. However, evidence accumulated over the last 15 years suggests that stavudine given at the equivalent of 20 mg BD leads to a significantly lower rate of lipoatrophy and of other mitochondrial adverse effects.[13,15-17]

The logistics and cost of switching all antiretroviral-treated individuals to non-stavudine therapy is significant. Generic tenofovir costs 6 times more per month than stavudine, while tenofovir co-formulated with emtricitibine costs 4 times more than a month's supply of stavudine and lamivudine combined.[18] In

addition, the use of tenofovir, which requires additional renal function monitoring, substantially increases the programme costs of safety monitoring.[19] Taking the costs of toxicity management into account, the cost-effectiveness ratio (measured in cost per year of life saved) of tenofovir is double that of stavudine (when ART is initiated at 350 CD4 cells/µl in a one-line setting) with similar 5-year survival (89% v. 87%) when using the incidence of stavudine toxicity associated with 40 mg BD.[20] Since the incidence of late adverse events due to stavudine is likely to be substantially reduced by using a more appropriate dose (20 mg BD), the advantages of tenofovir over stavudine may begin to dwindle. Given the escalating number of people being initiated on ART and the stress this places on existing ART programmes, it is unlikely that switching stable patients from stavudine to an alternative will be a high priority. In addition, for those initiated on alternative ART regimens, stavudine will probably remain an important second-line agent, especially in patients unable to tolerate or have affordable access to zidovudine or abacavir. Using stavudine in first-line therapy further preserves tenofovir for second line. Both the World Health Organization and the Clinton Health Access Initiative have forecast that approximately 1.4 million adults (18% of adults on ART) and 150 000 children (26% of children on ART) will still be on stavudine-based ART by the end of 2012[3] (personal communication, Joanna Sickler, Clinton Health Access Initiative). The authors therefore advocate a head-to-head randomised controlled trial comparing stavudine 20 mg BD with tenofovir 300 mg once daily, powered to show non-inferiority in adults.

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ORIGINAL ARTICLE

IDENTIFYING MISSED OPPORTUNITIES FOR EARLY INTERVENTION AMONG HIV-INFECTED PAEDIATRIC ADMISSIONS AT CHRIS HANI BARAGWANATH HOSPITAL, SOWETO, SOUTH AFRICA

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Background and design. HIV is a major contributor to childhood morbidity and mortality in South Africa. We describe HIV prevalence, disease profile, outcome and missed opportunities for early intervention in a cohort of HIV-infected children admitted to Chris Hani Baragwanath Hospital's general paediatric wards between 1 October 2007 and 31 December 2007.

Results. Of 1 510 admissions, 446 (29.5%) were HIV infected. Many children (238, 54.1%) were newly diagnosed in hospital and most had advanced HIV disease (405, 92%). The principal admission diagnoses were pneumonia (165, 37.5%), gastro-enteritis (97, 22%), sepsis (86, 19.5%) and tuberculosis (92, 21%). Of children identified as HIV infected before admission, 128/202 (63.4%) were not accessing antiretroviral treatment (ART), although 121/128 (94.5%) met ART eligibility criteria. Of 364 ART-naïve eligible children, only 15 (4.1%) were commenced on ART as inpatients. Problems with PMTCT implementation in infants under 6 months (*N*=166) included lack of maternal antenatal HIV testing (51, 30.7%); poor uptake of maternal/infant nevirapine prophylaxis (60, 36.2%); limited use of co-trimoxazole (CTX) prophylaxis (44/147, 29.9%); and delayed infant HIV polymerase chain reaction testing (98/147, 87.5%). Of infants known to be HIV infected prior to hospitalisation, 37/51 (73%) had not initiated ART. The in-hospital case fatality rate (CFR) among HIV-infected children was triple that of the combined HIV-uninfected, exposed and unknown group (12% v. 3.6%). Infants <12 months of age accounted for 73.6% of all HIV-related deaths (CFR 17.1%).

Conclusions. HIV remains highly prevalent and contributes to significant in-hospital mortality. Missed opportunities for PMTCT, HIV diagnosis and ART initiation are frequent. Interventions to optimise paediatric HIV outcomes should target maternal HIV diagnosis, early infant diagnosis, uptake of CTX prophylaxis and prompt initiation of ART, especially among infants. Hospitalised ART-eligible children should be prioritised for inpatient initiation of ART.

South Africa has 5.6 million people living with HIV, including approximately 280 000 children[1] who suffer disproportionate morbidity and double the mortality of their HIV-uninfected counterparts.[2,3] Past progress in reducing national child mortality has been reversed by paediatric HIV, with under-5 mortality rates (U5MR) increasing from 56 to 67 deaths per 1 000 live births between 1990 and 2008.[4] Much of the increase in the U5MR can be accounted for by deaths in young HIV-infected infants, many of whom progress rapidly to AIDS and death from opportunistic infections, without early initiation of antiretroviral therapy (ART).[5,6]

South Africa introduced the prevention of mother-to-child transmission (PMTCT) and ART programmes nationwide in 2001 and 2004, respectively. The national PMTCT guidelines at the time of this study (2007) recommended HAART for pregnant women with a CD4 count <200 cells/µl or zidovudine (AZT) from 28 weeks' gestation plus intrapartum single-dose nevirapine

(sdNVP) at CD4 counts >200 cells/µl. All infants were scheduled to receive sdNVP at delivery. The policy for early infant diagnosis (EID) at the time recommended HIV polymerase chain reaction (PCR) testing at 6 weeks of life, and for breastfed babies a repeat HIV PCR test 6 weeks after complete cessation of breastfeeding. ART initiation was recommended for any child with clinically advanced disease (WHO HIV stage 3 or 4) or immunological compromise (CD4 <20% in children less than 18 months of age and CD4 <15% in children over 18 months).[7] Despite national implementation of these programmes, coverage and uptake of PMTCT, EID and paediatric ART programmes were highly variable between provinces.[8] More recently, improved coverage of these interventions has been achieved; however, many infants miss entry points for the PMTCT programme and routine HIV testing. Others may be identified but are lost from the system or become ill before ART is initiated.[9] These children typically present to hospital with advanced HIV disease and consequently have high mortality rates.[10,11] Chris Hani Baragwanath hospital (CHBH) is South Africa's largest public sector hospital, delivering care to the burgeoning urban and low-income population of Soweto, Johannesburg. Paediatric HIV prevalence at CHBH (described in two previous studies prior to the implementation of PMTCT programmes) rose from 3% to 19%[12] to 29%[13] between 1992 and 1996. Over the same period the proportion of paediatric in-hospital mortality accounted for by HIV increased dramatically from 6.7% to 46.1%.[12] Similar trends in HIV prevalence and HIV-related mortality in other South African hospitals have been reported from a national data collection programme, Child PIP.[10,11] We report on paediatric HIV period prevalence, disease profile and outcome of children admitted to CHBH in the last quarter of 2007, several years after introduction of national PMTCT and paediatric HIV management programmes. In addition we describe missed opportunities for HIV prevention, diagnosis and medical intervention among this cohort of HIV-infected children.

METHODS

Ethics. The study was approved by University of the Witwatersrand Human Research Ethics Committee (reference No. M080202).

Study site. The study was undertaken at CHBH, Soweto, Johannesburg, in the Gauteng province of South Africa. This 2 964-bed referral hospital is the only public hospital serving approximately 3.5 million Sowetans and accepts referrals from local primary health care clinics, regional hospitals in Gauteng and neighbouring provinces of South Africa. In 2010, the estimated HIV prevalence in Gauteng province was 10.5%.[14] The province's health sector, although challenged by high TB and HIV prevalence, is relatively well resourced and staffed when compared with other areas of South Africa. The hospital and all referring institutions follow national PMTCT and HIV management guidelines. A dedicated paediatric HIV clinic on the hospital premises (Harriet Shezi clinic) provides outpatient services to more than 3 500 HIV-infected children and the Perinatal HIV Research Unit (PHRU) provides PMTCT support in the Soweto area.

Study design and sampling. A cross-sectional retrospective review of all children (from birth to 14 years of age) hospitalised in the general paediatric wards between 1 October 2007 and 31 December 2007 was performed. Newborns with reactive HIV PCR test results during their stay in the neonatal unit were not included in this study, unless they were subsequently admitted to the general paediatric wards during the 3-month study period. Patient admission numbers and profile over this 3-month period did not differ significantly from the preceding three-quarters of 2007. Two populations were of interest (Fig. 1). Firstly, admission register lists of all hospitalised children were used to determine HIV status (collected from laboratory and/or hospital records) and calculate HIV period prevalence. Secondly, individual patient records for children identified as HIV infected were reviewed. Monthly paediatric mortality reports were used to calculate in-hospital mortality. Self-reported data on PMTCT coverage were analysed only for HIV-infected infants less than 6 months of age, to minimise information recall bias. For analysis of missed opportunities in provision of co-trimoxazole (CTX) prophylaxis and uptake of EID, infants <6 weeks were excluded.

Determination of HIV status. All HIV tests were performed by the accredited National Health Laboratory Service (NHLS). A reactive HIV-DNA PCR test confirmed HIV-infected status in children under 18 months. A reactive HIV enzyme-linked immunosorbent assay (ELISA) confirmed HIV-infected status in children older than 18 months of age. Mothers' self-reported HIV status (as documented in hospital records) was used. Four definitions were used: HIV **uninfected** refers to the infant or child being confirmed HIV uninfected; HIV **infected** refers to the infant or child being confirmed HIV infected; if the mother's status was reportedly HIV infected and her infant had no HIV PCR result, the infant's status was classified as HIV **exposed**. If maternal HIV status was unknown or uninfected and the child had no HIV test result in laboratory or folder records, the status was classified as HIV **unknown**.

Case definitions and reference classifications. In cases where laboratory confirmation was not obtained, a working diagnosis was based on clinical suspicion and the World Health Organization (WHO) published case definitions[15] for the following conditions: *Pneumocystis jiroveci* pneumonia (PCP),[16,17] pulmonary tuberculosis (pTB), cytomegalovirus (CMV) pneumonitis or disseminated disease, septicaemia, meningitis and urinary tract infection. HIV disease severity was assessed using the WHO clinical staging system for children[15] and nutritional status using the WHO 2006 growth standards[18] for calculation of z-scores in children under 60 months of age. Calculation of ART eligibility was based on the South African national guidelines (2005)[7] at the time of the study, using immunological (CD4% <20% under 18 months of age; CD4% <15% above 18 months of age) and clinical criteria (WHO stage 3 and 4 disease) only. The WHO and the South African Department of Health published extensively revised guidelines for child ART initiation in 2010.

Statistical analysis. Data were analysed in SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Crude HIV period prevalence was calculated from ward records

as total HIV-infected admissions/total admissions. Case fatality rates in the HIV-infected and combined HIV-uninfected, HIV-unknown and HIV-exposed groups were calculated from total number of deaths/total number of admissions for each group. For the PMTCT sub-analysis, frequency calculations were performed for maternal HIV status, sdNVP exposure, CTX prophylaxis and place of birth. The uptake of PMTCT interventions was then compared by maternal HIV status grouping using the chi-square test. A *p*-value of <0.05 was considered to be statistically significant.

RESULTS

HIV PREVALENCE

Of 1 510 children admitted during the 3-month study period, 446 (29.5%) were HIV infected, 780 (51.7%) were HIV uninfected, 57 (3.8%) were HIV exposed and 227 (15%) were of unknown HIV status (Fig. 1). For the 446 children identified as HIV infected, 440 (98.7%) individual patient records were located.

HIV-INFECTED CHILDREN: PROFILE OF STUDY POPULATION

Table I outlines the demographic and disease profile of the 440 HIV-infected children. Almost 93% had advanced HIV disease (WHO stage 3 or 4) and 55.3% of children <5 years of age had severe malnutrition. Across all age groups, 225/320 children (70.3%) had severe immune suppression.

REASON FOR HOSPITALISATION

Infectious disease was the principal reason for hospitalisation (Table I). Lower respiratory tract infections (including presumed PCP and presumed *Cytomegalovirus* pneumonitis) accounted for the majority of admissions, with the highest prevalence among infants. One hundred and ten children (25%) had a confirmed bacterial, viral or fungal infection during their hospital admission. *Streptococcus pneumoniae* and CMV were the most common bacterial and viral pathogens isolated.

MISSED OPPORTUNITIES

Prevention of mother-to-child transmission of HIV

Self-reported maternal HIV status and sdNVP exposure were analysed in HIV-infected infants under the age of 6 months (*n*=166). Uptake of CTX prophylaxis and EID were analysed only for infants >6 weeks of age (*n*=147) so as to be consistent with programme guidelines. Fig. 2 highlights the multiple levels of missed opportunities for PMTCT implementation in infants (<6 months of age) whose mothers reported their status as HIV infected versus HIV uninfected versus HIV unknown. Lack of maternal antenatal HIV testing was documented among 51/166 (30.7%) mothers. There was poor uptake of maternal/infant NVP prophylaxis (60/166, 36.2%). Usage of CTX prophylaxis was limited (44/147, 29.9%) and in most cases infant HIV PCR testing was delayed or lacking (98/147, 87.5%). There was no association between place of birth (CHBH versus clinic/other hospital/home) and access to NVP or CTX (p=0.1288 and p=0.5818, respectively). Of the 147 HIV-infected infants 6 weeks - <6 months of age, 51 (34.7%) were known to be HIV infected while the remainder, 96 (65.3%), were newly diagnosed (i.e. had not previously had HIV PCR testing) at the time of hospital admission. Sixty-seven (45.6%) of the 147 infants received no PMTCT interventions at all. Only 20/147 (13.6%) infants received all recommended interventions, i.e. NVP and CTX and EID. Table I reflects additional missed opportunities for the provision of CTX prophylaxis among other categories of the study population.

HIV diagnosis and antiretroviral therapy (ART) eligibility and uptake

Most children, 238/440 (54.1%), were newly diagnosed at the time of hospitalisation at CHBH. Newly diagnosed children were younger than those already known to be HIV infected (median 6 v. 12 months of age) (p=0.001). Children known to be infected and already on ART had a median treatment duration of 2 months and were significantly older than ART-naïve children (median age 38 v. 7 months) (p<0.0001). Of children known to be infected but not on ART (128/202, 63.4%), nearly all (121/128, 94.5%) were eligible for ART based on advanced disease stage. Of 364 ART-naïve eligible children, only 15 (4.1%) were commenced on ART as inpatients (Fig. 1). Table II compares eligibility for ART with actual ART uptake among children who died.

OUTCOME OF HOSPITALISATION

Median duration of hospital stay was 7 days (interquartile range (IQR) 4 - 10.) Fifty-three children died (Table I) with a median duration of stay before death of 4 days (IQR 2 - 7.8). Only 13 children (3.0%) were admitted to an ICU or underwent mechanical ventilation in the high-care area of the acute admissions ward. Ten of these 13 children (76.9%) survived to hospital discharge.

Fifty-eight per cent of all paediatric deaths (53/91) occurred among the HIV-infected group. The overall case fatality rate in the HIV-infected children was 53/440 (12.0% (95% confidence interval (CI) 9.2 - 15.5%)). In contrast, the case fatality rate in the HIV-uninfected, HIV-exposed and HIV-unknown group over the study period was 38/1 064 (3.6% (95% CI 2.5 - 4.9%)). The highest case fatality rate by age group was in infants aged less than 12 months (Table I). The most prevalent causes of death included pneumonia/suspected PCP (18/53, 34%), TB (14/53, 26.3%) and gastro-enteritis (5/53, 9.4%). The inpatient mortality rate did not differ significantly between children receiving ART at the time of hospitalisation (7.9%, 6/76) versus ART-naïve children (13.6%, 47/345) (p=0.17, odds ratio 0.54).

DISCUSSION

HIV PREVALENCE

This paper reports the first published data on paediatric HIV prevalence, disease profile and outcome at CHBH subsequent to widespread implementation of PMTCT and paediatric HIV management programmes. The HIV period prevalence of 29.5% was almost identical to that found in 1996. However, the true HIV prevalence remains unquantified, since both cohorts had large numbers of untested children. Several years after national roll-out of PMTCT and ART programmes, there is therefore little evidence of a decreasing impact of paediatric HIV at CHBH. Possible explanations for this could include increasing antenatal HIV prevalence in Gauteng province (15.5 - 29.8% between 1996 and 2009)[19] with more vertical infections; failure of sdNVP PMTCT regimens; the

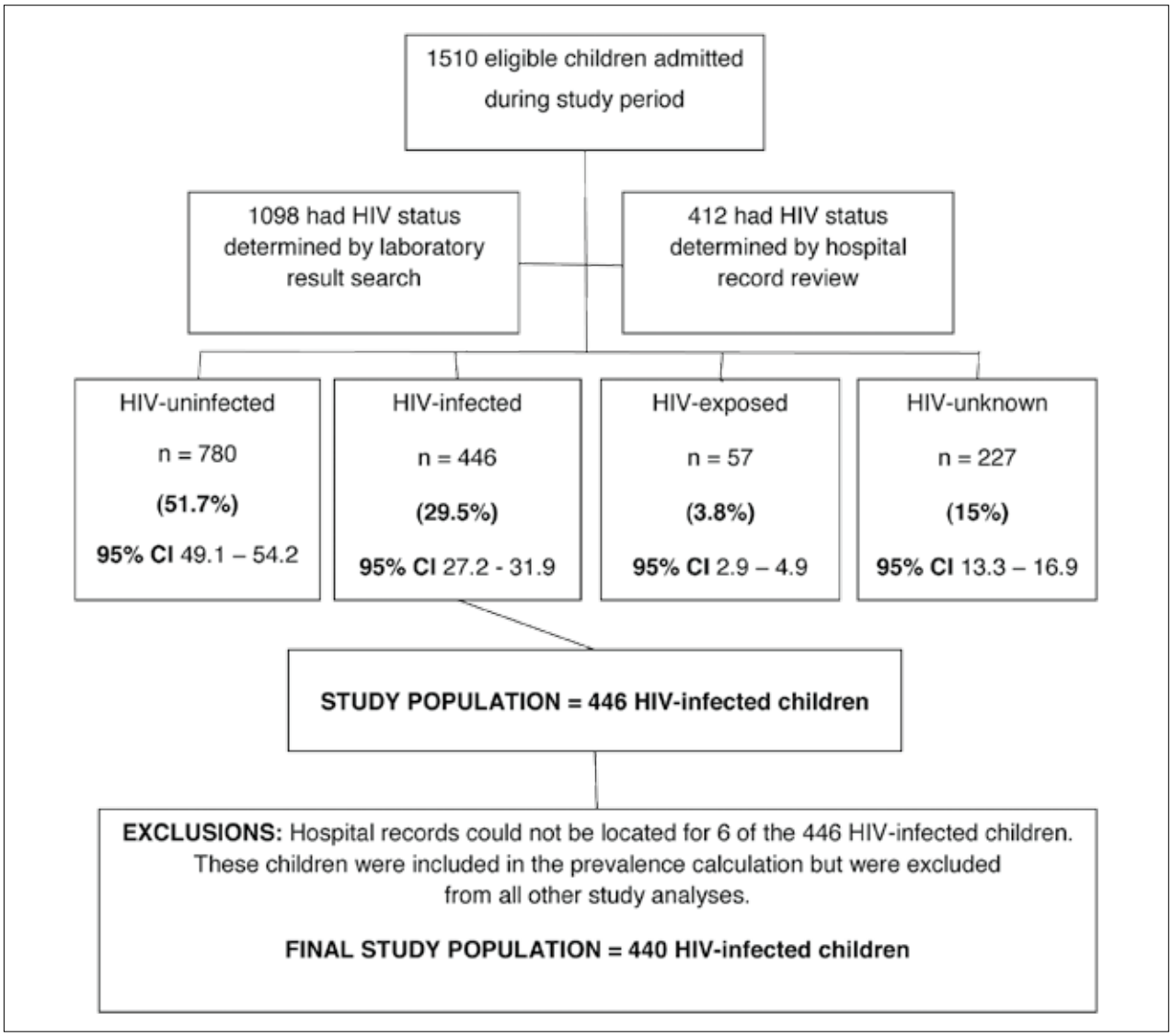

Fig. 1. Determination of HIV prevalence and study population and ART uptake among 440 HIV-infected children.

possibility of an even higher (undocumented) peak paediatric HIV prevalence reached between 1996 and 2007; poor PMTCT coverage; improved survival rates (particularly in older HIV-infected children on ART); and the establishment of a dedicated paediatric HIV clinic at CHBH (pooling children with complicated HIV disease).

MISSED OPPORTUNITIES

Prevention of mother-to-child transmission of HIV

A major limitation of the chosen study design is possible maternal recall bias regarding PMTCT interventions. In addition, reported maternal HIV status could not be verified in all cases. Healthcare workers' documentation of PMTCT interventions was poor. In order to decrease missed opportunities among HIV-exposed infants, all PMTCT interventions should be clearly explained to caregivers and documented in all patient records, especially the infants' Road to Health Card (RTHC). This is the most important linkage and communication tool for paediatric healthcare providers, especially when children access care at multiple facilities.

Uptake of PMTCT interventions was poor, with almost half of infants under 6 months of age receiving no PMTCT interventions at all. Of particular concern was the large proportion of mothers who reported their status as HIV uninfected (15.1%) or HIV unknown/untested (30.7%). There are several possible explanations for the 15.1% of mothers who reported their status as HIV uninfected: a negative test in early pregnancy with subsequent seroconversion before delivery (3% reported seroconversion of pregnant women);[20] postnatal HIV infection with breastfeeding transmission; or fear of stigmatisation after disclosure of HIV status. Antenatal identification of HIV-infected pregnant women is the gateway to a successful PMTCT programme, since all other interventions rely on this key step. Opt-out antenatal HIV testing, and repeat HIV testing late in pregnancy, during labour and at immunisation services, would maximise identification of HIV-infected mothers. In addition, clear recording of maternal HIV status on the infant's RTHC would increase awareness of HIV exposure and hopefully prompt prescription of CTX and uptake of infant HIV PCR testing. This would allow for earlier infant diagnosis and rapid ART initiation, resulting in improved infant outcomes.

The poor uptake rates reported for sdNVP and CTX prophylaxis in this study are alarming. Possible factors contributing to this problem include mothers who test

TABLE I. DISEASE PROFILE OF HIV-INFECTED CHILDREN (*N*=440)	
Gender	
Male	234 (53.2%)
Female	206 (46.8%)
Age category	
≤11 months	228 (51.8%)
12 - 35 months	85 (19.3%)
36 - 59 months	29 (6.6%)
≥5 years	98 (22.3%)
Timing of HIV diagnosis	
Newly diagnosed	238 (54.1%)
Known HIV-infected	202 (45.9%)
WHO HIV stage	
I	3 (0.7%)
II	29 (6.6%)
III	188 (42.7%)
IV	220 (50%)
Median (IQR) weight-for-age z-score (WAZ)* (*n*=342)	
≤11 months (*n*=228)	-3.53 (-4.59 - -2.44)
12 - 35 months (*n*=85)	-2.69 (-3.60 - -1.43)
36 - 59 months (*n*=29)	-1.89 (-3.03 - -1.41)
No. 0 - 59 months with WAZ -3 - -2 (%)	56 (16.4)
No. 0 - 59 months with WAZ <-3 (%)	189 (55.3)
Median (IQR) CD4 percentage by age group† (*n*=320)	
≤11 months (*n*=155)	18.6 (12.8 - 28)
12 - 35 months (*n*=57)	16.2 (9.6 - 23)
36 - 59 months (*n*=23)	9.1 (6.3 - 15.3)
≥5 years (*n*=85)	8.0 (4.5 - 14.7)
Median (IQR) CD4 absolute count (cells/µl) by age group† (*N*=320)	
≤11 months (*n*=155)	700 (361 - 1294)
12 - 35 months (*n*=57)	565 (422 - 909)
36 - 59 months (*n*=23)	414 (197 - 863)
≥5 years (*n*=85)	171 (45 - 379)
Severe immunosuppression (all ages)‡	225/320, 70.3.%
No. (%) of children receiving CTX prophylaxis	
All HIV-infected infants <12 months of age	73/228 (32%)
Known to be HIV-infected and not yet on ART	86/127 (67.7%)
Known to be HIV-infected and on ART <12 months	53/55 (96.4%)
Reason for hospitalisation	
Pneumonia	165 (37.5%)
Gastro-enteritis	97 (22%)
Tuberculosis (including pTB + extrapulmonary TB)	92 (21%)
Sepsis (including septicaemia (*n*=48), meningitis (*n*=23), and urinary tract infection (*n*=15)	86 (19.5%)
Outcome of hospitalisation	
Discharged alive	319 (72.5%)
Died	53 (12%)
Transferred to a step-down hospital facility	68 (15.5%)
Deaths by age group (case fatality rate§, 95% CI) by age group (*n*=53)	
≤11 months	39 (17.1%, 12.5 - 22.6)
12 -35 months	4 (4.7%, 1.3 - 11.6)
36 - 59 months	2 (6.9%, 0.8 - 22.8)
≥5 years	8 (8.2%, 3.6 - 15.5)

* Calculation of WAZ scores was only done for children 0 - 59 months of age (*n*=342).
†CD4-positive T-cell counts and percentages were analysed in a subgroup of the study population who had had CD4 testing at any point 1 month before, during or after hospitalisation (*n*=320/440).
‡Proportion of children with severe immunosuppression was defined using WHO (2007) criteria[11] as follows: <11 months of age, CD4 <25%; 12 - 35 months, CD4 <20%; 36 - 59 months, CD4 <15%; >5 years, CD4 <200 or <15%.
§Case fatality rate was calculated as total number of deaths per age group/total number of admissions per age group.

at a clinic and then deliver in hospital; 'cryptic' written communication between health facilities about patients' HIV status in an attempt to maintain confidentiality; women's reluctance to disclose HIV status due to stigma; and health care workers' reluctance to offer HIV testing or to enquire about HIV status. Failure to provide CTX prophylaxis represents a major missed opportunity to prevent early mortality from PCP, as demonstrated in this cohort with 15% of deaths ascribed to PCP. Since 2007 there has been considerable improvement (but

TABLE II. ELIGIBILITY FOR ART VERSUS ART ACCESS IN 53 HIV-INFECTED CHILDREN WHO DIED

Age categories	No. (%) with immunological criteria qualifying for ART*	No. (%) with clinically advanced disease (stage 3 or 4) qualifying for ART	No. (%) of eligible children actually receiving ART at time of death
All deaths (*n*=53)	18/27† (66.7)	50/53 (94.3)	6/50 (12)
Deaths <18 months (*n*=40)	10/17† (58.8)	38/40 (95)	6/38 (15.8)
Deaths >18 months (*n*=13)	8/10† (80)	12/13 (92.3)	0/12 (0)

*CD4 percentage <20% for children <18 months old, CD4 <15% for children >18 months old.
†The denominators differ from the overall group denominators because only a proportion of the 53 HIV-infected children who died had recent CD4 percentage results available.

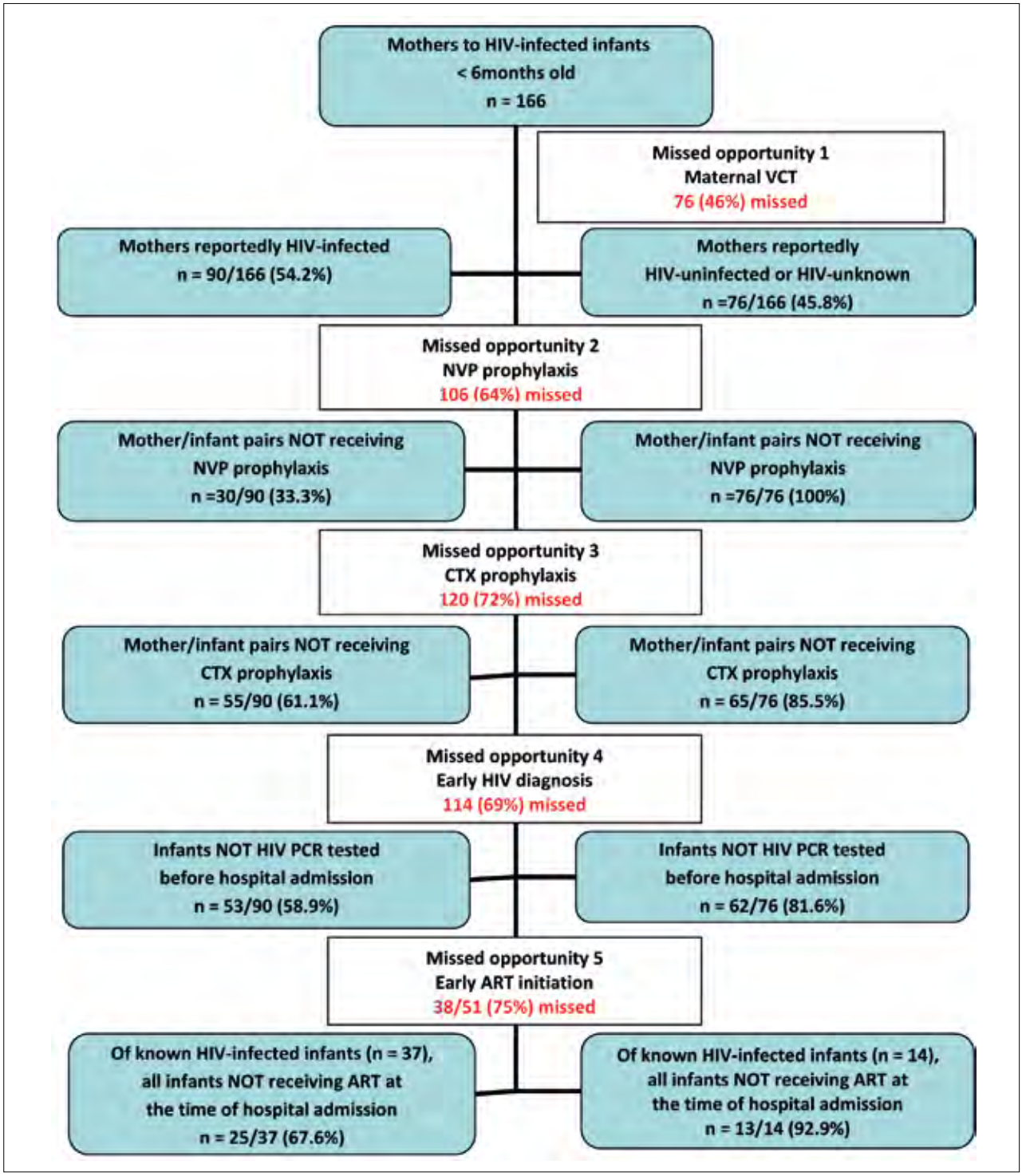

Fig. 2. Missed opportunities for PMTCT implementation, CTX prophylaxis, EID and ART initiation in infants (<6 months).

increased complexity) in PMTCT regimens. However, these changes will be not be effective unless universal uptake of PMTCT, CTX prophylaxis and early infant diagnosis is achieved. High loss to follow-up of HIV-exposed infants remains a major problem in the PMTCT programme, both at CHBH and at a national level as reported by previous studies.[21,22]

HIV diagnosis and antiretroviral therapy eligibility and uptake

Despite calls for universal testing, 15% of children admitted to CHBH had no documentation of HIV exposure status or HIV testing. In a subgroup (3.8%) noted to be HIV exposed and symptomatic (requiring hospitalisation), HIV PCR testing was not performed. Although usually recommended at 4 - 6 weeks of age, immediate HIV PCR testing should be performed in symptomatic HIV-exposed infants regardless of age so as to expedite ART initiation.[23] Maternal HIV status, PMTCT interventions and results of HIV PCR testing should be routinely enquired about at every infant's health care visit. Similarly, any child who presents with malnutrition must be screened for HIV, as reflected in this cohort, where 54.1% of children were newly diagnosed in hospital despite a background of malnutrition (in 72%) and previous hospitalisations. However, rapid HIV tests (used for screening or to establish HIV exposure status in infants) have high false-negative rates, especially among young infants.[24]

Despite growing awareness of the benefits of paediatric ART at the time, ART coverage of these hospitalised children was low (83% of eligible children were not accessing ART). The short treatment duration and older age of children on ART at CHBH highlights the fact that few children and even fewer infants had the benefit of early ART initiation. To ensure timeous and equitable access for children, ART must be initiated and monitored at entry levels of the health care system (primary health care clinics). Furthermore, hospitalised, symptomatic HIV-infected children should be fast-tracked for inpatient ART initiation. This measure should be strongly considered for every ART-eligible hospitalised child, and especially for infants ≤12 months of age, who are at highest risk of disease progression and death.[23] In our study setting (a hospital with an established paediatric ART service), only 4.1% of ART-naïve, ART-eligible children had treatment commenced as an inpatient, despite weekly ward visits by clinicians from the onsite HIV clinic. In addition, none of those commenced on ART as inpatients were infants, despite this being the age category with the highest case fatality rate. We postulate that multiple hurdles to inpatient ART initiation exist, such as parental illness or death, complex social circumstances, advanced HIV disease and clinician inexperience with or reluctance to commence HAART. Despite these obstacles, clinicians need to be more aggressive in identifying and treating ART-eligible infants and children during ward admission.

OUTCOME OF HOSPITALISATION

Infectious diseases such as diarrhoea, TB and PCP – which are preventable by immunisation, prophylaxis or early ART initiation – accounted for all of the deaths. Dual or multiple concurrent infections are well recognised among HIV-infected children with pneumonia. There were no documented cases in this cohort, but this may simply reflect the lack of aggressive screening for multiple respiratory pathogens. CMV was demonstrated on postmortem specimens from several patients. It was difficult to distinguish CMV infection from disease, additional laboratory testing was limited and ganciclovir treatment was not readily accessible at CHBH at the time of the study. The contribution of CMV disease to the burden of pneumonia and deaths in this cohort is therefore uncertain.

During the study, only 3% of HIV-infected children were admitted to ICU/high care; however, they demonstrated a 76.9% survival rate. Data on ICU candidate selection policies, duration of stay, incidence of complications and long-term morbidity and mortality compared with that of HIV-negative children admitted to ICU were not available. With expanding ART access and improved HIV outcomes, institutional policies for the admission of HIV-infected children to paediatric ICU facilities in South Africa should be reviewed.

AT CHBH from 1992 to 1996 the proportion of paediatric in-hospital mortality accounted for by HIV increased from 6.7% to 46.1% and in 2007 (this study) to 58%. This figure shows striking concordance with the 2008 South African statistics from the *Countdown to 2015* report, which attributed 57% of under-5 mortality to HIV/AIDS (current HIV-attributable mortality is 46%).[25] Despite implementation of PMTCT and paediatric ART programmes, HIV prevalence and in-hospital case fatality rates (among HIV-infected children under 5 years of age) have remained static between 1996 and 2007. Over the same period, however, mortality among uninfected children has declined. HIV-infected children at CHBH are at a 3-fold increased risk of death compared with HIV-uninfected, HIV-exposed and HIV-unknown children. Hospitalised HIV-infected infants under 12 months of age at CHBH are a particularly vulnerable group with a high case fatality rate (17.1%), and should be prioritised for early ART initiation.

ART status at the time of hospitalisation did not significantly impact on inpatient mortality; however, the median duration of ART in the treatment group was only 2 months, reducing the likelihood of treatment survival benefit. Early hospitalisations after initiation of ART are a well-documented phenomenon,[26] but no immune reconstitution inflammatory syndrome (IRIS) or ART adverse event-related admissions were documented in this cohort. It is possible that these conditions were unrecognised and thus under-reported owing to lack of experience of hospital staff at that time.

This study has several limitations that may impair its generalisability: a retrospective study design; small sample size; a short study period; and lack of an HIV-uninfected comparison group. The large percentage of children (15%) with unknown HIV status also limits the accuracy of the HIV prevalence data. Missed opportunities among HIV-exposed, status unknown

infants were also not captured. However, the data provide a 'snap-shot' of HIV impact at a large referral hospital and may reflect commonly encountered challenges to paediatric HIV care provision. Experiences after introduction of PMTCT and ART at CHBH may provide insights for other institutions struggling to implement best practice guidelines for paediatric HIV care.

CONCLUSION

HIV remains highly prevalent and contributes to significant in-hospital mortality at CHBH. Multiple missed opportunities for PMTCT, HIV diagnosis and ART initiation were identified, demonstrating the need to monitor and assist with HIV guideline implementation at service delivery level. Interventions to optimise paediatric HIV outcomes should target maternal HIV diagnosis, early infant diagnosis, uptake of CTX prophylaxis and prompt initiation of ART, especially among infants. Hospitalised ART-eligible children should be prioritised for inpatient initiation of ART. Ongoing surveillance of HIV prevalence, disease profile and mortality at CHBH and other hospitals may be used to identify programmatic problems, plan service improvement interventions and measure progress towards the millennium goal of a two-thirds reduction in U5MR by 2015.[27]

Declaration of competing interests. The authors declare that they have no competing interests.

Authors' contributions. All authors contributed to study design, data interpretation and critical revision of the manuscript. AD performed the data collection, data analysis (supervised by AG) and drafted the manuscript.

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ORIGINAL ARTICLE

PREVALENCE OF POSTNATAL DEPRESSION AND ASSOCIATED FACTORS AMONG HIV-POSITIVE WOMEN IN PRIMARY CARE IN NKANGALA DISTRICT, SOUTH AFRICA

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Background. The prevalence of postpartum depression in South Africa is high, but there is lack of prevalence data on postnatal depression among HIV-infected women.

Aim. The aim of this study was to determine the prevalence of depressed mood and associated factors in postnatal HIV-positive women in primary care facilities in Nkangala district, Mpumalanga, South Africa.

Methods. This cross-sectional study was carried out on 607 HIV-positive postnatal women in 48 primary health care clinics and community health centres in Nkangala district. Postnatal women were recruited by systematic sampling (every consecutive patient over a period of 2 months). Demographic and other data were obtained from all the women who responded to a questionnaire in the local language on male involvement, HIV test disclosure, delivery and infant profile, infant HIV diagnosis, stigma, discrimination, postnatal depression, attendance of support groups and social support.

Results. Overall, 45.1% of women reported a depressed mood in the postnatal period. Depressed mood in a multivariable analysis was significantly associated with internalised stigma (odds ratio (OR) 1.12, 95% confidence interval (CI) 1.05 - 1.19; *p*=0.000), discrimination experiences (OR 1.22, CI 1.03 - 1.46; *p*=0.023), lack of social support (OR 0.86, CI 0.74 - 0.99; *p*=0.037) and having had an STI in the past 12 months (OR 2.22, CI 1.21 - 4.04; *p*=0.010). There were no statistically significant correlations between the Edinburgh Postnatal Depression Scale (EPDS) scores of the women and age, marital status, level of education, employment status and number of own children.

Conclusion. Depressed mood is common among HIV-positive postpartum women. This is significantly associated with lack of social support, stigma and discrimination. Routine screening to identify those currently depressed or at risk of depression should be integrated into postnatal care settings to target those most needing intervention.

Postnatal depression is the most frequently recognised mental disorder after delivery and generally begins within 4 - 6 weeks after childbirth.[1] The symptoms include low mood, tiredness, insomnia, lack of energy, forgetfulness, irritability and poor functioning. The occurrence of depressive illness after childbirth can be detrimental to the mother, her marital relationship and her children and can have adverse long-term effects if not treated.[2] In addition, maternal postpartum depression poses significant risks for mother-child interaction and long-term infant outcomes.[2]

Although the prevalence of postpartum depression in South Africa is high (34.7%), there are few studies on the prevalence of postnatal depression among HIV-infected women.[3] The postpartum period is a time in which women are more vulnerable to depressive symptoms,[4] but most studies have only focused on depressive symptoms in HIV-positive individuals in general. In a study conducted in an urban setting in South Africa, maternal postpartum depression was measured using the Edinburgh Postnatal Depression Scale (EPDS) among 83 HIV-infected mother infant dyads and 42.2% of the women scored above the cut-off point for depression.[5] HIV-infected mothers are at high risk for a range of emotional and psychiatric problems that may impact on immunity and HIV disease progression.[4,6-8]

Preterm delivery[9] and difficulties with partners[10] have been found to be associated with postpartum depression. In addition, low levels of social support, particularly partner support and availability of people to depend on during the pregnancy and early postpartum, and a woman's relationship with her own parents were

found to be significant factors for both antenatal and postnatal depression.[11] Society expects women to be mothers, and yet at the same time it negatively judges HIV-positive women who choose to become pregnant.[12] Emotional support plays a role in depressive symptoms; with limited support, HIV-positive individuals are more likely to exhibit depressive symptoms.[13,14]

The present study aimed to determine the prevalence of depressed mood and associated factors in postnatal HIV-positive women in primary care facilities in Nkangala district, Mpumalanga, South Africa.

METHOD

STUDY SETTING

The study was conducted in Nkangala district, Mpumalanga, which is ranked the third most rural province in South Africa, with 60.9% of its population living in rural areas.[15] Nkangala district had a population of 1 121 839 people in 2008/9. At 28.4%, the unemployment rate is higher than the national unemployment rate (25.3%). More than a quarter (28.6%) of households in Nkangala earned less than R30 000 per year (R2 500 per month) in 2009.[15] It was estimated that 90% of the population was dependent on the state for the provision of all their health services.[16] The primary health care utilisation rate of 2.2 visits per person per year has been constant from 2008 to 2009.[17] The antenatal HIV prevalence rate in Nkangala district was 32.5% in 2009.[18]

SAMPLE AND PROCEDURE

The sample included 607 postnatal HIV-positive women with an infant aged 1 - 10 weeks (30.8%), 11 weeks - 6 months (36.7%) or 7 - 12 months (32.5%). Almost all (98%) were from a black African population group, mainly Zulu, Swati and Tswana. The inclusion criteria for the postnatal study were that the participant attended the clinic, was HIV positive, was 18 years of age and older, and had an infant less than 12 months old. Postnatal women were recruited by systematic sampling (every consecutive patient over a period of 2 months) from 48 primary care clinics and community health centres (of in total 74 clinics) in all 6 sub-districts of Nkangala district in Mpumalanga province. In all the 48 prevention of mother-to-child transmission (PMTCT) service points in the study area, every consecutive HIV-positive mother was invited to participate in the study through referrals by health care providers. These individuals were asked to inform HIV-positive mothers about the study when the mothers came to clinic visits, and to encourage them to volunteer. Trained interviewers conducted interviews with postnatal women at health care facilities, using structured questionnaires. The questionnaire was translated into the local language, isiZulu. Informed consent was obtained from each participant before she was interviewed. Study approval was obtained from the Human Sciences Research Council ethics committee and health authorities (provincial, district, sub-district and clinic level).

MEASURES

The questionnaire included socio-demographic items, male involvement, HIV test disclosure, delivery and infant profile, infant HIV diagnosis, stigma, discrimination, postnatal depression, attendance of support groups, and social support.

Male involvement was assessed with one item, 'Did the father of the baby accompany you to the clinic when you received antenatal care?' Response options were 'yes' or 'no'.

Postnatal depression. The 10-question Edinburgh Postnatal Depression Scale (EPDS) is a valuable and efficient way of identifying patients at risk for 'perinatal' depression.[19] The EPDS is easy to administer and has proved to be an effective screening tool. Mothers who score above 13 are likely to be suffering from a depressive illness of varying severity.[20,21] The EPDS score should not override clinical judgment. A careful clinical assessment should be carried out to confirm the diagnosis. The scale indicates how the mother has *felt during the previous week*. It has specificity and sensitivity greater than 76%,[22] has been validated antenatally and postnatally,[20] and has been validated in a black South African population.[23] The EPDS consists of 10-self-reported items, each response rated 0 - 3 based on severity, and summed to yield the total score (0 - 30). The scale has items related to anxiety and depressive symptoms such as anhedonia, anxiety, tearfulness, helplessness and motivation. The EPDS scale does not rely on somatic symptoms, which is common in postpartum women irrespective of depression. Research has supported the construct validity of an interviewer-administered isiXhosa version of the EPDS for use in South Africa.[24] In South Africa there have been two validation studies of the EPDS in community samples. The first found an optimal threshold of 11/12, or 12 and above, for women in the postnatal period.[25] The second found that a threshold of 13/14, or 14 and above, was optimal for classifying 'probable' cases of depression.[25] The present study uses the threshold of 14 as a basis for interpretation.[5] Cronbach's alpha for EPDS in this sample was 0.84.

HIV/AIDS discrimination experiences. To assess AIDS-related discrimination, we asked participants if they had experienced seven discrimination-related events. All items referred to discrimination experiences related to their HIV-positive status, e.g. 'Have you experienced discrimination because of HIV?' Each item was responded to dichotomously, yes or no; scale scores represent the sum total of endorsed items, range 0 - 7.[26] The Cronbach's alpha of this 7-item scale was 0.75. In addition, three items on discrimination experiences with health care providers were included. To assess exposure to discrimination experiences with the health care provider, interviewees were prompted with the following: 'People with HIV often sense discrimination from health care providers in subtle ways. Has anyone in the health care system ever done any of the following to you?' e.g. 'Has anyone in the health care system ever exhibited hostility or a lack of respect toward you?' Each item was responded to dichotomously, yes or no; scale scores represent the sum total of endorsed items, range 0 - 3. The Cronbach's alpha of this 3-item sub-scale was 0.83.

Internalised AIDS stigma. We used the 7-item internalised AIDS-related stigma scale for people infected with HIV.[27] Items reflected self-defacing beliefs and negative perceptions of people living with HIV/AIDS, e.g. 'It is difficult to tell other people about my HIV infection.' Response options ranged from 1 = strongly agree to 4 = strongly disagree. The Cronbach's alpha of this 7-item scale was 0.88.

Social support. Three items were drawn from the Social Support Questionnaire to assess perceived social support.[26] The items were selected to reflect perceived tangible and emotional support. The four response options ranged from 'completely true' to 'completely false'; scale scores represent the sum total of endorsed items, range 3 - 12. The Cronbach's alpha of this 3-item scale was 0.61.

In addition, three individual items were used to assess social support. Two items referred to support during pregnancy ('Saw a traditional birth attendent during pregnancy' and 'Father of baby accompanied to antenatal care'), and one item assessed the attendance of a support group. Response options were 'yes' or 'no'.

Alcohol use was assessed with one item, 'Did you ever drink alcohol (beer, wine, home-brewed beer or spirits) in the past month?' Response options were 'Yes' or 'No'.

DATA ANALYSIS

The Statistical Package for Social Sciences (SPSS version 18.0 for Windows; SPSS Inc., Chicago, IL, USA) was used for data analyses. Descriptive data on the total sample were first examined. Postnatal women were then classified as having depressed mood or not, based on a score greater than or equal to 14 on the EPDS. Significantly skewed variables such as discrimination experiences were transformed using the formula $\log_{10}(x+1)$. Bivariate analysis and multivariable logistic regressions were used to investigate associations between the socio-demographic, stressor, risk behaviour and social support variables and depressed mood. Unconditional logistic regression was then performed including the variables that had a significant ($p<0.05$) bivariate relationship with EPDS. Associations were considered significant at $p<0.05$.

RESULTS

SOCIO-DEMOGRAPHIC CHARACTERISTICS

Of the 615 women invited to participate in the study, 8 declined, resulting in a total sample of 607 participants (response rate 98.7%). The mean age of the women was 28.5 (standard deviation (SD) 5.8) years, with a range of 18 - 51 years. One hundred and eighty-seven (30.8%) of the participants had an infant aged 1 - 10 weeks, 223 (36.7%) an infant aged 11 weeks - 6 months and 197 (32.5%) an infant aged 7 - 12 months. Thirty-five per cent had grade 12 or higher formal education, 53.6% grade 8 - 11 education, and 11.4% grade 7 or less education. Most postnatal women (69.6%) had never been married, 28.4% were married or cohabitating and 2% were separated, divorced or widowed. Almost all came from a black African population group (98.3%), with the main ethnic groups being Ndebele (27.8%), Northern Sotho (26.8%) and Zulu (26.0%). Economically, few mothers were employed (11.4%) or receiving money from their partner (23.2%) or family (9.6%), while most received a child care support grant (66.4%) and/or disability grant (3%).

PREVALENCE AND CORRELATES OF DEPRESSED MOOD

Overall, 45.1% of women reported depressed mood in the postnatal period. Bivariate comparisons are presented in Table I. Having an HIV-positive sexual partner, no alcohol use in the past month, having been diagnosed with a sexually transmitted infection (STI) (other than HIV) in the past 12 months, inconsistent condom use with the primary partner, internalised stigma, discrimination experiences, lack of social support, and the baby's father not accompanying the woman to antenatal care were all found to be associated with depressed mood. Results from multivariable logistic regression are presented in Table II. In multivariable analysis, having been diagnosed with an STI (other than HIV) in the past 12 months, internalised stigma, discrimination experiences and lack of social support were associated with depressed mood.

DISCUSSION

Overall, 45.1% of women reported depressed mood in the postnatal period in the present study compared with 42.2% found in the study conducted by Hartley *et al*.[5] in Cape Town and 54% meeting DSM-IV criteria for depression among urban primary clinic attendees in Zimbabwe.[28]

The study found that the strongest predictors of depressed mood among postnatal women were having had an STI in the past 12 months, internalised stigma, discrimination experiences and lack of social support. In a large Canadian community study STIs among women also increased the risk of depression.[29] Diagnosis with an STI may contribute to the development of depression.[29] Further, in previous studies it was also found that discrimination experiences were common and internalised AIDS stigma was prevalent among people living with HIV/AIDS.[26] The results of the current study show a significant relationship between internalised stigma and depressed mood, and these results concurs with the study conducted by Ross *et al*.,[4] which found self-esteem to be the most powerful predictor of depressive symptoms among HIV-positive postpartum women and Wight's[30] finding that internalised stigma is related to the development of depressive symptoms. Social support was found to be a factor buffering against postnatal depression. In the multivariate analysis, lack of social support remained significantly associated with depressed mood, and this finding concurs with other studies.[5,14,31,32]

Having an unintended unplanned pregnancy, the infant being HIV positive and preterm delivery were not associated with a depressed mood in the current study. Tomlinson *et al*.[33] also found that having an unintended pregnancy was associated with a depressed mood. Alcohol use in the current study was not associated with depressed mood in multivariate analysis, although

TABLE I. SAMPLE CHARACTERISTICS AND EPDS (*N*=607)

	EPDS <14 (*n*=333)		**EPDS ≥14 (***n*=274)		Unadjusted OR (95% CI)	*p*-value
Socio-economic variables	*N* or mean	% or SD	*N* or mean	% or SD		
Age	28.7	5.9	28.3	5.7	0.99 (0.96 - 1.02)	0.440
Age of infant						
1 - 10 weeks	85	51.2	81	48.8	1.00	0.874
11 weeks - 6 months	110	53.1	97	46.9	0.97 (0.66 - 1.43)	0.506
7 - 12 months	102	56.0	80	44.0	0.87 (0.58 - 1.31)	
Education						
Grade 0 - 7	32	46.4	37	53.6	1.00	0.127
Grade 8 - 11	183	56.5	141	43.5	0.67 (0.40 - 1.12)	0.229
Grade 12+	116	54.7	91	45.3	0.72 (0.42 - 1.23)	
Single	232	55.4	187	44.6	1.00	0.462
Married/cohabitating	89	52.0	82	48.0	1.14 (0.80 - 1.63)	0.074
Separated/divorced/widowed	10	83.3	2	16.7	0.25 (0.05 - 1.15)	
Number of (own) children	2.2	1.2	2.2	1.6	0.98 (0.85 - 1.13)	0.784
Mother employed	44	63.8	25	36.2	1.00	
Mother receives child care grant	224	55.6	179	44.4	0.95 (0.64 - 1.39)	0.785
Mother receives money from partner	84	59.6	57	40.4	0.80 (0.53 - 1.21)	0.288
Mother receives money from family	25	43.1	33	56.9	1.57 (0.86 - 2.85)	0.140
Health status and reproductive health						
CD4 cell count <200 cells/µl	68	56.7	52	43.3	0.77 (0.51-1.18)	0.235
Had STI (other than HIV) in the past 12 months	49	34.8	92	25.6	2.66 (1.80 - 3.91)	0.000
Alcohol use in past month	29	74.4	10	25.6	0.40 (0.19 - 0.84)	0.016
Current baby unintended	186	51.5	175	48.5	1.33 (0.95 - 1.88)	0.102
Preterm (v. term) delivery)	31	63.3	18	36.7	0.68 (0.37 - 1.24)	0.209
Baby had hospital admission	75	56.0	59	44.0	0.80 (0.55 - 1.16)	0.234
Infant HIV positive	9	56.3	7	43.8	0.94 (0.35 - 2.57)	0.910
Sexual behaviour and partner characteristics						
Main sexual partner HIV positive	105	45.1	128	54.9	1.48 (1.04 - 2.11)	0.029
Intimate partner violence in past 12 months	16	44.4	20	55.6	1.49 (0.75 - 2.93)	0.253
More than one sexual partner in past 12 months	34	53.1	30	46.9	0.98 (0.58 - 1.65)	0.932
Casual partner in past 3 months	23	48.9	24	51.1	1.19 (0.66 - 2.17)	0.562
Inconsistent condom use with primary partner	166	49.1	172	50.9	1.47 (1.04 - 2.07)	0.030
Discrimination and stigma						
Internalised stigma score (range 7 - 28)	16.0	4.2	18.6	5.2	1.13 (1.08 - 1.17)	0.000
Discrimination experiences score (range 0 - 7)	0.9	1.3	1.4	1.7	1.28 (1.13 - 1.44)	0.000
Social support						
Social support score (range 3 - 12)	8.2	1.7	7.3	2.0	0.77 (0.70 - 0.84)	0.000
Saw a traditional birth attendant during pregnancy	68	45.6	81	54.4	1.35 (0.94 - 1.93)	0.105
Father of baby accompanied to antenatal care	77	67.0	38	33.0	0.51 (0.34 - 0.78)	0.002
Attended support group	62	51.2	59	48.8	1.20 (0.81 - 1.80)	0.368

OR = odds ratio; CI = confidence interval; SD = standard deviation.

it reached significance in the bivariate analysis. This concurs with the results of Hartley *et al*.[5] Other factors that were significantly associated with a depressed mood in the current study in bivariate analysis included having an HIV-positive partner and inconsistent condom use with the primary partner. This seems to indicate that partner dynamics may influence the wellbeing of HIV-infected mothers.

TABLE II. LOGISTIC REGRESSION ANALYSIS: PREDICTORS OF DEPRESSED MOOD (*N*=607)

	Adjusted OR (95% CI)*†	*p*-value
Health status, sexual behaviour and partner characteristics		
Had STI (other than HIV) in the past 12 months	2.22 (1.21 - 4.04)	0.010
Alcohol use in past month	0.43 (0.16 - 1.17)	0.099
Main sexual partner HIV positive	1.63 (0.97 - 2.71)	0.063
Inconsistent condom use with primary partner	1.51 (0.88 - 2.59)	0.140
Discrimination and stigma		
Discrimination experiences score (range 0 - 7)	1.22 (1.03 - 1.46)	0.023
Internalised stigma score (range 7 - 28)	1.12 (1.05 - 1.19)	0.000
Social support		
Social support score (range 3 - 12)	0.86 (0.74 - 0.99)	0.037
Father accompanied to antenatal care	0.55 (0.28-1.08)	0.084

*Using 'enter' logistic regression selection of variables.
†Hosmer and Lemeshow chi-square 14.55, df 8, 0.536; Cox and Snell R^2 0.20; Nagelkerke R^2 0.27.
OR = odds ratio; CI = confidence interval.

CONCLUSION

The study found a high prevalence of postnatal depression symptoms among HIV-positive women, and that several factors were associated with depression. The development of interventions can specifically address such factors, i.e. encouraging partner involvement campaigns, and training health workers to address their own and mothers' stigma towards HIV. It is feasible to screen for postnatal depression in primary care clinics using peer counsellors. We recommend that screening for postnatal depression and access to mental health interventions should be part of routine antenatal care for all women.

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CASE REPORT

SUCCESSFUL TREATMENT OF BILATERAL VISUAL LOSS CAUSED BY IDIOPATHIC OPTIC NEURITIS IN AN HIV-INFECTED PATIENT

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Optic neuritis is not an uncommon diagnosis in HIV-infected patients, but it is rarely idiopathic. We report a case of a young HIV-infected woman who developed optic neuritis as her presenting manifestation of HIV infection. She had initially experienced sudden-onset right-sided painful visual loss; the left eye had become involved within days. Bilateral swollen discs were apparent on fundoscopy. Investigations were performed for meningitis (including bacterial, cryptococcal, tuberculous and syphilitic types), auto-immune diseases, toxoplasma, rubella, cytomegalovirus, viral hepatitis, HTLV-1/2, HIV-1/2 and syphilis. The only positive result was a reactive HIV enzyme-linked immunosorbent assay. The CD4 count was 85 cells/µl. A post-contrast magnetic resonance imaging scan of the brain illustrated enhancement of the optic nerves. Treatment was 3 days of intravenous methylprednisolone 1 g daily, followed by 11 days of oral prednisone 60 mg daily. Highly active antiretroviral therapy was initiated after 2 weeks. Vision improved from day 6 after commencement of steroid therapy, with ongoing recovery at 5 months.

The human immunodeficiency virus (HIV) manifests in various ways in the eye. Several optic nerve disorders have been described, most commonly resulting from opportunistic infections, neoplasms and inflammatory causes.[1] HIV infection as a direct cause of optic neuropathy has been postulated. It is an uncommon presentation and a diagnosis of exclusion, with only a few case reports and case series in the literature. Mwanza *et al.* describe a sub-group of neurologically symptomatic HIV-infected patients from the Democratic Republic of Congo: optic neuropathies occurred in 31%, although only 7% of cases were ascribed solely to HIV.[1] We present a case of idiopathic optic neuritis in an HIV-infected person.

CASE PRESENTATION

A 26-year-old South African woman presented to the ophthalmology clinic of Dr George Mukhari Hospital in Ga-Rankuwa, Gauteng, on 6 January 2009. Her main complaint was a 1-week history of sudden-onset, painful visual loss that had originated in the right eye and had progressed over a few days to include the left eye. She described the pain as being 'deep within the eye' but unrelated to eye movements. On the second day she had attended her local community clinic, where she had been dispensed chloramphenicol eye ointment, which did not improve the condition.

There was no history of trauma. Her medical, surgical, ophthalmological and family histories were otherwise unremarkable, and she was not receiving any other medications.

General examination revealed a well-looking young woman. Her vital signs, including blood pressure, were within normal limits. Visual acuity of the right eye was recorded as counting fingers at 1 metre (<6/60), and testing with a Snellen visual acuity chart showed that of the left eye to be 6/60. A relative afferent pupil defect was present in the right eye. Extra-ocular movements were full and painless. On fundus examination, bilateral swollen optic discs with flame-shaped haemorrhages were apparent (Fig. 1). There were no cotton wool spots and no macular star in either eye. The cornea, anterior chamber, vitreous and retina were normal, as were intra-ocular pressure readings.

Optical coherence tomography objectively documented bilateral swollen optic discs (Fig. 2). Fluorescein angiography showed hyperfluorescence of the optic discs (Fig. 3).

The chest radiograph was normal. Although there were no unusual findings on computed tomography scanning of the brain, a magnetic resonance imaging scan of the brain illustrated enhancement of the optic nerves post-

Fig. 1. Fundus photo of the right eye. There is blurring of optic disc margins associated with disc haemorrhages indicative of optic nerve swelling. Findings in the left eye were similar.

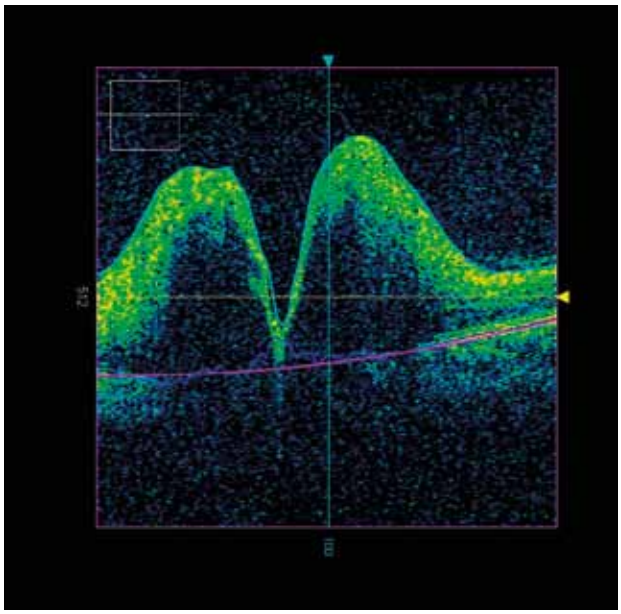

Fig. 2. Optical coherence tomography of the left disc, objectively demonstrating nerve fibre layer swelling at presentation.

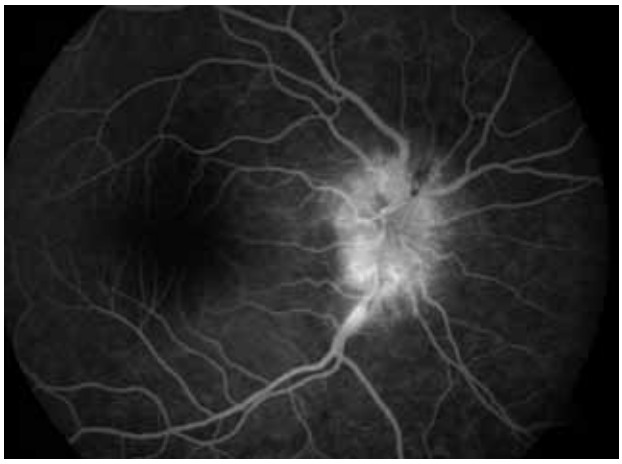

Fig. 3. Fluorescein angiogram of the right eye at presentation. The bright white areas (termed hyperfluorescence) surrounding the optic disc indicate leakage of sodium fluorescein dye and signify disc swelling.

contrast. There were no periventricular plaques and no other abnormalities were noted.

Lumbar puncture was performed and the opening pressure was noted as being within normal range. Cerebrospinal fluid chemistry and cytology were normal. Gram stain and bacterial culture, India ink and latex antigen tests for *Cryptococcus neoformans*, CSF adenosine deaminase (ADA) for tuberculosis and TPHA (*Treponema pallidum* haemagglutinin assay) syphilis tests were all negative.

The full blood count showed slight leukocytosis (white cell count $12\times10^9/1$) and neutrocytosis (83%). The erythrocyte sedimentation rate was slightly increased at 33 mm/h, but the C-reactive protein level was normal at 5.8 mg/l. Auto-immune studies (antinuclear antibodies, antimitochondrial antibodies, antiparietal cell antibodies

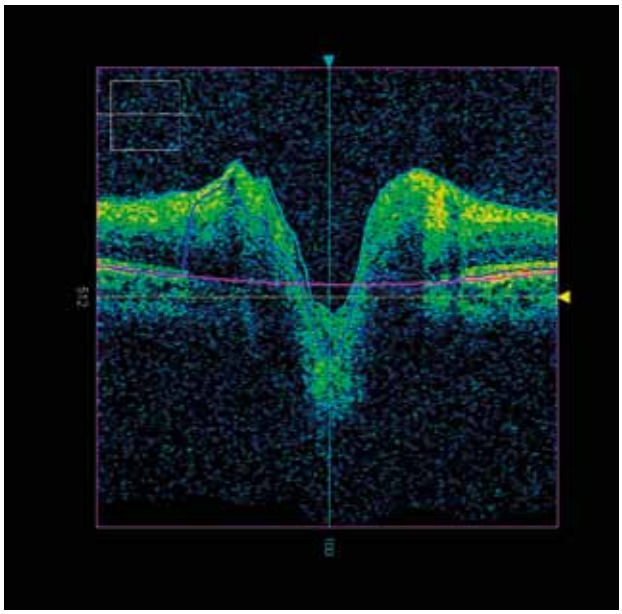

Fig. 4. Optical coherence tomography 2 months after treatment initiation, showing a decrease in disc swelling.

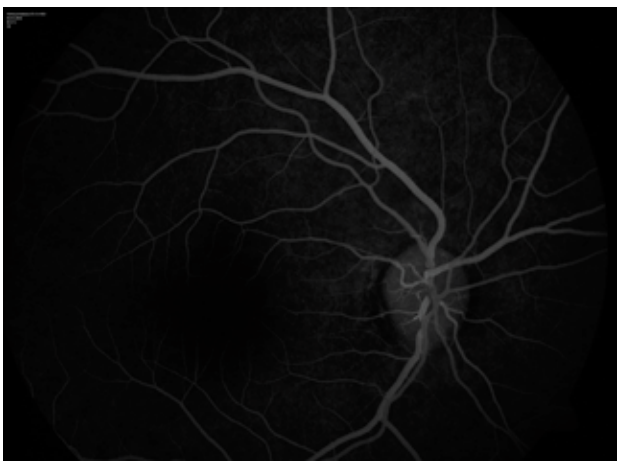

Fig. 5. Fluorescein angiogram of the right eye 2 months after treatment initiation.In comparison with Fig. 3 there is less fluorescein leakage, correlating with resolution of optic disc swelling.

and anti-smooth muscle antibodies) were negative. Serum angiotensin-converting enzyme for sarcoid was also negative. Vitamin B_{12} levels were normal. Tests for mitochondrial mutations associated with Leber's hereditary optic neuropathy were judged unnecessary. Infectious studies were all negative, including blood tests for *Toxoplasma*, rubella, cytomegalovirus (CMV) pp65 antigen, viral hepatitis screen, HTLV-1 and 2, RPR and TPHA for syphilis. The HIV enzyme-linked immunosorbent assay was reactive and the absolute CD4 count was 85 cells/μl.

The patient was admitted on the day of her presentation to our clinic. After 3 days she was treated with intravenous methylprednisolone 1 g daily for 3 days, followed by 11 days of oral prednisone 60 mg daily with subsequent gradual tapering to prevent possible steroid withdrawal symptoms. A diagnosis of idiopathic optic neuritis was subsequently made by exclusion of other causes.

On the 6th day of treatment, the patient reported improvements in her vision. Visual acuity of the right eye was unchanged, but in the left eye it improved to 6/24.

Two and a half weeks after her initial presentation to us, she started highly active antiretroviral therapy (HAART).

At a follow-up visit 2 months after presentation, and 5 weeks after HAART commencement, vision had improved bilaterally to 6/18 on the right and 6/12 on the left. There was complete resolution of disc swelling bilaterally, but some residual optic nerve pallor (Figs 4 and 5).

By the 5th month after presentation, the HIV-1 viral load was suppressed at <25 copies/μl and visual acuity remained 6/18 in the right eye but had improved to 6/6 in the left. The CD4 count improved to 265 cells/μl.

DISCUSSION

Optic neuritis is an inflammation of the optic nerve and a cause of acute visual loss. It may be categorised as typical or atypical.

Typical optic neuritis, the most common type, occurs in demyelinating conditions such as multiple sclerosis (MS). The International Headache Society (IHS) outlines five diagnostic criteria describing dull retrobulbar pain in one or both eyes of maximum 4 weeks' duration accompanied by impaired central or paracentral vision in the absence of a compressive lesion.[4] It has been proposed that the diagnostic criteria be used in conjunction with biomarkers and radiological evidence of multiple sclerosis.[4]

Atypical optic neuritis occurs in non-demyelinating conditions such as viral infections, toxin exposure, meningitis, tumour metastases, syphilis and neuromyelitis optica (Devic's disease), and in some cases it is idiopathic.[3] Features suggesting atypical optic neuritis include age (<12 years or >50 years), African or Asian race, bilateral disease, severe (no light perception) or progressive (>2 weeks) visual loss, unusual description of pain (painless visual loss or severe pain that restricts eye movements or wakes patient from sleep), unusual ocular findings (marked anterior and/or posterior segment inflammation), lack of any visual recovery within 5 weeks or continued deterioration in visual function, symptoms or signs of a systemic disorder other than MS, and corticosteroid-dependent optic neuropathy (deterioration in vision when corticosteroids are withdrawn).[5]

This patient had features suggesting an atypical optic neuritis, particularly haemorrhages that accompanied optic disc swelling. In addition to tests for auto-immune diseases, sarcoidosis, rubella, viral hepatitis and HTLV-1 and 2, investigations for opportunistic infections should also be done in the setting of HIV, and the possibility of false-negative results should be borne in mind. More sensitive tests include serum or CSF cryptococcal antigen for the fungus *C. neoformans*, serology for the protozoan *Toxoplasma gondii*, and pp65 antigen for CMV. Tests which should be interpreted with more caution include syphilis serology, which may revert to negative in HIV infection,[10] and tuberculosis tests because – despite the availability of multiple methods of investigation including microscopy, culture, CSF ADA and imaging – tuberculosis is noted to be cryptic in HIV infection.

Neuro-ophthalmic manifestations of HIV tend to present at an advanced stage of the disease when CD4 cell counts are depleted below 200 cells/μl.[6] Indeed, in patients with AIDS there is a 3 - 8% prevalence of neuro-ophthalmic diseases including eye movement disorders, cranial nerve palsies, neuroretinitis, retrobulbar optic neuropathy, anterior optic neuropathy, papilloedema, visual field defects, cortical blindness, optic atrophy and optic neuritis.[1] The latter manifestation was the presenting illness of HIV in our patient, who reported no prior HIV-related diseases even though her CD4 count at presentation was 85 cells/μl.

In HIV-infected patients, opportunistic infections such as syphilis, toxoplasmosis, tuberculosis and cytomegalovirus are by far the most common cause of optic nerve disorders.[7,8] In rare cases, mostly affecting males, mitochondrial toxicity caused by nucleoside reverse transcriptase inhibitor antiretroviral drugs such as stavudine and didanosine may trigger acute painless central visual loss if the 14484 mitochondrial DNA mutation of Leber's hereditary optic neuropathy is present.[9] We did not test for this mutation because the patient had not been on antiretroviral drugs, was not male, and had no family history of sudden visual loss.

To our knowledge at least 10 cases of idiopathic HIV-associated optic neuritis have been reported in the English literature.[8,10-14] In the 6 instances where CD4 counts were documented, they were well below 350 cells/μl in all cases except one of acute HIV syndrome. Nine of these 10 patients presented with decreased visual acuity in one or both eyes. Of the 9 cases where

visual outcomes were reported, there was improvement in 16 eyes and 2 eyes remained unchanged.

A direct causal link between HIV and optic neuritis has been suggested previously.[10] The mechanism by which HIV could cause primary optic neuritis remains unclear despite much research devoted to neurodegeneration in HIV infection.[1,10,11,15,16] The current widely accepted theory suggests that the pro-inflammatory cytokine tumour necrosis alpha (TNFα) plays a key role.[1,8,11] Other proposed mechanisms include damage secondary to activated microglia and macrophages releasing neurotoxic agents.[1] Consistent with this proposed inflammatory pathogenesis, steroid responsiveness is thought to be a feature of idiopathic optic neuritis in HIV-infected persons.[7,10]

The use of steroids in typical optic neuritis is well established. The prospective randomised and controlled Optic Neuritis Treatment Trial reported that oral prednisone alone had no benefit over placebo and may increase the future risk of repeat episodes of optic neuritis, while intravenous methylprednisolone 1 g daily for 3 days followed by 11 days of oral prednisone 1mg/kg/day was associated with slightly faster visual recovery compared with placebo.[17] Nevertheless, visual recovery within 2 weeks was marked for most participants, regardless of treatment arm.[17]

Treatment for atypical optic neuritis includes treating the underlying cause. The optimal treatment for optic neuritis in HIV- infected patients is controversial. On the one hand, spontaneous resolution of optic neuritis in HIV-infected patients after 2 weeks has been reported[12] and some (but not all) studies have demonstrated accelerated disease progression with the use of even short courses of immunosuppressive doses of steroids in patients with advanced HIV.[18] On the other hand, there are reported cases – ours being one of them – of visual recovery soon after the introduction of systemic steroid therapy.[7,10] It is also possible that antiretroviral therapy contributed to visual recovery in the medium term.[7,8,11]

Some authorities advocate the inclusion of penicillin at neurosyphilis treatment doses as part of empiric management for optic neuropathies of cryptic origin in HIV-infected individuals,[7,10] but we did not employ this strategy. The rationale underlying this approach reflects the attenuating sensitivity of laboratory tests for treponemal infection, which are antibody tests and may be non-reactive in advanced HIV illness.[7]

CONCLUSIONS

Underlying HIV should be considered in cases of atypical optic neuritis in patients at risk. Although uncommon, idiopathic optic neuritis in HIV-infected persons is a diagnosis of exclusion when there is a presentation of sudden visual loss and optic disc swelling. Management must include assessment for HAART, as the condition is linked with advanced disease. It may be reasonable to inform HIV-infected patients with optic neuritis about the possible risks versus benefits of steroid therapy and invite them to consent to the treatment of their choice.

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Author contributions. CC acquired and interpreted the data and drafted the manuscript. BM and FL critically revised ophthalmological and HIV-related sections of the manuscript, respectively. AP provided final review and approval of the manuscript.

Ethical considerations. The patient provided voluntary written informed consent to have her anonymous case details published.

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REVIEW

KHAYELITSHA 2001 - 2011: 10 YEARS OF PRIMARY CARE HIV AND TB PROGRAMMES

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Tuberculosis (TB) and HIV care in Khayelitsha, and in South Africa as a whole, has overcome numerous obstacles in the past three decades. This article highlights what has been achieved in Khayelitsha, describes the key clinical programme and policy changes that have supported universal coverage for HIV and TB care over the last 10 years, and outlines the challenges for the next decade.

The evolution of tuberculosis (TB) and HIV care in Khayelitsha, and in Africa as a whole, has overcome numerous obstacles in the past three decades: poor leadership in acknowledging the HIV crisis, inadequate provision of appropriate scientific interventions, and scepticism about the feasibility of treatment programmes in settings challenged with extreme resource constraints. Over the past 10 years in Khayelitsha, HIV has been transformed from less than 500 people tested for HIV and no one on antiretroviral therapy (ART) in 1998 to 50 000 tested and 20 000 on ART in 2011.[1] Stakeholders in the Khayelitsha sub-district have reflected in the course of the past year on the previous decade of service developments as part of commemorating 10 years of public sector ART provision. This article highlights what has been achieved collectively by several service providers (the City of Cape Town, Médecins Sans Frontières, the Western Cape province, academic institutions, the Treatment Action Campaign (TAC), non-governmental and community-based organisations), describes the key clinical programme and policy changes that have supported universal coverage for HIV and TB care over the past 10 years, and outlines the challenges for the next decade.

HIV PREVENTION AND INCIDENCE REDUCTION

Dedicated efforts have been made to scale up a combination of prevention interventions that has resulted in substantial changes in health outcomes over the past decade.

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV

The implementation of a prevention of mother-to-child transmission (PMTCT) programme in 1999, with antenatal and perinatal antiretroviral chemoprophylaxis and free exclusive formula feeding, marked the beginning of public sector antiretroviral-based services in South Africa. This programme, with progressive improvements and intensification in line with the evolution of national guidelines, has resulted in a reduction in documented mother-to-child transmission from 12.5% in 2002 to 2.5% in 2010 based on polymerase chain reaction (PCR) testing at 6 weeks (Fig. 1). This success is mirrored in many other sites in South Africa, and demonstrates that PMTCT to very low proportions of infants infected is both feasible and scalable.

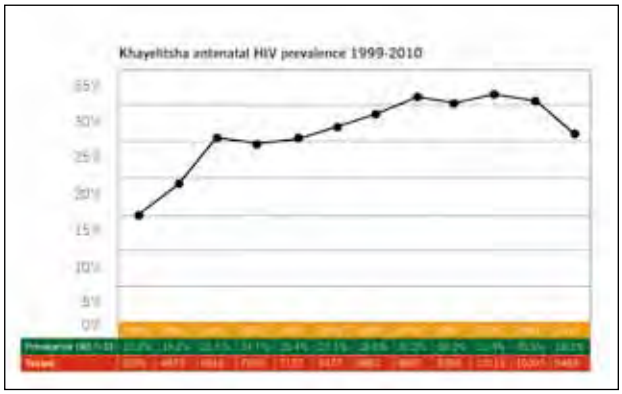

Fig. 1. Rate of mother-to-child HIV transmission, 2002 - 2010.

Box 1. Key elements of the programme

Khayelitsha is a large township with approximately 500 000 inhabitants, located on the outskirts of Cape Town. It has one of the highest burdens of both HIV and toberculosis (TB) in South Africa. An estimated 16% of the population is HIV infected; TB incidence is above 1 500/100 000 per year and TB/HIV co-infection is close to 70%. The incidence of drug-resistant TB is estimated at 50/100 000 per year.[11]

The Khayelitsha programme, started in 1999, was the first in South Africa to provide antiretroviral therapy (ART) at primary care level in the public sector and one of two pilot projects in the country to provide decentralised care for drug-resistant tuberculosis.[12] Key strategies implemented include:

- prevention of mother to child transmission with ART and formula
- large-scale HIV counselling and testing, including out-of-facility testing, youth clinics,and male clinics
- mass community condom distribution
- decentralisation of ART to all clinics in the sub-district
- 'one-stop-shop' integration of ART and TB services
- nurse management of HIV and TB care, including nurse-initiated ART and TB treatment
- doctor support and mentorship, with a strong secondary care referral system
- district level planning and co-ordination
- three-tier monitoring and evaluation system (paper register, electronic register,and electronic medical record in selected sites)
- ongoing training and mentoring at clinic and district level

Furthermore, the decentralisation of paediatric ART into primary care clinics, which started in 2004, resulted in a steady increase in children being initiated on ART each year, from 4 in 2001 to 145 in 2008. The numbers have decreased since then to 115 in 2010. The successful decentralisation of paediatric care has led to positive health outcomes; 87% of children started on ART in primary care remained in care, and 98% remained alive after 5 years on ART.

HIV TESTING

HIV testing has increased steadily since the advent of the programme. The programme started with enzyme-linked immunosorbent assay (ELISA) testing of 500 people in January 1999. The introduction of rapid HIV testing kits, PCR testing for infants, employment of lay counsellors to conduct HIV counselling and testing (HCT), community-based testing sites, wide-scale HCT campaigns, and targeted testing for TB patients/suspects, youth and males saw a dramatic increase in the numbers of people being tested each year. By the end of 2010, 22 centres were providing HCT and approximately 57 000 people were being tested annually. In a community survey conducted in 2004, 28% of men and 53% of women of reproductive age in Khayelitsha reported having been tested for HIV.[2]

COMMUNITY CONDOM DISTRIBUTION

Male condom distribution has been a major priority in the programme. The number of condoms distributed per year increased from 2 million in 2004 to more than 10 million in 2006; currently more than a million condoms are distributed every month. This was made possible through the combined efforts of the public sector, including the City of Cape Town, and non-governmental organisations, especially TAC. TAC expanded condom distribution from health care facilities to community distribution points, such as taxi ranks, public libraries, toilets and shebeens.[3] During the same period, the number of adults reported to have been treated for sexually transmitted infections (STIs) decreased fourfold, from 28 000 in 2004 to less than 5 000 in 2009.

OPENING OF A MALE-FRIENDLY CLINIC

Recognition of the need for a service dedicated to reaching men and providing HCT and STI treatment resulted in the opening of a male walk-in clinic at a taxi rank in 2007. This new service was widely advertised in the community through the use of taxi ranks and the local radio. This clinic has become the largest STI treatment site in the Cape Metro area, with the number of STIs treated increasing from 843 in 2007 to 2 547 in 2010. In the first half of 2011 the clinic counselled and tested as many men as were tested throughout 2010, and the number tested during 2010 in the male clinic represented 27% of all men tested in Khayelitsha. The clinic aims to promote and empower men to take ownership of their sexual health and safety and that of their partners. Its success demonstrates that men use health services that are adapted to their needs: short waiting times, close to a usual gathering place for men (taxi rank), and separate from public health services attended mostly by women and children. Two new male clinics are planned for 2011 to continue to reach out to men, who remain a group with limited access to care.

ANTIRETROVIRAL THERAPY

In May 2011 there were 20 000 patients on ART, which is estimated to represent 63% coverage of those in need in Khayelitsha, according to current World Health Organization (WHO) eligibility criteria. Retention in care at one year on ART has remained consistently above 85% since the beginning of the programme.[4] In addition, virological suppression among patients in care also remained above 87% in those tested,[4] thereby decreasing the community viral load given the relatively high proportion of infected adults who are on ART. It is therefore likely that this is contributing to a reduction in the number of new HIV infections.

EVOLUTION OF HIV PREVALENCE

HIV prevalence among women presenting for antenatal care has been routinely measured by the programme since 1999, and since 2003 the testing acceptance rate has been close to 100%. The antenatal HIV prevalence among those who test in routine care has stabilised since 2006 and may now be declining (Fig. 2). This decline is not mirrored by the annual anonymous antenatal survey, which might be explained by the fact that in routine care

women already on ART are often not retested for HIV, whereas during the annual survey all pregnant women are tested, regardless of whether they are on ART or not. Considering the decreased mortality, the absence of an increase in antenatal prevalence in recent years could be the result of the benefits of ART offsetting reduced new infections.

Emerging data illustrate that treatment serves as a powerful prevention tool,[5] and to decrease HIV incidence there is a need to combine wide-scale access to ART with available prevention tools, including HCT, PMTCT and condom distribution. In parallel, there is the need to focus on innovative tools to measure HIV incidence in order to adequately assess HIV prevention efforts.

DECREASING MORBIDITY

Increasing access to ART, as a result of decentralisation, task shifting and TB/HIV integration, has allowed patients to access and initiate treatment earlier. This in turn has resulted in decreasing HIV-related mortality and morbidity. Patients presenting to care earlier are also typically less complex to manage clinically, which facilitates increased nurse management of care.

EVIDENCE OF EARLIER ART ACCESS

Median CD4 counts of people starting ART increased from 43 cells/µl in 2001 to 162 cells/µl in 2010. In the same period the proportion of patients presenting with a WHO stage IV diagnosis decreased from 50% to 20%.

BETTER ART REGIMENS

The programme has also seen a gradual evolution towards improved first-line regimens. Documentation of high rates of adverse events with the use of stavudine (d4T) contributed to the growing evidence base that led to the WHO recommendation to replace d4T with better-tolerated alternatives.[6] A tenofovir-based regimen was introduced in 2005 in Khayelitsha for patients experiencing d4T toxicity, and was included in the national first-line regimen for all patients in 2010.

INTEGRATION OF TB AND HIV SERVICES

The 'one-stop-shop' integration of TB and HIV services began in 2004, and allowed co-infected patients to access TB and HIV services in the same clinic and from the same health staff.[7] In 2010, 99% of TB patients in TB/HIV integrated clinics were offered HCT, and 95% of them were being tested. Furthermore, 99% of co-infected patients had a CD4 count result recorded and over 95% were started on co-trimoxazole preventive therapy. The successful integration of the services has led to improvements in the detection rates of smear-negative pulmonary TB and extrapulmonary TB, as nurses' clinical skills in managing both diseases improved. In addition, integration has resulted in a decrease in the median time from the start of TB treatment to ART initiation.[7] Improved TB diagnostic methods, including smear-negative algorithms, systematic TB culture, line-probe assays, and the piloting of GeneXpert, as well as the systematic screening of HIV patients for TB, are all expected to contribute to increased TB diagnosis. The integration of HIV/TB care has been accompanied by improved TB cure rates (from 44% in 2005 to 81% in 2010), despite the increased caseload.

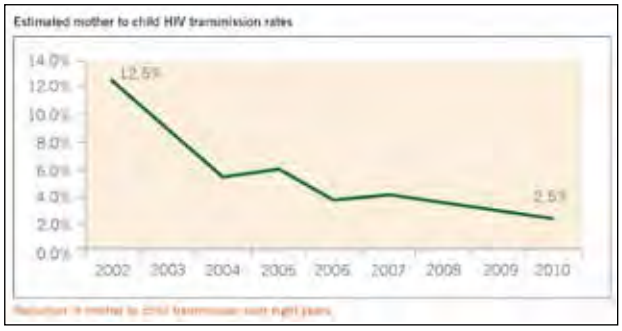

Fig. 2. Khayelitsha antenatal prevalence, 1999 - 2010.CHC = community health centre; City Clinic = City of Cape Town Clinic.

Box 2. Community-based model of care for drug-resistant tuberculosis

- Drug-resistant tuberculosis (DR-TB) refers to TB that has become resistant to first-line treatment and requires longer and more difficult treatment with second-line anti-TB drugs.
- Instead of attempting to hospitalise all DR-TB patients, the Khayelitsha model of care uses a patient-centred approach with community-based treatment through existing primary care services.
- Using lessons learned from the decentralisation of HIV care, diagnosis and treatment of DR-TB has been integrated into the routine TB and HIV programmes in Khayelitsha since early 2008.

COMMUNITY-BASED MANAGEMENT OF DRUG-RESISTANT TB

Before 2007, all patients with drug-resistant tuberculosis (DR-TB) in Khayelitsha had to be admitted to a central TB hospital to receive their treatment. Khayelitsha has piloted a community-based DR-TB programme in which drug-resistant TB is diagnosed and treated in primary care clinics as opposed to a centralised facility. The number of cases of DR-TB diagnosed increased from 14 in 2003 to 200 in 2010. Over 80% of patients diagnosed with DR-TB in 2009 and 2010 started treatment. The decentralisation of care was able to ensure that 71% of cases started treatment through the local clinic, while only 14% were admitted to the centralised specialist DR-TB hospital. In addition, the median time to treatment initiation decreased from 71 days in 2007 to 33 days in 2010.

DECREASING MORTALITY

DECENTRALISED, TB/HIV INTEGRATED, NURSE-MANAGED ART

Recorded mortality of adults at 3 months on ART decreased from 10% in 2002 to 2.2% in 2010, in part due to patients accessing ART earlier. While mortality ascertainment is less complete in recent years, there remains a year-on-year decline in mortality even after linkage to the national death registry to correct for mortality under-ascertainment.[4] Recorded mortality of adults at one year on ART decreased from under 15% to 8% between 2002 and 2007.[4] This decline in

early mortality and earlier access to ART has occurred alongside a dramatic increase from 100 people initiated on ART in 2001 to approximately 20 000 by mid-2011 (Fig. 3). The sharp rise in treatment enrolment was made possible due to decentralisation of ART to every clinic, TB/HIV integration, and nurse-managed ART and TB care. Decentralised care began in 2006 and new clinics were accredited as ART sites each year thereafter. National guidelines allowed for nurse-initiated TB/HIV integrated ART in April 2010, and all 11 clinics in Khayelitsha were providing ART by the end of 2010. In terms of longer-term outcomes, previous data based on death registry linkage have also confirmed that 4 out of 5 patients who started treatment were alive 5 years after starting treatment.[4]

PATIENTS TREATED FOR DRUG-RESISTANT TUBERCULOSIS

While there has been an increase in the detection of DR-TB, the Khayelitsha programme has seen an improvement in the survival of people with DR-TB. Of those diagnosed with DR-TB in 2008, 62.4% remained alive after 18 months, reflecting an overall mortality of 38%. While mortality levels remain high, given that 76% of all DR-TB patients are HIV infected, this represents significant improvements in health outcomes among people with DR-TB compared with other settings.[8]

CHALLENGES

RETENTION IN CARE

While the programme has achieved many successes, several challenges remain in ensuring universal access to ART. With the advent of improved drug regimens and models of care, HIV has become a manageable chronic disease. Approximately 85% of patients are retained in care after 12 months, while only 65% of patients are still in care at 5 years on treatment; this highlights the need for further innovations to improve long-term retention. With increased enrolment came increased losses to follow-up, probably due to saturation of services, patient mobility and death. This trend in patient losses to follow-up stabilised and even began to decrease in the later years as a result of the adoption of measures to adapt to the high numbers of patients on treatment. Innovative models of care included the introduction of adherence clubs and nurse management of patients.

MEN

The proportion of men among adults starting ART remains lower than expected. Although the male walk-in clinic has driven an increase in men testing for HIV and seeking treatment for STIs, men still represent only 30% of adults in care after 10 years of ART treatment in Khayelitsha. There is a need to develop programmes that cater to men's needs in order to improve their access to health services. Furthermore, given that men rarely accompany their partners to antenatal services, innovative mechanisms will be required to identify serodiscordant couples in light of emerging guidelines that will recommend the use of ART to reduce the risk of HIV transmission to the negative partner.[5]

Fig. 3. Monthly patient ART enrollment, 2001 - 2010.

YOUTH

Pre-ART loss to follow up is particularly high among youth. In 2010, up to 70% of eligible young people in the youth clinics were lost to care before starting ART; 60% of these losses occurred immediately after HIV testing. Youth on ART were also more likely than older adults to be lost to follow-up.[9] Recognition of the need to focus specific interventions targeted at this high-risk group led to the establishment in 2005 of two youth clinics that provide adapted and targeted services. Although pre-ART loss to follow-up declined in 2010 – from 70% and 60% in the first quarter to 45% and 29% in the last quarter for the two youth clinics, respectively – early loss to care remains high and is indicative of the need to continue to adapt services and interventions that cater appropriately to the needs of youth.

TREATMENT FAILURE

At 5 years on ART, approximately 14% of patients had confirmed virological failure and 12% were on second-line ART.[4] Mortality and treatment failure are found to be high in patients on second-line treatment. Out of the 32% of patients who failed second-line ART, 60% had poor adherence, and 30% returned to undetectable viral loads after enhanced adherence support; the remainder were switched to a third-line regimen. This highlights the need for early detection of poor adherence in order to provide targeted enhanced adherence support. A recent study in Khayelitsha demonstrated that a viral load performed at 3 months resulted in better virological outcomes than one performed at 6 months,[10] demonstrating the usefulness of the viral load for early detection of poor adherence and virological failure. Third-line drugs are currently not available in the public sector due to their high costs. As access to and time on ART increases, the number of patients requiring second- and third-line regimens is rising, and prices for these drugs will need to be driven down.

THE FUTURE

The key clinical challenges for the next decade will be to achieve universal coverage of patients in need of ART, retain patients in care, and decrease the number of new infections. This will necessitate innovative models of care to decrease the burden of patients on chronic treatment on health facilities – thereby allowing the facilities to increase enrolment on ART – and improve long-term adherence and retention, as well as the implementation of combination prevention strategies.

Box 3. Strategies for the future – innovation and wide implementation

- Further out-of-facility community-based testing (in schools, taxi ranks, community halls)
- Initiation of antiretroviral therapy at higher CD4 thresholds, potentially up to CD4s of 500 cells/μl and/or high viral load thresholds, to further reduce viral circulation and infectiousness at community level (treatment as prevention, TASP)
- Community-based delivery of ART by community health workers and/or chronic dispensing units
- Increased investment in pre-ART (e.g. by creating pre-ART adherence clubs)
- New pre-exposure prophylaxis strategies targeting young female adolescents combined with development of new long-acting antiretroviral formulations and other biomedical preventive interventions.

These strategies will have to be supported by new drug formulations and technologies, including:

- fixed-dose combinations for first- and second-line regimens
- semi-quantitative point of care viral load dipstick to monitor adherence and identify early treatment failures
- POC CD4 devices to reduce pre-ART loss to follow-up, mostly among adolescents
- more robust regimens with a better safety profile, including drugs like darunavir, which maintains a low toxicity in the long term once the viral load has become undetectable
- ensure appropriate access to reproductive health services, including Pap smears for all women including those living with HIV and medical termination of pregnancy at the primary health level.

ADHERENCE CLUBS

Adherence clubs were established to improve clinic efficiency (decongest clinics and allow clinicians time for initiating patients), sustain high enrolment targets, and improve long-term adherence. The adherence clubs are group clinic visits for stable patients that are run by lay health workers and meet every 2 months. On club days patients receive their medication and are screened for opportunistic infections and adverse events, and are referred to a clinician if necessary. In addition, patients receive an educational talk on the day of their visit.

By the end of 2010, a total of 30 clubs were created, 23 of them situated in the community and 7 in the Ubuntu Clinic in Khayelitsha. More than 750 people were enrolled in total. An early evaluation revealed that after 1 year of enrolment in the clubs, 99.2% of the patients were alive; at 2 years this figure stood at 97.5%. After the first year of enrolment, loss to follow-up was 1.1% and mortality 0.7%. This model is currently being expanded to other clinics in order to increase coverage. With the adoption of new national regulations, community health care workers will now be able to manage these clubs effectively. There is still a need to adapt the drug distribution system further in order to allow for regulated and quality-assured chronic drug dispensing units that are able to provide medications more conveniently to patients in the community, thereby ensuring that there is increased access to treatment closer to patient's homes.

REDUCING HIV AND TB INCIDENCE

Despite some early positive signs, the national target of a 50% reduction in HIV incidence is not close to being achieved. An exception to this is in the area of PMTCT, where transmission has been reduced by 80% since the beginning of the programme. There is a need to continue to focus on sustained behavioural interventions, including widespread condom distribution, out-of-facility community-based testing, and biomedical interventions to reduce HIV incidence. New targeted pre-exposure prophylaxis strategies (particularly for women wishing to have children), initiation of ART at a CD4 count of 500 cells/μl, new drug formulations and technologies including fixed-dose combinations, point-of-care viral load and CD4 testing, and robust low-toxicity regimens must be explored.

Furthermore, there is a need to continue to focus on the early diagnosis and treatment of TB and DR-TB, both to improve individual patient outcomes and to reduce transmission. Despite dramatic improvements in case detection for DR-TB, only half of all estimated DR-TB cases are diagnosed in Khayelitsha, and there is a need to increase case detection to curb HIV transmission. Access to molecular diagnostics, including GeneXpert, shows promising results in increasing detection of TB and DR-TB. This could also provide a sensitive screening tool for the provision of INH prophylaxis in TB-negative patients.

DISCUSSION

The success in scaling up HIV/TB service provision in Khayelitsha is attributed to the collaborative efforts of service providers, policy makers, academics, civil society and the community at large. The Khayelitsha programme was successful in achieving community buy-in because it offered a reliable service within the community, was supported through partnerships, and was complemented by widespread treatment literacy.

While the district is best known for its role in demonstrating the feasibility of ART in resource-constrained settings, some of the most important lessons have come in more recent years, where the latent capacity of South Africa's public health system has been demonstrated when subjected to energy, innovation and meaningful collaboration. In spite of the numerous partnerships, Khayelitsha remains a difficult environment in which to deliver services, but it has nevertheless been possible to achieve coverage and scale for a number of activities beyond the most optimistic outlooks of a decade ago. In the areas of PMTCT and ART provision this is being demonstrated in South Africa as a whole, where expectations have been exceeded in recent years.

Increased funding for antiretrovirals and the resulting increase in access to care helped to strengthen the

overall health system, and the implementation of a large-scale TB/HIV programme resulted in decreased rates of both illness and death among people living with HIV as well as a likely reduction in the number of new HIV infections. This unique clinical programme contributed to national policy changes that have had a tangible impact on the lives of thousands of people living with HIV and TB in South Africa, and has demonstrated the possibility of achieving universal coverage of ART and positive patient outcomes in resource constrained settings.

Challenges ahead include the need to reduce HIV transmission in the community. The Khayelitsha programme has paved the way for innovative approaches to treatment provision that have allowed an increasing number of people to access quality treatment closer to their communities. The future of HIV and TB treatment and care will require a focus on combination prevention and treatment interventions, in addition to the adoption of new innovations that can have a tangible impact on the spread of the dual epidemics.

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LETTER

MISINTERPRETATION OF THE 'SAFE SEX/NO SEX' PREVENTION STRATEGY

To the Editor: We refer to the letter to the editor by MacPhail *et al.*[1] discussing the specifics of Whiteside and Parkhurst's article in the April 2010 issue of the *Journal*.[2] MacPhail et al. reported that they theoretically agreed with Whiteside and Parkhurst that refraining from sex during the acute HIV infection period might reduce the rate of HIV transmission when implemented on a wide scale.[1] They summarised the scientific logic of the 'safe sex/no sex' prevention strategy, and explained what the acute HIV infection period is and how critical it is in the transmission of HIV.

MacPhail and her colleagues showed interest in the 'safe sex/no sex' behavioural intervention and its potential significant contribution to global prevention efforts. However, they misrepresent the core arguments Whiteside and Parkhurst propose. In their letter they present the 'safe sex/no sex' strategy incompletely. For example, they report that 'The authors suggest that a limited period of population-wide sexual abstinence might be an effective and low-cost method of interrupting the transmission of HIV' and that 'a limited period of abstinence might be theoretically infective in limiting HIV transmission', suggesting that the strategy focuses solely on abstinence. While an important aspect of the strategy, abstinence is not the entire approach, and indeed the benefits of a month-long commitment to 'safe sex' behaviour should not be disregarded owing to the perceived infeasibility of a month-long commitment to 'no sex'.

Along with considering a limited period of abstinence, Whiteside and Parkhurst promote 'safe sex' or sexual activity engaged in by people who have taken precautions to protect themselves against HIV infection, for instance by adhering to correct and consistent condom use, reducing concurrency, and promoting circumcision and microbicide gel use and other HIV prevention measures. The key arguments for the 'safe sex/no sex' prevention strategy are therefore not completely expressed, being reduced to just abstinence. Whiteside and Parkhurst's article clearly elucidated that the potential intervention would be an aggressive national campaign to ensure that everyone who is sexually active in a population, whether HIV positive or negative, either commit to 100% condom use or refrain from sexual intercourse over a period of a month or longer.[2]

MacPhail *et al.* reported on research with 37 individuals in Lilongwe, Malawi, and Johannesburg, South Africa, to test this theory. Their research tested the 'no sex' and 'safe sex' aspects of the proposed prevention strategy as two distinct and potential interventions to interrupt HIV transmission during the acute infection period. As a result, their findings that there was limited support for the strategy in a population of individuals with known HIV infection, and that there is likely to be even less support from individuals who do not know their status or do not perceive themselves to be at risk of HIV infection, do not adequately indicate the potential challenges the 'safe sex/no sex' prevention strategy is likely to encounter, as the study investigated 'safe sex' and 'no sex' as different interventions, not one as proposed in the 'safe sex/no sex' prevention strategy. This does not mean that MacPhail *et al*.'s research is not important – it will help to articulate the difficulties with a straight 'no sex' approach to the intervention, as well as pointing towards other potential barriers. It does not invalidate the intervention strategy, and perhaps even suggests the need to test out a strategy that is focused on both abstinence and safe sex.

We have reason to believe that, while difficult, an intervention that focuses on promoting both 'safe sex' and 'no sex' has the potential to be successful. In a recent qualitative study of the 'conceptual impact' of this strategy, we found that most of the participants (members of non-governmental organisations (NGOs), academia, the Department of Health, the media and HIV/AIDS researchers) were in favour of the 'safe sex/no sex' prevention strategy (unpublished data). The great majority of the positive respondents reported that it should be implemented because it focuses on both infected and uninfected individuals without necessarily requiring people to know their HIV status. The concern of many participants was the personal or individual willingness and commitment of both infected and uninfected individuals to abstain or engage in safe sex, and not the support they would get in the population to abstain or engage in safe sex, as reported by MacPhail *et al*.[1] In our study, a handful of participants, 2 out of 4, were not in favour of the idea that reported that the 'safe sex/no sex' prevention strategy would not work due to lack of interpersonal support in the population.[3]

In our study, participants in favour of the 'safe sex/no sex' prevention strategy believed that it would uphold and promote rights of privacy of individuals and therefore cause less stigma and discrimination based on HIV status. Participants explained that this would make it easy to mobilise individuals and communities to abstain from sex or engage in safe sex, as it can be done without distinction of whether one is HIV-positive or negative. However, organisers of the prevention strategy

would be aware of the HIV status of the populations as this would help them to monitor the average HIV viral load in the population before, during and after the period of abstinence and safe sex to see how much it impacted on infectiousness, and to get better estimates of effectiveness in practices. The argument by MacPhail *et al.* that the 'safe sex/no sex' prevention strategy may have less support from individuals because they did not know their status or perceived that they were not at risk of HIV infection[1] was not reported as a barrier (in our study) to the feasibility and acceptability of the 'safe sex/no sex' prevention strategy.[3] This is attributed to the fact that the study investigated the feasibility and acceptability of both 'safe sex' and 'no sex' as one strategy, implied by the 'safe sex/no sex' prevention strategy championed by Whiteside and Parkhurst.

As we have found that in theory there is wide support for this prevention strategy (including support by MacPhail *et al*.), it would be of benefit to the entire HIV/AIDS research community for it to be properly articulated and debated. To reduce the strategy to a period of abstinence, as MacPhail *et al*.'s letter to the editor did, obscures the proposed strategy and may prevent us from properly engaging with a very promising prevention effort.

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CPD QUESTIONS

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Regarding missed opportunities to prevent HIV-related paediatric admissions:

1. True (A) or false (B):
   Gastro-enteritis was the most common reason for admission in the sample of 440 HIV-infected children admitted to Baragwanath Hospital.
2. True (A) or false (B):
   In this study, most HIV-infected children admitted to hospital were known to be HIV-infected prior to admission.
3. True (A) or false (B):
   Postnatal uptake of co-trimoxozole was very high in this study and was not commonly related to the reason for admission.
4. True (A) or false (B):
   Failure to receive appropriate PMTCT interventions contributes to a large proportion of paediatric admissions related to HIV infection.

Regarding health services for individuals who do not yet require ART:

5. True (A) or false (B):
   Loss to follow-up among HIV-infected individuals who are not yet on ART is common, but is unlikely to be related to long-term health outcomes.
6. True (A) or false (B):
   A simple package of services may help to improve retention in pre-ART care and thus facilitate regular CD4 cell count testing.

Regarding optic neuritis in HIV-infected individuals:

7. True (A) or false (B):
   The most common cause of optic neuritis in HIV is NRTI-related mitochondrial toxicity.
8. True (A) or false (B):
   There is now consensus that high-dose steroids are part of the definitive management of optic neuritis in HIV-infected individuals.
9. True (A) or false (B):
   In a patient not on antiretroviral therapy (ART), initiation of ART may be part of the effective management of optic neuritis.
10. True (A) or false (B):
    Cytomegalovirus, toxoplasmosis and cryptococcus are common opportunistic infections with ophthalmological manifestations.

Regarding postnatal depression in HIV-infected women:

11. True (A) or false (B):
    Postnatal depression occurs in up to 40% of all HIV-infected women, and typically begins within 6 weeks of birth.
12. True (A) or false (B):
    Postnatal depression does not have HIV-related risk factors (e.g. related to stigmatisation of HIV infection or non-disclosure of HIV status) and does not appear more commonly in HIV-infected compared with uninfected women.
13. True (A) or false (B):
    Key symptoms of postnatal depression are fatigue, irritability and poor functioning, including child care.

Regarding the development of HIV services in Khayelitsha, Cape Town:

14. True (A) or false (B):
    Decentralised management of drug-resistant tuberculosis (TB) to primary care clinics (rather than hospital-based care for all patients with drug-resistant TB) can decrease the average time to treatment initiation.
15. True (A) or false (B):
    Evidence from Khayelitsha suggests that an early viral load after 3 months on ART is a better predictor of subsequent virological failure than viral load testing at 6 months.
16. True (A) or false (B):
    Development of 'male-friendly' clinics located away from traditional public sector clinics (e.g. around taxi ranks) can help to increase the uptake of services as well as detection and effective treatment of men with sexually transmitted infections.

Regarding the use of stavudine:

17. True (A) or false (B):
    Stavudine is appreciably more expensive than tenofovir or abacavir, and cost is the principal reason why tenofovir replaced stavudine in first-line ART regimens in South Africa.
18. True (A) or false (B):
    Randomised controlled trials have shown that stavudine 20 mg given twice daily is as effective as 40 mg given twice daily.
19. True (A) or false (B):
    Lipoatrophy related to stavudine use typically manifests within the first year on treatment.
20. True (A) or false (B):
    Lipoatrophy related to stavudine use is usually dose-related, and occurs less frequently at lower doses.