it is usually irreversible.5 Timing can be crucial because, “Upon first line ART failure diagnosis which relied on clinical and CD4 monitoring, extensive resistance was present to NRTI/NNRTI agents. These findings have profound implications for the optimal time to switch treatment.”6

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5
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6
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FROM THE EDITOR

A recently released report by United Nations Secretary-General Ban Ki-moon, titled *Uniting for Universal Access: Towards Zero New HIV Infections, Zero Discrimination and Zero AIDS-related Deaths*, highlights the facts that the global rate of new HIV infections is declining, treatment access is expanding, and the world has made significant strides in reducing transmission from mother to child.

The Secretary-General makes five suggestions to strengthen the AIDS response. We are encouraged to harness the energy of young people for an HIV prevention revolution, revitalise the push towards achieving universal access to HIV prevention, treatment, care and support by 2015, work with countries to make HIV programmes more cost effective, efficient and sustainable, promote the health, human rights and dignity of women and girls, and ensure mutual accountability to translate commitments into action.

His goal setting is ambitious: to reduce the sexual transmission of HIV by 50%, and prevent all new HIV infections resulting from injecting drug use; to eliminate transmission from mother to child; to reduce tuberculosis deaths in people living with HIV by 50%; to ensure HIV treatment for 13 million people; to reduce by 50% the number of countries with HIV-related restrictions on entry, stay and residence; and to ensure equal access to education for children orphaned and made vulnerable by AIDS.

With these challenges in mind this journal continues to press forward with the goal of keeping you informed, very much with a philosophy of ‘learning by sharing’.

In this edition, Campbell makes an eloquent case for an evidence-based approach to palliative care for children. Gounden compares outcomes in a private and a public sector cohort on antiretroviral therapy and finds some interesting prescribing differences between the two groups, although outcomes were very similar. The recent national testing campaign has included expansion into schools, and Pfaff and De Beer describe a youth-friendly testing campaign that has been implemented by an NGO in the Manguzi district. The surveillance and causes of infant mortality in South Africa was a passion of a very much missed colleague, David Bourne, who unexpectedly passed away in February 2009. The paper by Boule and colleagues is dedicated to David and acknowledges his work. Polyclonal gammopathy is a common finding in HIV, and Tathiah and colleagues present a retrospective study of serum electrophoresis patterns in patients in KZN.

Readers have expressed great interest in case reports. The benefit in learning from real clinical cases is acknowledged by the review committee, so this edition is full of interesting case reports. Continuing our important guidelines series, we present the management of hepatitis B infection as a co-infection with HIV. Thanks to the Southern African HIV Clinicians Society for this excellent collaboration. Coming soon are guidelines for safer conception, HIV-infected health care worker protection, and pre-exposure prophylaxis.

Exciting news is that in 2011 the editorial office is undergoing revitalisation and will have increased resources. This will be good news for those of you who have waited so patiently for reviews of your submissions. I sincerely apologise to frustrated authors who have found our current system tardy. This will be improved in 2011. Please continue to submit copy!

LINDA-GAIL BEKKER
Editor

MESSAGE FROM THE EXECUTIVE

Several things are coming to completion in this important year for the Society. A new board of interim directors has been elected to construct our new constitution, or ‘Memorandum of Association’, legalese from the new Companies Act that is about to come into force. It will be presented to the old executive for discussion, and then circulated for comment, in the next few months. I welcome Tim Tucker, one of South Africa’s unsung heroes from the vaccine enterprise, and Eric Hefer, who is known by reputation to many of you and is a long-time Exco member, to the interim board. They’ll also be advising on our new structure, and how we take the organisation towards new elections in November.

The Society bids a sad farewell to Linda-Gail Bekker as an editor. It has been a tough tenure — the Journal has to compete with many others, and clinicians are not all polite, naturally gifted researchers or writers. Despite this, we distribute over 15 000 copies of every issue, and the feedback is that you love it. LGB has all our gratitude. Incoming editor will be Dr Landon Myer, another Cape Town find, who has experience with international journals and an impressive research CV.

We have secured a further grant from Atlantic Philanthropies, which will allow the Society’s transition to this new structure as well as support our advocacy and networking work. In addition, we have met with the Monument Trust, who fund our nurse/ NiMART work and want this programme expanded even further. On top of all this, all our other activities carry on, and are very successful.

FRANCOIS VENTER
President
There is an urgent need to develop and/or expand palliative care for children in South Africa, and this editorial emphasises the scarcity of an evidence base on which to base clinical and operational decisions.

Children in Africa are more likely to face illness and death before the age of 5 years than anywhere else in the world. In South Africa, HIV infection is the leading cause of death among children aged less than 5 years, and there are approximately 300 000 children living with HIV/AIDS.

An essential tool in the spectrum of care offered to HIV-infected South African children is antiretroviral therapy (ART), and South Africa's children's ART programme is the largest in the world. Un fortunately, according to the national guidelines the programme currently reaches less than half of the children estimated to need ART. If the revised World Health Organization (WHO) guidelines for ART are considered, the proportion of children who need ART but are not accessing it is even greater.

Paediatric wards in South African government hospitals are occupied predominantly by children with HIV and AIDS-related illnesses. Providing hospital care for HIV-infected children is extremely stressful for both health care providers and caregivers, and sick children may face demoralising cycles of repeated hospital admissions. The needs of very ill young children are many and complex, and may be overlooked in busy, overstretched health care facilities.

Furthermore, not all sick children reach a health care facility and therefore are cared for in their own homes, placing a heavy burden on families, communities and informal cadres of health care workers, such as home-based care workers. In an attempt to broaden health care coverage the South African government has adopted a home-based care strategy premised on the belief that families are in the best position, with support from home-based care workers, to deliver a continuum of holistic care from infection through illness and death.

Holistic, ongoing care for very ill, dying and bereaved children and their families is situated within the emerging sub-specialty of paediatric palliative care, which focuses on achieving the best quality of life for children with life-threatening illnesses and their families. Children's palliative care is especially important in an African context because it can be delivered by a range of health care providers (professional and non-professional) and can be delivered both in health care facilities and in the home.

In South Africa, a number of health care facilities, hospices, non-governmental organisations, universities and the Department of Health are already delivering and developing aspects of children's palliative care. The Hospice and Palliative Care Association of South Africa is affiliated to a wider African Palliative Care Association and has been active in children's palliative care, particularly in advocacy and education.

Some existing home-based interventions cover components of children's palliative care; however, palliative care in the form of a comprehensive framework that considers the holistic needs of the child and family is currently limited. In particular, current home-based care programmes may lack an element of support and supervision by professionally trained palliative care providers. Little attention has been paid to the effectiveness and sustainability of home-based care interventions in providing children's palliative care.

Research elsewhere in Africa shows that when a nurse-led community-based children's palliative care intervention is available there are increased referrals, increased prescriptions of essential drugs and improved compliance with treatment regimens. However, the findings from such studies cannot be directly transcribed to the South African context, where care of children is conducted by relatively unskilled home-based care workers, perhaps with little or no support from professionals trained in palliative care.

The marginalisation of palliative care research in Africa is well documented. Reasons given for this marginalisation include lack of skills and knowledge, professional isolation, poor patient accrual, high attrition, lack of agreement on outcome measures, and lack of a common language. There are also unique challenges in developing rigour in sampling design and in reporting. Importantly, there are ethical challenges to be considered when researching very sick children who are HIV infected.
Given the numbers of children affected and the need for palliative care to reach large numbers, I advocate that providing an evidence base for children's palliative care must be a priority. Any research should consider including perceptions and experiences of both caregivers and children, and researchers must consider cultural, language and ethical issues.

REFERENCES
The South African government antiretroviral (ARV) programme was designed as a structured, regulated programme utilising standardised treatment guidelines and multidisciplinary concepts. A major reason for these protocols was achieving maximal and durable suppression of viral replication and stemming development of ARV resistance.\textsuperscript{1-3} In contrast, the private sector is not regulated by such controls. Unregulation over prescribing practices has resulted in use of various treatment combinations. Inevitably, some private patients have entered the government programme. Private sector ARV provision appears to have been overlooked. No formal study has been conducted in South Africa comparing the two sectors with regard to treatment provision to HIV-infected patients. The present study defined a subgroup within the government programme, viz. patients previously treated in the private sector, and compared them with never-treated patients commencing ARVs. Immunological, virological and clinical parameters were used as a means of comparative assessment.

### Objectives
A comparison of the effects of highly active antiretroviral therapy (HAART) on the immunological, virological and clinical status of two groups of patients in the South African government antiretroviral (ARV) programme in KwaZulu-Natal, viz. patients previously treated with ARVs in the private sector and then entering the government programme (private group), and ARV-naïve patients entering the programme directly (government group).

### Methods
A retrospective, cohort study was performed by reviewing records of 58 former private sector patients and 98 patients initiated on ARV treatment in the government sector. Treatment regimens, CD4 cell counts, viral loads and regimen modifications were analysed.

### Results
The study found that use of various classes of ARV drugs varied between the private sector and the government sector. Median distribution of CD4 cell count increased from 158.5 to 419 cells/µl for the private group (42 patients (72.4%)) and from 101 to 358 cells/µl for the government group (95 patients (96.9%)), over an average time span ranging from 29 to 30 months. Median viral load decreased in the private group (29 patients (50%)) and the government group (66 patients (67.3%)) to approximately 3.22 log copies/ml (25 copies/ml) over an average time span ranging from 27 to 29 months. The rate of change of CD4 cell count ($p=0.47$) and viral load ($p=0.097$) between the two groups was not significantly different.

### Conclusion
This study showed that even for patients with prior experience with ARVs, virological and immunological success is still achievable with the use of standardised HAART regimens in the government programme.
(government group) were patients who were initiated on ART in the government sector. Both index and control subjects met inclusion criteria.

Inclusion criteria:

- Adult patients (over 18 years)
- For CD4 count and viral load analysis, at least three sets of measurements were required
- All patients regarded as control subjects (government group) had to be ARV naïve, i.e. no prior exposure to antiretrovirals.

Exclusion criterion:

- Trial patients, i.e. initiated on ART as clinical trial participants and then entering the programme.

In the study, for every index subject identified, the next 2 subjects (consecutive numbering hospital record-keeping system) were selected as control subjects. The rationale for this was that the time frame for both indexes and controls would correlate closely.

Measurements analysed were:

- Baseline patient characteristics
- CD4 cell count
- HIV plasma RNA levels
- Comparison of regimen modifications and reasons for these
- Death.

The study was designed with a statistical power of 80%, with a sample size of 30 index subjects and 60 controls deemed sufficient to detect an effect size of 1.5 between the two groups. The α-level of significance was specified at 0.05, with a confidence level of 0.95.

Following commencement of government ARVs, measurements were recorded at baseline and subsequent intervals of 2 - 13, 14 - 25 and 26 - 41 months. In intervals containing more than one measurement, the average was taken. All data were analysed using Stata software (Windows).

The plotting of line graphs comparing CD4 cell counts and viral load changes only included patients with data in all four time intervals. Patients presenting with baseline and last recorded readings were included in rate of change and distribution analyses.

Measurements of rates of change for CD4 counts and viral loads were taken as functions of the difference between the baseline and latest measurements and follow-up time. The two-sample Wilcoxon rank-sum (Mann-Whitney) test was used for analysis of rates of change for CD4 and viral load. Distribution of CD4 cell counts and viral loads were calculated using median values and interquartile ranges (IQRs).

RESULTS

Patient baseline characteristics are set out in Table I.

COMPARING ANTIRETROVIRAL USE IN THE PRIVATE SECTOR VERSUS THE GOVERNMENT SECTOR

During this study, first-line regimens in the government sector consisted of lamivudine, stavudine and efavirenz/nevirapine. The second-line regimen was zidovudine, didanosine and lopinavir/ritonavir.

Figs 1 - 3 illustrate percentages of private sector patients on individual ARVs before entry into government hospitals, and percentages of all patients studied (both private and government initiates) on individual ARVs in the government programme.

Lamivudine formed the backbone of first-line regimens in the government sector (98%) (N=156), compared with 62% (N=58) in the private sector. Zidovudine was

<table>
<thead>
<tr>
<th>Characteristics (N=156)</th>
<th>Private group (N=58)</th>
<th>Government group (N=98)</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Females</td>
<td>67</td>
<td>80</td>
<td>75</td>
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<tr>
<td>Males</td>
<td>33</td>
<td>20</td>
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<td>1</td>
<td>3</td>
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<tr>
<td>Indian</td>
<td>12</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>White</td>
<td>4</td>
<td>1</td>
<td>2</td>
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<td>WHO staging (baseline)</td>
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<tr>
<td>Stage 1</td>
<td>33</td>
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<tr>
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</tr>
<tr>
<td>Opportunistic infections</td>
<td>32</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>Oesophageal candidiasis</td>
<td>2</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>12</td>
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<td>16</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>AIDS-related wasting syndrome</td>
<td>7</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
the second most frequently used nucleoside reverse transcriptase inhibitor (NRTI) (59%) \((N=58)\) among private patients.

Stavudine was used in regimens of 96% of all government patients compared with 50% of private sector patients. Among private patients, 47% had previous experience with didanosine compared with 7% of all government patients. Abacavir and tenofovir constituted the private regimens of 2% of patients.

Efavirenz was commonly used in both the private (55%) and government (74%) sectors. In the private sector, 19% had experience with nevirapine, compared with 37% in the government sector.

In the private sector 28% of patients had protease inhibitor (PI)-containing regimens. In many cases, PIs constituted part of first-line treatment. The most commonly used PI was lopinavir/ritonavir (used by 12% of patients in the private sector). Lopinavir/ritonavir was used in 9% of government sector regimens.

Ritonovir was used individually in 5% of private sector regimens. Indinavir and saquinavir, and nelfinavir and atazanavir, were used in 5% and 2%, respectively, of private sector regimens.

In the private sector sample, 69% began treatment privately in 2003 or 2004. Twenty-five per cent of these patients were placed on dual therapy at some stage during private treatment. The majority of these regimens included single-class drugs, viz. NRTIs. On commencing government ARVs, the majority of these patients (82.7%) were placed on first-line regimens. The remainder were either placed on regimen 2 or remained on their private sector regimen.

**COMPARING CD4 CELL COUNT CHANGES IN THE PRIVATE GROUP VERSUS THE GOVERNMENT GROUP**

Twenty-six private group patients (44.8%) and 63 government group patients (64.3%) presented with baseline median CD4 counts of 156 cells/µl and 106 cells/µl, respectively (Fig. 4). Commencement of ARVs in the government group resulted in an initial higher rate of increase in CD4 count. This subsequently diminished after 12 months, while the private group’s median count increased steadily. The last recorded median CD4 counts were 419 cells/µl for the private group and 360 cells/µl for the government group.

**CD4 CELL COUNT DISTRIBUTION**

Both groups displayed variable CD4 count distribution, so median values and IQRs were calculated. Distribution of CD4 counts (cells/µl) at baseline showed:
- private group \((N=42)\): median/IQR – 158.5 (111 - 325)
- government group \((N=95)\): median/IQR – 101 (33 - 153)
- both groups \((N=137)\): median/IQR – 122( 46 - 175).

Distribution of last recorded CD4 counts (cells/µl) showed:
- private group \((N=42)\): median/IQR – 419 (231 - 706)
- government group \((N=95)\): median/IQR – 358 (263 - 506)
- both groups \((N=137)\): median/IQR – 368 (254 - 538).
The private group's median CD4 count increased from 158.5 cells/µl to 419 cells/µl over an average of 29 months. In the government group, the baseline median (101 cells/µl) reached 358 cells/µl over an average of 30 months.

The majority of observations (75%) in the private group and government group recorded baseline counts of 325 cells/µl and 153 cells/µl, respectively. These values increased substantially after commencement of government ARVs. The last recorded readings indicated that 75% of patients in the private and government group had attained median CD4 counts of 706 cells/µl and 506 cells/µl, respectively.

**AVERAGE RATE OF CHANGE OF CD4 CELL COUNT**
The average rates of change of the CD4 cell count in the government group and the private group were 9.74 cells/µl and 8.81 cells/µl per month, respectively.

The two-sample Wilcoxon rank-sum (Mann-Whitney) test compared rate of change in CD4 count between 42 patients in the private group (72.4%) and 95 patients in the government group (96.9%). Average follow-up time for the private group and government group was 29 months and 30 months, respectively. Using a significance level of α=0.05, the test concluded that there was no significant difference in rate of change of CD4 count (p=0.47) between the two groups.

**COMPARING VIRAL LOAD CHANGE IN THE PRIVATE GROUP VERSUS THE GOVERNMENT GROUP**
In the government group 43 patients (43.9%) presented with a median baseline viral load of 10.61 log copies/ml (40 000 copies/ml) (Fig. 5), compared with 7.82 log copies/ml (almost 2 500 copies/ml) in 17 patients in the private group (29.3%). Commencement of government ARVs achieved rapid viral load suppression in the first 8 months in the government group, compared with the private group. However, both groups eventually reached log 3.22 copies/ml (<25 copies/ml – undetectable levels).

**VIRAL LOAD VALUE DISTRIBUTION**
Distribution of viral load values was variable. Distribution of viral load values (log copies/ml) at baseline showed:

In the private group, median viral load decreased from 8.88461 log copies/ml (7 200 copies/ml) to 3.218876 log copies/ml (<25 copies/ml – undetectable levels), over an average of 27 months. The government group's median viral load decreased from 10.7425 log copies/ml (>46 000 copies/ml) to undetectable levels, over an average of 29 months.

Seventy-five per cent of patients in the private group and government group presented with baseline viral load levels of 11.39275 log copies/ml (>88 000 copies/ml) and 12.10071 log copies/ml (180 000 copies/ml), respectively. Viral load decreased after commencement of government ARVs. The private group and the government group showed last recorded readings of 5.703783 log copies/ml (300 copies/ml) and undetectable levels, respectively.

**AVERAGE RATE OF CHANGE OF VIRAL LOAD**
The average rates of change in viral load for the government group and the private group were 0.345804252 log copies/ml (1.41 copies/ml) per month and 0.328619966 log copies/ml (1.39 copies/ml) per month, respectively.

The two-sample Wilcoxon rank-sum (Mann-Whitney) test compared rates of change in viral load between 29 patients in the private group (50%) and 66 patients in the government group (67.3%). Average follow-up times for the private group and the government group were 27 months and 29 months, respectively. Using a significance level of α=0.05, the test concluded that there was no significant difference in rate of change of viral load (p=0.097) between the two groups.

**REGIMEN MODIFICATION AND CAUSES**
In the private group, 46.5% of regimen modifications occurred after commencing government ARVs, while the government group recorded 45.9%. Major causes for modifications in both groups were lactic acidosis, peripheral neuropathy, tuberculosis, lipodystrophy and virological failure.

In the private group and the government group, 12% and 7% of patients, respectively, experienced symptoms of lactic acidosis or hyperlactataemia. In all episodes stavudine was changed to zidovudine. Ninety per cent of patients (both groups) who experienced symptoms of
hyperlactataemia were female. Median ages recorded in the private group and the government group were 34 and 40 years, respectively.

Nine per cent of private patients and 5% of government patients were diagnosed with lipodystrophy. In all patients stavudine was implicated and replaced with zidovudine. Overall, 80% of these patients were female and the median age for both groups was 40 years. The baseline median CD4 counts for patients diagnosed with lipodystrophy in the private group (249.5 cells/µl) and the government group (194 cells/µl) correlated with observations of baseline CD4 counts below 350 cells/µl being a risk factor for development of lipodystrophy.5

Seven per cent of the private group and 19% of the government group experienced peripheral neuropathy. Stavudine was implicated in most cases and replaced with zidovudine.

In the private group and the government group, 3% and 5% of patients, respectively, were co-infected with tuberculosis while on government ARVs, necessitating regimen modification.

The second most common factor for regimen changes in the private group was virological failure. Approximately 10.3% of private patients developed virological failure. In the government group only 1 patient developed virological failure.

Approximately 5.2% of private patients were lost to follow-up, probably due to death. This assumption was based on their last recorded CD4 counts (low). However, confirmation of death was incomplete and presumed from loss of follow-up data. No patient deaths were recorded in the government group.

**DISCUSSION AND CONCLUSION**

This study hypothesised that due to prior ARV use, and in many instances use of sub-therapeutic regimens and treatment interruption, treatment in the private group would not be as successful in terms of immunological, virological and clinical improvement as in the ARV-naïve government group.

However, it was observed that with implementation of standardised highly active antiretroviral therapy (HAART) regimens for the private group, there was immunological and virological improvement. On commencement of government HAART, there was no significant difference in rate of change of CD4 count (p=0.47) or viral load (p=0.097) between the two groups.

However, while both groups showed decreased viral loads, an important point in terms of distribution analysis was that over 27 months 75% of patients in the private group recorded a median viral load of 300 copies/ml, while in the government group the majority recorded undetectable levels (<25 copies/ml). This implies that a better pharmacological response to HAART was possibly achieved in the ARV-naïve group compared with the previously treated group. This assumption is further enhanced by higher percentages of virological failure (10.3% v. 1%) and death (presumed) (5.2% v. nil) occurring in the private group.

Usage of various ARV classes varied between the two sectors. During this study, drugs reserved as second line in the government sector (didanosine and zidovudine) often formed part of first-line regimens in the private sector. The only PI available in the government sector at the time was lopinavir/ritonavir, which was used by 9% of patients as part of second-line treatment. In the private sector 28% of patients had PI-containing regimens, often as part of first-line treatment. A quarter of private sector patients studied were placed on dual therapy (associated with partial viral suppression) at some stage during private treatment. This may be attributed to non-standardised prescribing trends in the private sector. Studies have found that prescribing practices of physicians may be influenced by interactions with pharmaceutical representatives regarding awareness, preference and rapid prescribing of new drugs.6

In both groups, 90% of patients with hyperlactataemia were female, corresponding with studies showing female gender to be a prognostic factor.7 The higher percentage of lipodystrophy in the private group corresponds with observations of prior ARV experience being a risk factor.5 Peripheral neuropathy was the most frequently observed toxicity in the government group and was linked to stavudine use.

This study has shown that even with previous ARV exposure, immunological and virological success is achievable. Potent standardised regimens, counselling, regular follow-up and management of side-effects are essential. Overall the success achieved in both groups may be attributed to implementation of standardised treatment guidelines and multidisciplinary approach of the government programme. The private sector should seek to be guided by the same approach.

The above was submitted as part of the requirements for a Masters in Medical Science (Clinical Pharmacology), supervisor Professor Viren Rambiritch, PhD. The degree was awarded cum laude by the University of KwaZulu-Natal on 24 April 2009.

Ethics approval was obtained from the University of KZN and the KZN Department of Health. There was no conflict of interest or competing interests.

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South Africa’s HIV epidemic disproportionately affects the youth. The importance of knowing one’s status via voluntary counselling and testing (VCT) is recognised as a key strategy in fighting the epidemic and is reflected in the National Strategic Plan (NSP), which has set targets of 70% of all adults knowing their status by 2011 and 25% of all adults having been tested in the past 12 months. The Human Sciences Research Council survey in 2008 showed that 50.8% of all South Africans 15 years and older have had an HIV test, pointing to wider acceptance of VCT. As a further response to reaching the NSP target, the national HIV counselling and testing campaign was launched in April 2010 with a focus on mobilising all South Africans to be tested for HIV and ensuring that every South African knows their HIV status. Both the NSP and the national HIV testing campaign recognise the importance of community mobilisation and community-based models of VCT to achieve these targets. The NSP in particular has a goal to expand successful strategies of testing outside health care facilities to cover 70% of all districts by 2011.

Young people are reluctant to use health care facilities, and several ‘youth friendly’ strategies have been tried to target adolescents. This case study serves to document the successes of one such community-based VCT strategy, aimed at young people in northern KwaZulu-Natal, South Africa.

STUDY SETTING
Tholulwazi Uzivikele (TU) is a non-profit organisation serving the communities surrounding Manguzi Hospital in northern KwaZulu-Natal. The area borders Mozambique and is extremely rural with poor access on sandy roads. Unemployment is estimated at 70% and the antenatal HIV prevalence is 28%. TU was founded in 2002 by concerned staff members at Manguzi Hospital wanting to mitigate the effect of the HIV epidemic on the surrounding community. The organisation started with an emphasis on orphans and vulnerable children and home-based care, but has subsequently expanded to include programmes for poverty relief, HIV prevention, and access to medical and social services. Antiretroviral treatment (ART) is available at Manguzi Hospital and all 10 local clinics. CD4 tests can be done and ART initiated at any of these sites. Patients can usually commence treatment within 2 weeks of a diagnosis, and most of the population lives within a 10 km radius of such a clinic.

DESCRIPTION OF ACTIVITIES
The VCT programme was started by TU in August 2007. The aim of the programme was to increase HIV awareness and offer VCT in schools, using drama to sensitise, educate and encourage participation among the learners. This programme was made possible by close co-operation with the Department of Education and local school principals and teachers and financial and technical support from Oxfam OHAP. TU has built credibility over the years with these role-players, initially through the orphan programme. Principals realise the difficulties that learners face in accessing VCT and recognise that the programme meets an unmet learner need to access a non-judgemental, youth-friendly information service. Before this programme started, learners wanting to access VCT could only do so by going to the clinic, which often required the whole day away from school as most government VCT activities were not available on weekends.

In order to increase levels of participation by learners during the education process, it was decided to use ‘forum drama’. While drama has been used for many years in the HIV/AIDS field, forum drama specifically encourages the audience to intervene and make decisions for the actors at various stages of the drama. The audience thus determines the eventual outcome of the story by the choices they have made, simulating real life. An organisation skilled in using forum drama for HIV awareness, Dramatic Change, provided training for all the actors. At the same time, all the actors were also trained as VCT counsellors by the Foundation for Professional Development, supported by funding from USAID.
Of the 64 high schools in the Manguzi sub-district, 19 were initially targeted, being secondary level schools. The team visited each school on a 5-day programme. Most programme activities, such as sensitisation and drama, occurred during school hours. These activities were integrated into the school syllabus in subjects such as Life Orientation and sport with the participation of teachers.

The team consisted of four actors, who also functioned as educators and had all been trained as VCT counsellors. Several of the actors were HIV positive. During the first two days, the actors were invited as guest teachers and taught classes during the Life Orientation lessons at the schools. Topics covered included life skills, goal setting, vision and romantic relationships, moving on to the origin of HIV/AIDS, HIV as an infectious disease, stigma, transmission, prevention and VCT. On the third day the forum drama was performed for the entire school. The story line consisted of friends discussing relationships, social situations touching on peer pressure, abuse, and choices made with an emphasis on knowing one’s status and avoiding risky situations. It was interrupted at regular intervals by a narrator who gave the audience the chance to make decisions for the actors or even to come on stage and play their role. The sessions were very interactive, as learners were given the opportunity to dramatise events from their own experience.

On the fourth day confidential counselling was offered to all students who might decide to test for HIV. The counselling and testing was conducted in temporary tent structures that allowed for discretion in terms of location. Learners could access testing at any time during the school day. The actors conducted the counselling and testing, with support from a nurse. The service was promoted as a health and life skills counselling service — not all learners who accessed the service were necessarily tested. The emphasis was placed on gaining more information and was rooted in psychosocial support and risk management strategies flowing from the drama of the previous day. Learners were provided with information, and only given the option of testing once they were comfortable. Learners who were diagnosed and confirmed as being HIV positive were referred to a local clinic, where CD4 testing and ART were available. The VCT team also provided ongoing psychosocial support for diagnosed individuals by phoning them within a week of the test being conducted and linking individuals in need of support to a local support group.

On the fifth day a talent search was conducted as a closure event, strengthening the relations with the programme and encouraging ongoing dialogue between learners. Often learners presented different drama plays around HIV awareness, from which the VCT team in turn learnt more about the context.

Through interaction with concerned school principals and teachers the VCT team also facilitated the establishment of ‘HIV Champions’ at schools. HIV Champions were teachers or student leaders who augmented the knowledge of students and teachers in a specific school and were selected on the basis of their willingness to lead and their interest in the future of youth. Support groups were also organised in the schools and structured as social clubs or sports clubs, without discriminating on the basis of HIV status.

**OUTCOMES**

During 2008 and 2009 all 19 secondary schools were visited once and 13 were visited twice; 12 996 beneficiaries were reached with the awareness drama, and 2 394 students were tested. HIV prevalence in the tested population was 2.8%

In October 2009 the last three secondary schools on the schedule were visited again in order to evaluate the programme. The counsellors went to each school, surveying clients who had been tested previously. In each of the three schools, questionnaires were handed out to the first 79 clients who were found of the total of 217 who had been tested. All 79 forms were returned. Of the respondents, 91% felt that the counsellor was sympathetic throughout the counselling session, 94% felt that the service was done with confidentiality and privacy, and 100% said they would recommend the service to someone else. When asked how the service could be improved, most made comments such as ‘well done’ and ‘keep it up’. Nine respondents gave minor suggestions as to how the service could be improved, e.g. by handing out T-shirts or refreshments after testing, and one respondent suggested that testing be done in a building rather than in a tent.

Evaluation of how many accessed ART or underwent any behaviour change will need to be more detailed and has not yet been done.

**DISCUSSION**

VCT services have been identified as an essential component of comprehensive HIV care. VCT is both an entry point to antiretroviral care and may promote behaviour change, particularly for those who test positive. However, VCT services are often under-utilised. In South Africa, although rates of testing in adults aged 15 years and above increased from 21.4% in 2002 to 30.5% in 2005 and 50.8% in 2008, still almost half of South Africans have never had an HIV test. The 2005 study showed that those in informal rural areas were less likely to know their status than those living in formal urban areas (19.3% v. 40.4%).

There are several reasons for low uptake of VCT services, including confidentiality, concern about reaction from male partners, lack of access to free testing, transport costs, trust, stigma of being seen at a health care facility, and lack of perceived personal risk.

Community-based strategies of VCT have been proposed as one way to address these barriers. Community-based strategies move the services closer to the people, but may also overcome stigma and confidentiality issues that are concerns in visiting a health care facility. Community-based VCT has been shown to increase acceptability and rates of testing in several studies. Moving VCT to...
Another community-based strategy has been to offer VCT in the home. After collecting blood as part of a door-to-door health census, delivery of results to the home as opposed to collecting them at a facility increased the number of adults aged 25 - 54 who accessed their results from 10% to 46%. Travel distance, facility waiting time and issues of confidentiality, including emotional composure during the walk home, were all cited by participants as factors favouring home-based VCT. Youth, however, were reluctant to receive results in the home, stating that the visit would invite questions and speculation by other family members. A recent Cochrane review of home-based VCT found that home-based testing or delivering results to the home rather than collecting them at the clinic leads to a higher uptake in testing, but cautioned that the literature was too limited to recommend large-scale implementation.  

Young people in particular are reluctant to use health services, and several strategies to target adolescents have been tried. The Department of Health has piloted a programme of ‘youth friendly’ clinics under the National Adolescent Friendly Clinic Initiative to try to address this situation. Several community-based VCT strategies have also been specifically aimed at making VCT more accessible to young people and increasing uptake. A review of these initiatives has highlighted their diversity and emphasised that there is no one ideal model for VCT in young people and that programmes must be innovative and tailored to meet the specific context and reach a specific target of young people. The review did note several key principles that these diverse youth-centred VCT programmes had in common. These included involving learners in the planning and delivery process, mobilising community-based peer educators, ensuring suitable accommodation to enable privacy, training providers in youth-friendly approaches, integrating post-testing services, and supplying educational material and condoms. Many of these principles feature in the TU VCT programme. Drama has been recognised as a key medium to reach young people and has been used successfully to motivate adolescents to undertake HIV testing, both in South Africa and in Malawi. In Khayelitsha HIV testing increased by 172% in sites that had received a drama presentation compared with sites that had not.

However, none of these drama programmes were combined with offering HIV testing as part of the same programme. Similarly, very little has been written about the process of taking VCT into the schools. In Uganda many clients were found to prefer a mobile van to facility-based testing.

The HIV prevalence in students who were tested in Manguzi was 2.8%. This is similar to the experience of Mpondi, where an HIV prevalence of 2.7% was found among high-school students who underwent voluntary testing (personal communication). Both programmes indicate that offering VCT in schools is both feasible and acceptable as part of a package of increasing provision of HIV care to young people.

CONCLUSION

South Africa has an ambitious NSP, but more needs to be done if the targets are to be met with the time remaining. The TU VCT programme is an example of a successful community-based VCT strategy that has been effective in reaching young people.

REFERENCES

The response to HIV in sub-Saharan Africa (SSA) in the past decade has resulted in one of the largest and most dramatic health interventions in recent history, with the provision of antiretroviral therapy (ART) both as treatment to infected adults and children and to prevent vertical transmission of HIV from mother to child.

Where monitoring systems have been able to track outcomes of large-scale ART programmes in SSA, they appear to be effective. However, outside of small demographic surveillance sites weak vital registration systems limit our ability to demonstrate the population-level impact of these interventions. South Africa is unique in having a high burden of HIV disease together with one of the most complete vital registration systems on the continent, in which 80% of deaths are currently estimated to be registered. We have previously demonstrated in South Africa at a national level that infant deaths (at ages 1 - 11 months) increased over the period 1997 - 2002, with the greatest increase at 2 - 3 months of age. This peak in early infant deaths at age 2 - 3 months did not occur during the period 1997 - 2007. It is possible that these interventions have averted the greater increase in early infant deaths seen in the rest of South Africa over this period.
infant deaths could not be ascribed solely to improving registration of deaths over time, and was consistent with cohort studies of HIV-infected infants.9–10

In this present analysis we describe post-neonatal infant mortality by age in months across the 9 provinces in South Africa from 1997 to 2007, and reflect on the relationship between the early peak in infant deaths and province-specific HIV epidemic and intervention characteristics.

**SETTING**

Antenatal HIV-1 seroprevalence had reached 17.0% in pregnant women in South Africa by 1996, rose steadily to 30.2% by 2005, and has subsequently remained around this level.11 In 2005, the HIV seroprevalence varied between provinces from 15.7% in the Western Cape to 39.1% in KwaZulu-Natal (Table I). There have also been large inter-provincial variations in both timing and coverage of antiretroviral interventions in South Africa.12

**METHODS**

We obtained South African infant mortality counts by age at death for the period 1997 - 2007 from Statistics South Africa. Infant deaths under 1 month were excluded from analysis because of the potential misclassification of live and stillbirths. Absolute counts of infant deaths were considered by province, year and age at death in months, starting at 1 month of age. For graphical presentation purposes, counts were averaged across the periods 1997 - 1999, 2000 - 2001, 2002 - 2003, 2004 - 2005 and 2006 - 2007. All analyses were conducted using Stata statistical software v11.0 (Stata-Corp Inc, College Station, Texas). The study was approved by the University of Cape Town Research Ethics Committee.

**RESULTS**

The total number of registered deaths in infants aged 1 - 11 months increased from 15 404 in 1997 to 34 479 in 2006 (32 828 in 2007). Eight of the 9 provinces experienced an annual peak in registered infant deaths at 2 - 3 months of age between 1997 and 2007 (Fig. 1). This peak in mortality was not observed in the Western Cape. In 7 of 9 provinces registered post-neonatal infant deaths did not rise markedly in 2007 compared with 2005 (Table I). Expressed as a ratio to deaths at 11 months of age (which compensates for increasing registration over time), this peak was still present in 2006 - 2007 in the 8 provinces where it was observed, but had declined in 5 compared with the ratios seen in previous calendar periods.

**DISCUSSION**

Our previous study demonstrated, at a national level for the period 1997 - 2002, a year-on-year increase in infant mortality at each age of death (1 - 11 months), with the greatest increase at 2 - 3 months.8 This current analysis by province for the period 1997 - 2007 demonstrates the continued presence of a peak in infant deaths at 2 - 3 months of age in the context of the evolving HIV epidemic in South Africa, with reported mortality stabilising in most

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**Fig. 1. Registered post-neonatal deaths in South African infants by age in months, province and year of death registration (note that the scale differs between provinces).**
provinces in 2006 - 2007. The analysis further identifies the absence of a peak in mortality at 2 - 3 months in the Western Cape.

The rapid rise in registered deaths over the period 1997 - 2005 is largely attributable to improvements in the registration of infant deaths, but could also in part be due to increasing levels of maternal HIV prevalence, which have led to increasing levels of vertical HIV transmission and AIDS mortality. The absence of a further increase after 2005 in registered early infant deaths in 7 of the 9 provinces could potentially be ascribed to the slowing of the year-on-year increases in the completeness of infant death registration, the stable proportion of pregnant women with HIV since 2005, and the accelerated scale-up of prevention of mother-to-child transmission (PMTCT) and ART interventions after 2005 (Table I). The absence of this peak in the Western Cape corresponds with a delayed provincial HIV epidemic, and exceptionally high coverage of pregnant women with PMTCT interventions of increasing effectiveness.

PMTCT was first introduced in the Western Cape in 1999 in Khayelitsha, following the protocols that had been effective in Thailand. At the time this was the sub-district in the province with the highest antenatal HIV seroprevalence (22% in 2001). Between 2000 and

<table>
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<th>TABLE I. BIRTHS, INFANT DEATHS, AND HIV AND ANTIRETROVIRAL INTERVENTION CHARACTERISTICS IN SOUTH AFRICA BY PROVINCE</th>
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*Source: Actuarial Society of South Africa AIDS and Demographic Model.  
†Source: Antenatal Surveys from the National Department of Health.  
‡Source: Child Gauge 2009.  
§Coverage reflects the ratio of new enrolments to the number of individuals anticipated to be newly AIDS symptomatic in each year, based on (*) above.  
*Coverage is from an alternative source.
A decline in under-2 mortality has recently been described in a rural KwaZulu-Natal setting after 2004, ascribed in part to the PMTCT programme that was rapidly scaled up in the surveillance area before the observed decline. The KwaZulu-Natal study found that the major part of this decline was in post-neonatal infant deaths, in keeping with the currently presented data.

The current study has a number of limitations. The ecological design cautions us to consider alternative explanations for our observations. As discussed, the lack of clarity on the completeness of infant death registration complicates the interpretation of these data. Further, we did not attempt to analyse mortality trends by cause of death, owing to the low proportion of HIV-related deaths recorded as being due to HIV. We have, however, demonstrated previously that the peak at 2 - 3 months of age was absent in the small proportion of infant deaths where HIV was unlikely to be related to the underlying cause.

We have identified a single province out of 9 South African provinces in which a peak in early infant deaths at 2 - 3 months of age did not occur during the period 1997 - 2007. This was the province with the earliest and highest coverage of ARV interventions from 1999 onwards. It is possible that these interventions have averted the greater increase in early infant deaths seen in the rest of South Africa over this period. Prospective monitoring of the age pattern of infant deaths by province could in future prove an important tool for assessing the impact of ARV and PMTCT interventions on child survival in South Africa as the completeness of infant death registration stabilises, and the coverage and effectiveness of interventions are further intensified.
Objective. To describe the effect of HIV serostatus on serum proteins, serum protein electrophoresis (SPEP) patterns and monoclonal bands.

Setting. Inkosi Albert Luthuli Central Hospital, Durban.

Design. Retrospective, anonymous analysis of routine laboratory results.

Results. Monoclonal bands were not increased in HIV-positive patients, who were younger and had increased polyclonal and oligoclonal bands and total proteins when compared with HIV-negative patients.

The hallmark of HIV infection is impairment and dysregulation of the immune system. Specific defects in the humoral arm of the immune system, such as polyclonal activation of B cells, have been widely described in HIV infection. An increased incidence of plasma cell disorders, such as benign polyclonal gammapathy, monoclonal gammapathy, oligoclonal gammapathy, B-cell lymphomas and multiple myeloma, has also been reported in HIV-positive individuals. These abnormalities occur at a significantly younger age (mean 33 years) than in HIV-negative patients.

Hyperactivated B cells secrete HIV-specific and nonspecific antibodies. Serum protein electrophoresis (SPEP) is a technique that separates proteins on the basis of their electrical charge in order to determine specific patterns in certain diseases. HIV and other infections may have an influence on serum electrophoresis patterns. There may also be ethnic and racial differences in the effects of HIV on immunoglobulin production.\(^1\) The prevalence of monoclonal gammapathies, for example, is significantly different between racial groups.\(^2\) Immunoglobulin levels may also vary depending on differing risk behaviours.\(^3\) There is also controversy regarding the association between HIV infection and multiple myeloma. Some studies have documented an increased risk (approximately 4.5-fold) of multiple myeloma in HIV/AIDS patients,\(^4,5\) while other studies have not.\(^6\)

Previous studies in South Africa have not shown a link between multiple myeloma and HIV infection.\(^3,4,6\) However, the diagnosis of myeloma may be difficult or delayed in HIV-positive patients because features such as anaemia and recurrent bacterial infections occur both in multiple myeloma and HIV infection.\(^5\)

The hallmark laboratory feature of multiple myeloma is the presence of monoclonal bands on SPEP, although these bands may appear with other conditions. The aims of this study were to determine whether there was a higher prevalence of monoclonal bands in HIV-positive patients and to describe differences in serum protein concentrations and electrophoresis patterns in HIV-positive and HIV-negative patients in KwaZulu-Natal province.

METHODS

This retrospective anonymous database study utilised results of routine tests conducted at Inkosi Albert Luthuli Central Hospital, Durban. All patients who had SPEP performed at this hospital during 2006 were entered into the study. Approximately 20% of these patients had clinically suspected haematological malignancies. Serum protein levels, electrophoresis patterns, basic demographic data and HIV enzyme-linked immunosorbent assay (ELISA) results were downloaded anonymously and compared and described in HIV-positive and negative patients. Patients without HIV results were excluded. The chi-square test and Fisher’s exact test were used for
the comparison of categorical data, and Student’s t-test for the comparison of continuous variables. Statistical analysis was performed on STATA™10 (StataCorp, Texas, USA). The study was approved by the Biomedical Research Ethics Committee of the Nelson R Mandela School of Medicine, University of KwaZulu-Natal.

RESULTS
Results are set out in Table I.

DISCUSSION
HIV-positive patients in whom electrophoretograms were performed were significantly younger than those who were HIV negative. These data are similar to those of other studies, in which indications for SPEP occur in HIV-positive individuals at a significantly younger age (mean 33 years) than in HIV-negative patients.3

The serum protein abnormalities and SPEP patterns concur with other studies in HIV-positive individuals.7 The increase in total proteins in HIV-positive individuals may be due to the increase in the IgG fraction of the gamma globulins. This is likely to be caused by hyperactivation of B cells due to chronic antigenic stimulation by antigens of HIV, viruses such as hepatitis C, or other opportunistic infections. Polyclonal gammapathy and oligoclonal bands were significantly increased in HIV-positive patients. The majority of oligoclonal bands were present on a background of polyclonal gammopathy, suggesting simultaneous polyclonal B-cell activation and selective B-cell oligoclonal proliferation. The pathologist interpreting the electrophoretograms in this scenario should repeat the SPEP, with dilutions, to minimise the interference of the background polyclonal gammapathy. Immune paresis, which results from the suppression of normal globulins due to the uncontrolled proliferation of the clone causing the B-cell malignancy, was, as expected, higher in the HIV-negative group.

The prevalence of monoclonal bands in HIV-positive patients was 8%, which is higher than previously described (2.5%); estimates of the prevalence of monoclonal bands, however, vary widely. There was no statistical difference in the prevalence of monoclonal gammapathy between the HIV-seronegative and positive groups. However, it is possible that monoclonal bands in HIV-positive patients may be obscured by the background polyclonal gammapathy. The absence of a monoclonal spike therefore does not altogether exclude the possibility of a monoclonal plasma cell disorder in HIV-positive patients.

This study is biased because only patients who had indications for both SPEP and HIV tests were included. However, multiple myeloma and SPEP abnormalities are likely to be even less prevalent in patients who have no indications for either of these tests. The conclusion of this study, that monoclonal bands are not significantly increased in HIV-positive patients, is therefore valid despite this bias.

CONCLUSION
HIV-positive patients often succumb to opportunistic infections and other malignancies at a relatively young age. With the roll-out of antiretroviral therapy in South Africa, the incidence of multiple myeloma and other

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<th>TABLE I. AGE, PROTEIN LEVELS AND SPEP FINDINGS IN HIV-POSITIVE AND NEGATIVE PATIENTS (N=331)</th>
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<td><strong>C-reactive protein (mg/l)</strong></td>
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<td><strong>SPEP patterns</strong></td>
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<td><strong>Polyclonal gammapathy</strong></td>
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<td><strong>Oligoclonal bands</strong></td>
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<td><strong>Immunoparesis</strong></td>
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p-values in bold are significant at α=0.05.
Figures in parentheses are percentages where indicated, or otherwise represent the 95% confidence intervals.
* t-test.
† Chi-square test.
‡ Fisher’s exact test.
malignancies may increase as patients on highly active antiretroviral therapy (HAART) survive longer. Furthermore, the increase in CD4 T-cell numbers following HAART may promote B-cell maturation and differentiation to mature plasma cells, with possible emergence of neoplastic clones. Although monoclonal bands were not increased in HIV-positive patients in this study, vigilance is nevertheless prudent, since multiple myeloma may occur at a younger age (<40 years) and the interpretation of SPEP patterns is complex in HIV-positive patients.

REFERENCES
Hepatitis B virus infection is a global health problem with an estimated 350 million people chronically infected. Routes of transmission differ between geographical regions, with acquisition in developed-world settings characteristically occurring in adulthood, predominantly in high-risk groups through parenteral or sexual exposure. In contrast, perinatal or horizontal transmission during childhood is the norm in most sub-Saharan African regions that do not routinely vaccinate children in the first year of life. Age at HBV infection determines the risk of chronicity of disease, with the highest rates developing in perinatally acquired HBV from mothers who are HBeAg positive (90%). In contrast, 25 - 30% of children infected with HBV develop chronic infection, whereas this figure drops to <5% in adults.2-5

Chronic HBV is endemic in sub-Saharan Africa, where HBsAg prevalence varies between 0.3% and 15%6 and rates of exposure as determined by HBcIgG are between 5% and 80% depending on socio-economic groups and geographical location.7 HIV infection adversely affects the course of HBV in co-infected patients (Table I). Few studies of HIV-HBV co-infection rates have been conducted in southern Africa and no community-based data are available. However, two studies from urban clinics in Johannesburg documented HBsAg positivity rates in HIV patients of 5%8 and 4.8%,9 with a higher rate of 17% reported from an industrial clinic setting.10

This guideline is intended to update and expand on those included in the ‘Antiretroviral therapy in adults’ guideline published in the Southern African Journal of HIV Medicine of January 2008 (Vol. 9, No. 1 (Summer issue), pp. 18-31). The exclusion of HBsAg screening at entry into the ART treatment programme adopted by the National Department of Health (NDOH) in 201011 is at odds with the guidelines that we present in this document. It is the belief of the authors that further discussion with the NDOH is needed to reconcile the programmatic approach to HIV-HBV management with the recognition that HBV-related liver disease in HIV-infected patients may be prevented by early screening and treatment, thereby positively affecting quality of life, morbidity and mortality.

1. SCREENING FOR HEPATITIS B INFECTION IN HIV-INFECTED PATIENTS

The current Southern African HIV Clinicians Society guideline on screening for HBV in HIV-infected patients indicates that all patients should be tested for HBV using blood HBsAg as the marker of infection, although no direction is given as to when screening should take place. The consensus from international guidelines is that screening should be undertaken at the time of diagnosis of HIV to allow for early decisions on specific treatments for HBV and HIV, as well as vaccination of HBV-uninfected individuals.12-15 These guidelines were produced to direct management in developed, resource-rich nations with higher rates of HBV acquisition in adulthood. In southern Africa, HBV is predominantly acquired between the age of 6 months and 5 years.

DEFINITION OF TERMS

Chronic hepatitis B: Persistence of hepatitis B surface antigen positivity for >6 months. There may be evidence of necro-inflammatory change on histological examination of the liver. Alanine transaminase and the HBV DNA level in blood may fluctuate over time.

Occult hepatitis B: HBsAg negative but hepatitis B core IgG antibody positive, with low-level HBV DNA in blood, usually <200 IU/ml.

Hepatitis B viral flare: An intermittent elevation of aminotransferase activity, often to >10 times the upper limit of normal, or a change of more than twice the baseline value.
KEY SUMMARY POINTS

- To reduce the burden of hepatitis B virus (HBV) infection in sub-Saharan Africa, countries within the region that have not already instigated a programme of HBV vaccination in children should be encouraged to incorporate the vaccine as part of their extended programme of immunisation (EPI).
- HIV-infected patients should be screened for HBV infection using the hepatitis B surface antigen (HBsAg) test at the time of HIV diagnosis.
- HIV-HBV co-infected patients should have a CD4 T-cell count performed after diagnosis. If the CD4 count is <350 cells/µl, the patient should be entered into the highly active antiretroviral therapy (HAART) programme. HAART must include two agents with anti-HBV activity, namely tenofovir plus lamivudine or emtricitabine, in addition to a non-nucleoside reverse transcriptase inhibitor or protease inhibitor (PI).
- Owing to the propensity of nevirapine to cause hepatitis, its use should be avoided in HIV-HBV co-infected patients whenever possible.
- To prevent HBV ‘flares’, co-infected patients taking tenofovir plus lamivudine or emtricitabine who require a change in antiretroviral regimen should continue tenofovir plus lamivudine or emtricitabine in addition to the new antiretrovirals, unless severe adverse effects from these drugs preclude their use.
- Co-infected patients whose CD4 count is ≥350 cells/µl should be assessed for symptomatic liver disease and have the secretory protein hepatitis B envelope antigen (HBeAg) and alanine transaminase (ALT) tested. If HBeAg is positive, and/or ALT is more than twice the upper limit of normal, the patient should be referred for tenofovir plus lamivudine or emtricitabine-based antiretroviral therapy (ART), as above. Similarly, any co-infected patient with symptomatic liver disease or chronic liver disease should be referred for ART, irrespective of the CD4 count.
- Co-infected patients whose CD4 count is ≥350 cells/µl but who test HBeAg negative and whose ALT level is less than twice the upper limit of normal should have their ALT re-checked every 6 months, or before if clinical events dictate. If ALT increases to more than twice the upper limit of normal, the patient should be referred for tenofovir plus lamivudine or emtricitabine-based ART.
- Co-infected children should be referred to/ discussed with a specialist paediatrician for further management.
- HIV-infected patients who are HBsAg negative on screening, but are at high risk of acquiring HBV infection, should be tested for the presence of hepatitis B core IgG antibody (HBcIgG) and if negative, should be offered vaccination against HBV.
- Vaccination should not be attempted in patients with CD4 counts <200 cells/µl as protective efficacy is poor. Rather, withhold vaccination until immune reconstitution has been achieved on ART.
- Vaccination should include a total of 3 doses administered at 0, 1 and 6 months. Double-dose vaccination should be considered in patients with CD4 counts of ≥350 cells/µl. If using the rapid schedule, for example for post-exposure prophylaxis or for babies born to infected mothers, a 4-dose schedule is used, administered at 0, 1, 2 and 12 months.
- All HIV-infected pregnant women must be tested for HBsAg and may require ART.
- Although not directly related to HIV-HBV co-infection, this guideline strongly supports the testing of all pregnant women for HBsAg to identify at-risk babies, irrespective of their HIV status.
- Babies born to mothers who are HIV-HBV co-infected must receive hepatitis B immunoglobulin (HBIG) and the first dose of HBV vaccine at two distinct sites within 12 hours of birth. A 4-dose vaccination course should be completed and the baby tested for presence of HBsAg and hepatitis B surface antibodies (HBsAb) at 6 months of age. HBIG should be repeated at 1 month if the mother is HBeAg positive. If the baby is HBsAb negative at 6 months of age, a repeat vaccination course is required.
- Co-infected babies should be referred to a specialist paediatrician for further management.
- All co-infected patients should be counselled with regard to lifestyle modifications to reduce hepatotoxicity, including alcohol, substance abuse, and co-prescription of herbal and traditional medicines.
- All co-infected patients should be tested for hepatitis C virus (HCV) infection, and those who are co-infected should be discussed with a specialist for advice on management.
- All HIV-HBV co-infected patients with evidence of chronic liver disease should be tested for hepatitis A immunity and immunised if non-immune. Resource constraints and the high level of hepatitis A infection in the South African population as a whole do not support routine testing for all HIV-HBV co-infected patients.

TABLE I. INFLUENCE OF HIV ON THE COURSE OF HEPATITIS B VIRUS INFECTION

- Higher rates of chronicity after acute HBV infection
- Decreased rates of spontaneous HBsAg and HBeAg seroconversion
- Increased rates of HBV DNA replication
- More severe liver disease, with increased rates of cirrhosis and hepatocellular carcinoma
- Increased rates of liver-related mortality
- Increased rates of occult HBV infection
- Increased rate of reactivation and seroreversion with decreasing CD4 counts
- Increased risk of HBV flare after starting HAART due to HBV-immune reconstitution inflammatory syndrome (HBV-IRIS)
However, no studies have been conducted on the rate of acquisition of new HBV infection in HIV-infected adults, so the applicability of developed-world guidelines to the southern African setting remains unknown. Despite this, screening for HBV at the time of diagnosis of HIV has considerable potential benefits, both for the individual and for public health programmes.

- Early diagnosis of co-infection allows assessment of the requirement for specific anti-HBV treatment. This applies to co-infected patients who qualify for ART because of CD4 count or stage of disease, as well as those who, despite not qualifying for ART on those grounds, have signs of active liver disease. This is in line with regional advice such as South African national policy, which advises early ART (to include specific anti-HBV drugs) irrespective of CD4 count in these patients.
- Early instigation of specific anti-HBV therapy to reduce viral replication will decrease infectivity of the patient to others.
- Early identification of co-infected women and appropriate counselling will alert them to the need for targeted HBV intervention for their babies, should they be chronically infected.
- Early identification of HIV-HBV co-infection allows intervention in terms of counselling to affect lifestyle modifications that may reduce liver damage:
  - alcohol
  - substance abuse
  - traditional or herbal medicines
  - screening and intervention for patients who are co-infected with hepatitis C.
  - Hepatitis A vaccination in patients with chronic liver disease, if non-immune.
  - Identification of HBV seronegative HIV-infected individuals will allow for the option of vaccination against HBV.

### 1. OCCULT HEPATITIS B INFECTION

Screening for chronic hepatitis B using HBsAg will fail to detect a small proportion of patients who have occult HBV, i.e. HBsAg negative, HBcIgG positive and low level of HBV DNA in blood, typically <200 IU/mL. Data on the prevalence and significance of occult HBV infection in HIV-infected patients are limited, particularly in the southern African setting. A prospective observational cohort of patients attending an urban ART-preparedness clinic in Johannesburg found that 10.6% of clinic attendees were positive for anti-HBc alone, 88% of whom had evidence of HBV DNA in blood. In a second study looking retrospectively at 192 stored sera from HIV-infected patients initiating ART, 23% were HBsAg positive and a further 23% had occult HBV. Whether occult HBV infection poses a significant clinical problem to co-infected patients remains undetermined and needs to be the focus of longitudinal studies in the southern African setting. Of note, 81% of patients with occult HBV in the prospective cohort study had blood HBV DNA levels of <10^4 copies/ml. Such low levels of DNA replication are less likely to cause significant liver damage, although the long-term natural history remains unknown. Both prospective and retrospective studies suggest that the true rate of chronic HBV infection in HIV co-infected patients is higher than our current understanding based on HBsAg screening alone. However, with the limited amount of evidence and the major cost implications that additional screening tests would impose (see appendix), we are unable to advocate extension of screening tests to include HBcIgG and HBV DNA until further studies clarify the significance of occult HBV infection in our setting.

### 1.2 HEPATOCELLULAR CARCINOMA

Hepatitis B is a recognised risk factor for development of hepatocellular carcinoma (HCC). HCC screening requires measurement of alpha-fetoprotein (AFP) and specialist ultrasonography, which are not practical in the southern African setting, where resources should be directed towards preventing infection and treating infected persons with effective antiviral therapy.

In summary, these guidelines advocate the continued use of HBsAg as the screening test for HIV-HBV co-infection. However, screening should be brought forward from entry into the ART programme to the time of HIV diagnosis so as to identify co-infected patients early in the course of their disease, allowing the option of early ART to include anti-HBV drugs in those who qualify for treatment.

### 2. VACCINATION OF HIV-INFECTED PATIENTS WHO SCREEN NEGATIVE FOR HBV

As indicated previously, it is currently not known how common HBV acquisition is in adulthood in southern Africa. However, we do know that acquisition of HBV infection by HIV-infected persons adversely affects morbidity and causes appreciable mortality. Hence, there is a rationale for advocating for HBV vaccination in all HIV-infected persons who are not already infected with HBV. HBV vaccination responses depend on CD4 counts; vaccination during the early stages of HIV disease when CD4 counts are preserved will result in improved protection. Patients who are eligible for HBV vaccination but who have CD4 counts <200 cells/ml mount poor antibody responses to HBV vaccine. It is therefore generally recommended, that vaccination in these individuals be delayed until immune reconstitution is achieved by ART. The exception to this rule is in the event of occupational or non-occupational exposure to blood or potentially infectious material from an HBV-infected source. In that case, if the recipient is HBV-infected and non-immune to HBV, hepatitis B immunoglobulin and vaccination should be offered regardless of CD4 count.

In countries such as South Africa where a universal childhood HBV vaccination programme has been adopted, vaccination will have a long-term positive impact in reducing HIV-HBV co-infection. However, there has been no catch-up vaccination programme, and until this impact is felt, unvaccinated HIV-infected adolescents and adults remain at risk of a preventable disease. Three approaches could be adopted:

- Do not offer HBV vaccine to HBV-uninfected persons.
- Target HBV vaccine to high-risk groups – acquisition of
HBV infection is increased in intravenous drug users (IVDUs), men who have sex with men (MSM) and partners of HBsAg-positive patients. Other high-risk groups that might be targeted include sex workers, patients with chronic liver disease, home-based caregivers of HBV patients, travellers, prisoners, police, traditional healers, and people involved in high-risk contact sports such as boxing.

- Universal HBV vaccination for all HIV-infected persons who have not yet been infected by HBV.

Adoption of a particular policy will be country-specific, depending on current vaccination policy, HBV seroprevalence profile and resources. However, it is the opinion of the authors that all HIV mono-infected persons should be offered HBV vaccination, as the impact of this simple intervention could radically alter the course of HIV disease if the person was to be infected with HBV. The vaccination schedule should comprise 3 doses at 0, 1 and 6 months. Results of a randomised controlled trial of single- versus double-dose recombinant HBV vaccine in HIV-infected persons showed an increased seroconversion rate (anti-HBsAb titre ≥10 mIU/ml) in the double-dose arm in the group whose CD4 count was ≥350 cells/µl (64% for the double dose v. 39% for the single dose). At CD4 counts <350 cells/µl, although there was a trend towards increased seroconversion in the double-dose arm, it was not statistically significant. Follow-up testing for seroconversion is generally not advocated due to resource limitations. However, certain high-risk groups with anticipated repeat exposure, such as health care workers and IVDUs, should have their antibody titres checked as a once-off. If anti-HBS antibody titres are <10 mIU/ml, consult an infectious diseases specialist for further advice. Guidelines for the management of health care workers exposed to an HBsAg-positive or unknown source are detailed in Table II.

### 3. MANAGEMENT OF HIV-HBV CO-INFECTED PATIENTS

#### 3.1 LIFESTYLE MODIFICATION

HIV-HBV co-infected patients will require additional counselling and support over and above that given to patients diagnosed with HIV mono-infection. There is a need to concentrate on lifestyle modifications that will reduce the risk of further liver injury, as well as for explanation of why a more tailored ART regimen to include ARVs active against both viruses is necessary. All HIV-HBV co-infected patients, irrespective of whether they qualify for ART or not, must be counselled on the lifestyle modifications outlined in Table III.

<table>
<thead>
<tr>
<th>Vaccinated status of exposed worker</th>
<th>Anti-HBs</th>
<th>HBIG (0.06 ml/kg)</th>
<th>HBV vaccine</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous vaccination and known responder</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Not vaccinated</td>
<td>If anti-HBs &gt;10 mIU/ml, no treatment</td>
<td>If anti-HBs &lt;10 mIU/ml, give stat HBIG and repeat at 1 month</td>
<td>1st dose stat and proceed to accelerated schedule 1 - 2 - 12 months</td>
<td>HBIG and HBV vaccine can be administered concomitantly at different sites</td>
</tr>
<tr>
<td>Incomplete vaccination or unsure</td>
<td>As above</td>
<td>Single dose stat</td>
<td>Complete depending on documentation or restart 0 - 1 - 2 - 12 months</td>
<td>As above</td>
</tr>
<tr>
<td>Vaccinated, but unknown response</td>
<td>As above</td>
<td>As above</td>
<td>Single booster stat</td>
<td>As above</td>
</tr>
<tr>
<td>Non-responder to primary vaccination</td>
<td>No</td>
<td>1 dose stat repeated after 1 month</td>
<td>1st dose stat and proceed to accelerated schedule 1 - 2 - 12 months</td>
<td>As above</td>
</tr>
<tr>
<td>Previously vaccinated with 4 doses or 2 completed vaccine series but non-responder</td>
<td>As above</td>
<td>As above</td>
<td>Consider alternative vaccine</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from the European recommendations for the management of health care workers occupationally exposed to hepatitis B virus and hepatitis C virus.
The choice of ART in co-infected patients must take into account the need for drugs active against both HIV and HBV, and the need to limit the emergence of drug-resistant HBV strains; 14 - 32% of patients at 1 year of lamivudine monotherapy and 50 - 90% at 5 years have developed a mutation in the YMDD motif of HBV DNA polymerase that confers resistance to the lamivudine.19 Emergence of lamivudine resistance in patients on ART regimens containing lamivudine as the only drug active against HBV is associated with viral breakthrough and hepatitis flares. Hence, to limit the emergence of HBV resistant strains and optimise control of HBV replication, HIV-HBV co-infected patients should be started on an ART regimen that includes 2 drugs active against HBV, tenofovir plus either lamivudine or emtricitabine. Tenofovir is contraindicated in patients with significant renal impairment (creatinine clearance <50 ml/min), and the choice of ART in such patients should be discussed with an HIV specialist.

In order to limit the incidence of hepatitis flares, once started, anti-HBV drugs in the ART regimen of co-infected patients should not be stopped, even when changes to ARVs are required due to HIV virological failure or intolerance to other antiretrovirals. Hence, other than severe clinical adverse events or grade 3 or 4 laboratory abnormalities ascribed to tenofovir or lamivudine/emtricitabine, co-infected patients should remain on these drugs lifelong.

### 3.3 MANAGEMENT OF CO-INFECTED PATIENTS WITH A CD4 COUNT >350 CELLS/µL

Although there is increasing evidence of a reduction in disease progression (including non-AIDS-related events) when HIV-infected patients are started on ART at CD4 counts >350 cells/µL, owing to resource constraints throughout southern Africa we cannot advocate starting ART in all co-infected patients with higher CD4 counts at this time. Most international guidelines use the HBV DNA level in blood to guide the use of ART in co-infected patients with higher CD4 counts. Again, resource limitations put this expensive test (see appendix) outside our reach as a decision-making tool. However, for ARV-naïve patients with CD4 counts >500 cells/µL and chronic hepatitis B, where resources allow, the clinician is encouraged to refer/discuss the case with a hepatologist with regard to pegylated interferon.

HIV-HBV co-infected patients with ALT ≥2 times the upper limit of normal are at increased risk of HBV disease progression. Hence, in line with international guidelines, we advocate starting tenofovir + lamivudine or emtricitabine-containing ART in patients with CD4 counts > 350 cells/µL if either HBeAg is positive or ALT is 2 times the upper limit of normal. Furthermore, in line with current national policy, ART is recommended for any co-infected patient with CD4 counts >350 cells/µL who has symptomatic liver disease.

Patients with CD4 counts of >350 cells/µL who are asymptomatic, HBeAg negative and have an ALT <2 times the upper limit of normal should be closely monitored with repeat ALT recordings 6-monthly. If there are signs of liver dysfunction without evidence of a cause other than HBV disease progression, the patient should start tenofovir + lamivudine or emtricitabine-based ART.

### 3.4 CHOICE OF THE THIRD DRUG IN AN ART REGIMEN FOR CO-INFECTED PATIENTS

In constructing an ART regimen for co-infected patients, apart from needing to choose drugs with dual activity against HIV and HBV, it is also of paramount importance to try to limit further hepatotoxicity. Given this, we advise avoiding the use of nevirapine in co-infected patients. We recommend efavirenz for first-line ART whenever possible. In women of childbearing age, a boosted PI regimen should be considered if injectable contraception and condom use are not adhered to.

---

**TABLE III. LIFESTYLE MODIFICATION TO LIMIT LIVER INJURY IN HIV-HBV CO-INFECTED PERSONS**

<table>
<thead>
<tr>
<th>Lifestyle Modification</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Abstinence from alcohol should be encouraged. Heavy alcohol intake (&gt;20 g/day in women and &gt;30 g/day in men) is a risk factor for developing cirrhosis</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>Intravenous drug use should be discouraged to reduce risk of new infection or re-infection with HBV and/or HCV</td>
</tr>
<tr>
<td>Safe sex</td>
<td>Although this will already be stressed as part of preventing HIV transmission to others, safe sex practices are to be strongly advocated to reduce transmission of HBV. Mucosal traumatic sexual practices associated with high-risk blood contact should be discouraged</td>
</tr>
<tr>
<td>Other measures to reduce risk of transmission</td>
<td>Attention to prompt clean-up of blood spills with detergent or bleach and avoid sharing razors</td>
</tr>
</tbody>
</table>

---

**Fig. 1. Algorithm for management of HIV-HBV co-infected patients.**

The choice of ART in co-infected patients must take into account the need for drugs active against both HIV and HBV, and the need to limit the emergence of drug-resistant HBV strains; 14 - 32% of patients at 1 year of lamivudine monotherapy and 50 - 90% at 5 years have developed a mutation in the YMDD motif of HBV DNA polymerase that confers resistance to the lamivudine.19 Emergence of lamivudine resistance in patients on ART regimens containing lamivudine as the only drug active against HBV is associated with viral breakthrough and hepatitis flares. Hence, to limit the emergence of HBV resistant strains and optimise control of HBV replication, HIV-HBV co-infected patients should be started on an ART regimen that includes 2 drugs active against HBV, tenofovir plus either lamivudine or emtricitabine. Tenofovir is contraindicated in patients with significant renal impairment (creatinine clearance <50 ml/min), and the choice of ART in such patients should be discussed with an HIV specialist.

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In constructing an ART regimen for co-infected patients, apart from needing to choose drugs with dual activity against HIV and HBV, it is also of paramount importance to try to limit further hepatotoxicity. Given this, we advise avoiding the use of nevirapine in co-infected patients. We recommend efavirenz for first-line ART whenever possible. In women of childbearing age, a boosted PI regimen should be considered if injectable contraception and condom use are not adhered to.
3.5 Hepatitis Flares in HIV-Infected Persons Who Do Not Know That They Are HBV Infected

There is no current policy in place for ‘catch-up’ HBV testing in HIV-infected patients who started ART before the onset of HBV screening. Furthermore, if current national policy is adhered to, there will be an increasing number of HIV-HBV co-infected patients who do not know that they are infected with HBV. These patients may be on ART regimens that include lamivudine as the sole active drug against HBV. Lamivudine resistance will develop in up to 90% at 5 years, at which time a viral breakthrough and hepatitis flare may develop. Since there is a wide range of possible causes for sudden deterioration in liver function during ART, a clinical approach to the co-infected patient on ART who develops liver dysfunction is required. One such approach is depicted in Fig. 2.

4. Special Groups

4.1 Pregnant Women

Screening for HBV infection in pregnant women to prevent mother-to-child transmission is a well-established, evidence-based standard of care in developed countries. Furthermore, a systematic review of randomised controlled trials in 2006 found that prophylaxis (vaccination and/or immunoglobulin) given to newborns of mothers infected with HBV reduced perinatal transmission of the virus.20 This is the critical reason why screening for HBV infection in pregnant women is so important, be it in women who turn out to be co-infected or HBV mono-infected.

Although there are theoretical concerns about the use of tenofovir in pregnancy in relation to bone mineral density and skeletal development of the newborn, the benefit of dual therapy, which includes tenofovir for pregnant co-infected women, outweighs the risk. Similarly, in order to avoid nevirapine, we advocate for the use of efavirenz after 20 weeks’ gestation. Boosted lopinavir is an alternative third drug in the co-infected pregnant woman.

4.2 Newborns

The risk of developing chronic HBV infection is greatest in newborns who are infected perinatally (90%). Hence any intervention that prevents transmission will have a major impact on long-term morbidity and mortality as well as reducing transmission of HBV to others during childhood and once the person becomes sexually active. If the mother is known to be HBV infected, post-exposure prophylaxis becomes an option.

All newborn babies of mothers infected with HBV, be they mono-infected or co-infected with HIV, should receive HBIG plus the first dose of the hepatitis B vaccine within the first 12 hours after delivery. HBIG and vaccine should be administered at different sites and the 4-dose vaccination schedule completed. If the mother is known to be HBsAg positive, with evidence of high-level viral replication and infectivity, HBIG should be repeated at 1 month. Babies should be tested for the presence of HBsAg at 6 months to determine whether post-exposure prophylaxis was successful.

4.3 Children

Perinatal and horizontal transmission during childhood is the predominant mode of HBV acquisition in southern Africa. Although the principles underlying treatment of adults and children with HIV-HBV co-infection are similar, there are important differences. Only pegylated interferon-alpha, adefovir and lamivudine are licensed for use in children with HBV. Although the efficacy of interferon-alpha in children is similar to that in adults if they are in the immune clearance phase of HBV infection, most children, particularly those in the immune tolerant phase, have normal ALT with high HBV DNA levels, and <10% of these children will clear HBeAg with interferon-alpha.21

Tenofovir is not licensed for use in children <18 years of age, although it has been used off-label as part of salvage therapy. Tenofovir is available as an un-scored 300 mg tablet and the suggested childhood dose is 8 mg/kg/day. This means that it is effectively contraindicated in any child weighing <37 kg. A recent study of the use of tenofovir in children in the UK and Ireland as part of ART found evidence of considerable under- and over-dosing.22 There are also theoretical concerns regarding the use of tenofovir in respect of depletion of bone mineral density. As tenofovir is therefore limited in many infants and children, this effectively leaves lamivudine monotherapy to treat HBV in the face of HIV co-infection. Perinatal and childhood-acquired infection is associated with a high HBV viral load, which increases the risk of acquiring lamivudine resistance if the patient is on monotherapy. The options for management include the use of ART with lamivudine or withholding lamivudine in the regimen until tenofovir can be used. This will depend on the age of the child and the activity/stage of the liver disease, and should be discussed with a specialist paediatrician and hepatologist.

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*Fig. 2. Clinical approach to management of HIV-HBV co-infected patients who develop liver dysfunction on ART.*
4.4 ALTERNATIVE TREATMENT OPTIONS FOR CO-INFECTED PATIENTS WITH HIGH CD4 COUNTS

Alternative therapy for HBV co-infected patients with high CD4 counts is limited primarily by cost (see appendix). The efficacy of pegylated interferon-alpha depends on viral load, ALT level, genotype and the degree of necro-inflammation on liver biopsy. Although good trial evidence is lacking for its use in HIV-HBV co-infection, expert opinion suggests that patients who are HBeAg positive, have elevated transaminases and high CD4 counts, and are found to have necro-inflammation on liver biopsy are most likely to benefit from pegylated interferon-alpha.

REFERENCES

APPENDIX. COST OF LABORATORY TESTS FOR HBV IN THE STATE AND PRIVATE SECTORS, 2010/2011

(Provided by the National Health Laboratory Service) and Drugs Used in Treatment of HBV Infection (Prices are Subject to Change – Current Prices at the Time of Going to Print)

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>State sector</th>
<th>Private sector</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>R 105.89</td>
<td>R171.30</td>
</tr>
<tr>
<td>HBeAg</td>
<td>R 105.89</td>
<td>R171.30</td>
</tr>
<tr>
<td>Anti-HBc IgG</td>
<td>R 105.89</td>
<td>R171.30</td>
</tr>
<tr>
<td>Anti-HBs antibody</td>
<td>R 1 141.22</td>
<td>R1 772.60</td>
</tr>
<tr>
<td>HBV DNA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drugs used in the treatment of HBV

<table>
<thead>
<tr>
<th>Drug</th>
<th>State sector</th>
<th>Private sector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir (Aspen)</td>
<td>R210.90 (1 month, incl. of VAT)</td>
<td></td>
</tr>
<tr>
<td>Lamivudine (Adcock)</td>
<td>R96.51 (1 month, incl. of VAT)</td>
<td></td>
</tr>
<tr>
<td>Lamivudine (Sonke)</td>
<td>R44.40 (1 month, incl. of VAT)</td>
<td></td>
</tr>
<tr>
<td>Truvada (tenofovir + emtricitabine) (Aspen)</td>
<td>R313.50 (1 month, incl. of VAT)</td>
<td></td>
</tr>
<tr>
<td>Pegylated interferon-alpha</td>
<td>R11 000/month for adults</td>
<td></td>
</tr>
</tbody>
</table>

Declaration of interests and support within the last 3 years (sponsors, managed care and pharmaceutical organisations)

Marc Mendelson receives support from PEPFAR/USAID through ANOVA Health care, Wendy Spearman has received travel and conference support from Roche, and Mark Sonderup has received conference support from Hoffman-La Roche.

CASE STUDIES – HIV AND LUNG DISEASE

NONSPECIFIC RADIOGRAPHIC MANIFESTATIONS OF CYTOMEGALOVIRUS INFECTION IN 4 HIV-POSITIVE ADULTS – DIAGNOSIS THROUGH TRANSBRONCHIAL BIOPSY

Matthew Goodier, MB ChB
Grace Rubin, MB ChB, DA (SA), FCRad (Diag) (SA)
Department of Radiology, University of the Witwatersrand, Johannesburg

We report on 4 HIV-positive adult patients who presented (over a 2-year period) with clinically significant cytomegalovirus (CMV) pneumonia requiring transbronchial biopsy for diagnosis. The patients were not on antiretroviral therapy. Clinical findings were nonspecific, sputum samples were negative, blood test results were non-contributory, and empirical treatment had failed. Radiological findings were extensive but nonspecific. Three of the 4 patients were co-infected with Pneumocystis jirovecii (PJP) pneumonia, further confounding the radiological diagnosis.

CASE 1
A 45-year-old man with a history of previous tuberculosis (TB) infection presented with a cough and chest pain. Sputum results and blood cultures were negative. The chest radiograph (CXR) demonstrated bilateral multifocal areas of patchy airspace disease, as well as a dominant focal area of density in the right upper lobe (Fig. 1). No effusions were noted. A presumed diagnosis of PJP was made, but the patient did not respond to treatment. Bronchoscopic biopsy confirmed CMV infection.

CASE 2
A 43-year-old woman with no history of TB or TB contacts presented with a cough and haemoptysis, loss of weight, low fever and rigors. The white cell count (WCC) was 6.4×10⁹/l, and sputum results and blood cultures were negative. The CXR revealed bilateral reticular-nodular and ground-glass opacities without any effusions (Fig. 2, a). The differential diagnosis included TB and PJP. Bronchoscopic biopsy confirmed the diagnosis of both CMV and PJP infections.

CASE 3
A 30-year-old woman presented with shortness of breath, a dry cough, loss of weight and fever. The WCC was 13×10⁹/l and the CD4 count 481 cells/µl. The CXR demonstrated bilateral reticular and ground-glass opacities (Fig. 2, b). Treatment for TB and PJP was started, but the patient showed no clinical improvement. Bronchoscopic biopsy confirmed both CMV and pneumocystis pneumonia (PCP).

CASE 4
A 29-year-old woman presented with a cough, chest pain, loss of weight and shortness of breath. The WCC was 9.1×10⁹/l and the CD4 count 14 cells/µl. On the CXR there were bilateral, diffuse, reticular and airspace shadows with no effusions (Fig. 2, c). Both TB and PJP were considered in the differential diagnosis. Transbronchial biopsy revealed CMV and PJP infections.

Transbronchial biopsy in all patients demonstrated alveolar tissue containing CMV with nuclear and cytoplasmic inclusions (Fig. 3). This was accompanied by alveolitis and an associated inflammatory cell infiltrate.

Fig. 1. The chest radiograph in patient 1 demonstrates bilateral multifocal areas of patchy airspace disease, as well as a dominant focal area of density in the right upper lobe.
of the alveolar walls. Ziehl-Neelsen staining and culture for TB were negative in all patients.

DISCUSSION

CMV is a relatively commonly identified pathogen in immunocompromised patients. This was first recognised in patients on immunosuppressive therapy for haematological malignancies or bone marrow and other organ transplants. In the South African setting, most CMV infections occur in patients with HIV/AIDS. CMV disease usually occurs in patients with low CD4 counts (<100 cells/µl).1 Disseminated infection is relatively common and may manifest clinically as retinitis, encephalitis, hepatitis, oesophagitis or colitis. Clinically significant pulmonary infection is uncommon. However, CMV may be isolated in more than half of broncho-alveolar lavage (BAL) specimens in AIDS patients with pulmonary symptoms.2

In most patients, CMV infection co-exists with other opportunistic infections, particularly PCP. In this setting, there is doubt regarding to what extent CMV is acting as a pathogen.3 The diagnosis of CMV pneumonitis is therefore often based on typical symptoms of fever, shortness of breath, hypoxaemia and diffuse infiltrates on the CXR in combination with detection of the virus in BAL fluid and the absence of other pathogens.4 However, because of the high rates of co-infection, a definitive diagnosis of CMV requires identification of CMV intranuclear or cytoplasmic inclusion bodies in transbronchial biopsy specimens (used in our patients) or open lung biopsy specimens.5

Routinely securing a tissue diagnosis in the local setting is impractical and may be dangerous in patients with certain conditions, e.g. thrombocytopenia.6 In one study examining AIDS patients undergoing diagnostic bronchoscopy for pulmonary symptoms, 72% had CMV cultured from BAL fluid but only 2 had pathological
evidence of CMV pneumonitis. Only 1 of these patients had autopsy confirmation that the cause of death was CMV pneumonitis. In practice, treatment is therefore usually aimed at all other organisms, and only if the patient does not improve is anti-CMV therapy initiated.

In patients with pathologically proven CMV pneumonia, CXRs usually show bilateral, reticular, interstitial disease that classically begins in the periphery of the lower lobes and spreads centrally and superiorly, as seen in 3 of our patients. Focal infiltrates, nodules and diffuse alveolar infiltrates are less common findings and were noted in 2 of our patients. Because of the nonspecific clinical presentation, clinicians tend to rely on imaging to distinguish between CMV and PJP. However, it is usually impossible to differentiate between these two conditions on the basis of radiographic findings. In this context some consider thin-section computed tomography (CT) to be the investigation of choice. CT scans may reveal bilateral or focal ground-glass or consolidative changes, as well as (less commonly) well-defined solitary or multiple nodules measuring up to 3 cm in diameter, which makes CT also poor at differentiating between PCP and CMV infection. In a study comparing CT findings in these two infections in 58 immunocompromised HIV-negative patients, small and centrilobular nodules, unsharp demarcation of the ground-glass infiltrates and consolidation favoured CMV pneumonia, while an apical distribution and the occurrence of a mosaic pattern suggested PCP. Although CMV usually mimics PCP, the radiological differential diagnosis of diffuse interstitial pulmonary infiltrates in AIDS also includes infections with other organisms.

**CONCLUSION**

Even though CMV is a relatively commonly identified organism in BAL specimens from immunocompromised HIV patients, CMV pneumonia is uncommon. As demonstrated in our patients, CMV pneumonitis typically has a nonspecific plain radiographic presentation which overlaps with that of PCP, a common co-infection. The diagnosis then relies on transbronchial biopsy. In sub-Saharan Africa, where a large proportion of patients are not yet on antiretroviral therapy and have low CD4 counts, CMV remains an important differential diagnosis in pneumonia in HIV/AIDS. Where there are resource limitations for performing bronchoscopic biopsy, failure of a trial of therapy and diffuse interstitial or patchy airspace disease on CXR should prompt the clinician to initiate treatment for CMV.

**REFERENCES**

The mechanisms behind accelerated emphysema in adults with HIV infection and the HIV-infected smoking population are both multifactorial and unclear. However, the association of HIV and emphysematous lung disease is recognised. We describe a patient with HIV infection and accelerated emphysema, highlighting the facts that no other background disease predisposed him to these lung changes, and that smoking in conjunction with HIV infection acted synergistically to produce the changes.

CASE REPORT

A 38-year-old man with a 3-day history of shortness of breath, productive cough and pleuritic chest pain presented to the medical department at Helen Joseph Hospital, Johannesburg. There was no history of tuberculosis or other lung disease, but the patient had been a smoker for 10 years. He was on no medication. On examination he presented with a respiratory rate of 20/min, tachycardia (164 beats/min), and a blood pressure of 98/66 mmHg. He had decreased air entry on auscultation of the left chest. An initial chest radiograph revealed a differential transradiancy of the hemithoraces, and a diagnosis of spontaneous left pneumothorax was made. The patient was placed on oxygen and an intercostal drain (ICD) inserted. Blood tests revealed that he was HIV infected, with a CD4 count of 469 cells/µl and a white cell count of 469 x 10⁹/l. He was not on antiretroviral therapy. Once his condition had stabilised, a high-resolution computed tomography scan of the chest was done (Figs 1 and 2). This revealed large bilateral, diffuse, predominantly apical, medial and lateral bullous lung disease associated with a small residual left pneumothorax. The underlying lung parenchyma deep to the paraseptal bullae was not affected. No radiological features of pre-existing consolidation, cavities or cysts were present, and there were no nodules, reticules or bronchiectasis. There was no lymphadenopathy or effusions. The diagnosis of spontaneous pneumothorax secondary to bullous lung disease in an HIV-positive male smoker was made.

Near-total re-expansion of the left lung occurred. The ICD was removed and the patient was discharged to an outpatient clinic.

DISCUSSION

Emphysematous lung disease has become a known pulmonary complication of HIV and AIDS. HIV-related bullous lung disease was first reported in the late 1980s. Subsequently numerous studies have indicated that the HIV virus itself is a predisposing factor in the pathogenesis of bullous lung disease.¹³ In 1989 a publication by Kuhlman et al. compared the incidence of bullous lung damage in a group of HIV-positive patients with that in a similar group of immunocompromised patients with acute leukaemia.⁴ Bullous lung damage was found in 42% of the HIV-positive group, as opposed to 16% of the acute leukaemia group. The average age of the HIV-positive group was also significantly lower than that of the leukaemia group. The study documented the distribution of bullous
changes to be predominantly apical and peripheral. Of the patients 70% had a history of previous documented pulmonary infections (in particular *Pneumocystis jirovecii* pneumonia) and 13% did not, emphasising the direct effect of HIV itself on the lung parenchyma. Spontaneous pneumothoraces were a common complication in patients with bullous lung disease.

Other studies also emphasise the role of HIV in premature emphysema and bullous lung disease. HIV-infected subjects have significantly more emphysematous lung damage than HIV-negative smokers.\textsuperscript{1,5} HIV-associated emphysema also occurs over a much shorter period of time than smoking-related emphysema in HIV-negative patients. This is thought to reflect an increase in and a susceptibility to damage caused by cigarette smoking in HIV-positive patients.\textsuperscript{1}

In 2000 Diaz and co-workers compared the incidence of emphysema in an HIV-positive group and an HIV-negative group matched for age and smoking history.\textsuperscript{5} The incidence of emphysema was 15% for the HIV-positive and 2% for the HIV-negative group. Smoking was the single most important risk factor in the HIV-positive group, contributing to 37% of the patients with emphysema in this group, compared with 0% in the HIV-negative group.

The differential diagnosis of bullous lung disease includes tobacco smoking, intravenous drug use (methyphenidate, heroin, cocaine), marijuana and cocaine smoking, and a long list of diseases including α\textsubscript{1}-antitrypsin deficiency, HIV infection, auto-immune and connective tissue disorders, bullous sarcoidosis, idiopathic giant bullous emphysema and neurofibromatosis.\textsuperscript{2}

A higher percentage of cytotoxic lymphocytes has been demonstrated in broncho-alveolar lavage specimens of HIV-infected patients than in uninfected subjects.\textsuperscript{1,5} In the 1990s reports of accumulation of CD8 cytotoxic T lymphocytes in the lungs of patients with severe chronic obstructive pulmonary disease (COPD) appeared. This may explain the accelerated emphysema in HIV-infected patients, whose lung response to the HIV infection is characterised by the accumulation of CD8 lymphocytes in alveolar spaces. Lymphocytic alveolitis, defined as more than 15% lymphocytes in broncho-alveolar lavage, is a common finding in HIV-infected subjects.\textsuperscript{1}

More recently, highly active retroviral therapy (HAART) has been associated with a significant decrease in the number of CD8 cells in broncho-alveolar lavage. This raises the interesting possibility that the incidence of COPD in HIV-infected subjects may decrease significantly in the HAART era.\textsuperscript{1}

**CONCLUSION**

The spectrum of HIV-associated accelerated emphysematous lung changes carries significant morbidity. It is therefore important to recognise early lung changes as well as understand the predisposing factors associated with accelerated bullous lung disease in the hope that prevention, early detection and treatment will decrease morbidity and mortality in these patients.

**REFERENCES**


CASE REPORT

A 34-year-old woman presented with a 1-week history of occipital headache and acute-onset bilateral facial weakness that resulted in her being unable to close her mouth and eyes. No visual deficits were noted, but her sense of taste was markedly reduced. She had no past medical history of note and was on no medications. On examination she was apyrexial, with a blood pressure of 140/123 mmHg and a pulse rate of 113 beats/min. There was complete bilateral lower motor neuron 7th cranial nerve palsy in keeping with bilateral Bell’s palsy. She was unable to close her eyes or mouth on request and could not speak without the support of her hand. No other focal neurology was present. There was a small aphthous ulcer on her upper palate.

A lumbar puncture, which was unfortunately traumatic, resulted in a cerebrospinal fluid reading with elevated erythrocytes (10,000×10⁹/l) and protein 4.16 g/l. However, after corrections were made using blood sample cell levels the CSF showed evidence of aseptic meningitis with elevated polymorphs (5×10⁹/l) and lymphocytes (299×10⁹/l) as well as a glucose level towards the lower end of normal at 2.3 mmol/l. Consent to conduct HIV testing was obtained, and while the rapid test was negative, the CD4 count was reduced at 352 cells/µl and the viral load was elevated at 5,300 counts/ml (log = 3.72), in keeping with acute HIV infection. Bell’s palsy is a known complication of seroconversion – 13 cases have been reported worldwide. To our knowledge this is the first reported case in South Africa.

DISCUSSION

Bilateral facial nerve palsy is a rare but recognised complication of seroconversion, the process by which the HIV virus becomes widespread throughout the body.1 The presence of acute HIV infection in this case is supported by the low CD4 count and high viral load. In 40 - 90% of patients with a new HIV infection an acute seroconversion illness occurs between 2 and 6 weeks after exposure. Typical symptoms include fever, fatigue, pharyngitis, weight loss, night sweats, lymphadenopathy, myalgias, headache, nausea and diarrhea.1 While this patient did not suffer from the majority of these symptoms, she did have a severe headache (resulting in vomiting) and aseptic meningitis, both of which have previously been described in seroconversion.1

The first case of bilateral 7th cranial nerve palsy as part of an acute seroconversion reaction was reported in 1989 in a 45-year-old homosexual postgraduate student in California.2 Since then only 14 other cases have been reported in the literature worldwide, including our own (which to our knowledge is the first case in South Africa).3 In the 14 cases described, ages ranged from 21 to 73 years, and 71.4% were men.2 Sexual transmission was the means of acquiring HIV in 64.3% of cases, and the median interval between the onset of symptoms of HIV infection and the development of 7th cranial nerve palsy was 15 days (range 2 - 180 days). Aseptic meningitis and a maculopapular rash were present in the majority of
cases. All patients who had a recorded CD4 cell count had counts over 300 cells/µl (range 323 - 825 cells/µl). Three patients had additional neurological symptoms at diagnosis, while just one patient received antiretroviral therapy. All but one patient made a complete recovery in terms of their nerve paralysis.

The pathogenic mechanism of bilateral Bell’s palsy in patients with acute HIV infection is not completely understood. There are several schools of thought as to how this rare sign appears, including a proposed direct insult to the nerve by the HIV virus. Another possibility would be immunologically mediated inflammatory polyradiculopathy, similar to a regional Guillain-Barré syndrome, which would make more sense immunologically and therefore has slightly more scientific merit; however, neither theory has yet been fully tested.³

Facial nerve paralysis has a high predictive value for HIV infection in populations with high rates of seroconversion, including those who engage in high-risk activities such as intravenous drug users and men who have sex with men, and patients from HIV-endemic areas such as sub-Saharan Africa.⁴ This case and the supportive evidence from the literature would indicate the necessity of including acute seroconversion syndrome in a list of differential diagnoses for bilateral facial nerve palsy, especially in sexually active patients who have had a prior acute febrile illness with rash or headache. A full HIV work-up should form part of the investigation of bilateral Bell’s palsy.

This case report was approved by the Health Research Ethics Committee, Stellenbosch University.

REFERENCES
CASE STUDY – HIV AND THE KIDNEYS

EFFECTS OF DUAL RENIN-ANGIOTENSIN SYSTEM BLOCKADE ON PROTEINURIA IN A HYPERTENSIVE BLACK AFRICAN HIV-INFECTED PATIENT

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Kidney diseases manifesting as proteinuria or elevated creatinine are increasingly prevalent complications of HIV infection. We report the effects of dual renin-angiotensin system blockade on proteinuria in a hypertensive black African HIV-infected patient.

Kidney diseases manifesting as proteinuria or elevated creatinine are increasingly prevalent complications of HIV infection. Today HIV-associated nephropathy (HIVAN) is a main cause of end-stage renal disease in HIV-infected African-Americans, and it is likely to be a result of a recently identified genetic predisposition based on polymorphisms of the myosin heavy-chain 9 (MYH9) gene.1 However, a variety of other histopathological renal diseases affect HIV-infected subjects of all ethnic groups.1 HIV-associated renal disease with overt proteinuria has been associated with poorer outcomes and increased mortality.2 Moreover, an increased rate of urinary albumin excretion, even in the micro-albuminuric range, is an indicator of glomerular damage and has been found to be associated with an increased risk of cardiovascular disease (CVD) and mortality in the general population.2

The pathophysiological mechanisms underlying urinary albumin excretion and the increased risk of CVD are not fully understood. Both HIV-related and non-HIV-related factors may play a role. There are few studies of albuminuria in HIV-infected patients, and most of these have been undertaken in selected small cohorts limited to the pre-combination antiretroviral therapy (cART) era.

The renin-angiotensin system (RAS) is a major regulator of blood pressure and vascular response to injury. Continual activation of the RAS is associated with hypertension and end-organ damage, including renal disease and CVD. Inhibitors of the RAS have become a cornerstone for the treatment of hypertension. Use of these agents in patients with underlying renal disease has revealed that RAS inhibition exerts an anti-proteinuric effect independent of blood pressure reduction.3 Because RAS intervention can be targeted at various points, it has been postulated that combining more than one of these intervention points could lead to more effective inhibition of the RAS and a more robust decrement in protein excretion. Several studies support the use of combination therapy with angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) in the general population,4 but there are no data on dual RAS blockade effects in HIV-positive patients with proteinuria.

CASE REPORT

A 45-year-old HIV-infected black African man (CDC A2) came to the Infectious Disease Clinic at SS Annunziata Hospital, Chieti, Italy, for follow-up. He had been treated with tenofovir + emtricitabine + efavirenz for one year at another centre in Italy. His personal history included multiple sexual partners, use of illegal injected drugs, tobacco smoking and chronic HCV infection. On admission the CD4+ level was 603 cells/µl, the CD4/CD8 ratio 0.44, the HIV-RNA level <40 copies/ml, and the HCV-RNA level >5×10⁵ copies/ml. Levels of the transaminases and glucose and lipid parameters were within normal limits, the glomerular filtration rate (GFR) assessed by the MDRD logarithmic model (MDRD-GFR) was 114 ml/min/1.73 m², and the urinary albumin level was 1.5 g/l. The blood pressure (BP), measured with a mercury sphygmomanometer with an appropriately sized cuff after the patient had rested in a seated position, was elevated at 150/100 mmHg. Treatment with 10 mg lercanidipine daily was started, strictly monitoring possible side-effects and interactions with cART. After 1 month of antihypertensive therapy the BP had fallen to...
120/90 mmHg without adverse effects, while the urinary albumin level and MDRD-GFR were 1.21 g/l and 106 ml/min/1.73 m², respectively. A change in cART, withdrawing tenofovir, was proposed, but the patient refused it. As a consequence, in spite of the improved mean BP (130/85 mmHg), the albuminuria progressively worsened over the following months (to 2.52 g/l, with the MDRD-GFR rising to 117 ml/min/173 m²). The patient refused renal biopsy or cART changes. Administration of 300 mg irbesartan daily was then started in order to improve the renal dysfunction; after a month, while the BP and MDRD-GFR remained stable, the urinary albumin level had decreased only to 150 mg/dl. We therefore added lisinopril 20 mg/d to achieve dual blockade of the RAS. After 5 months the urinary albumin level had fallen to 0.285 g/l without any change in BP, MDRD-GFR or viro-immunological parameters (Fig. 1).

DISCUSSION

HIV infection is a strong risk factor for renal disease because of the presence of proteinuria, independent of other risk factors. Previously reported risk factors for HIV-related proteinuria include both traditional HIV-specific markers, such as CD4 lymphocyte count and HIV RNA levels, and several traditional renal and cardiovascular risk factors, such as higher systolic BP and insulin resistance. African-Americans, older people and those with a lower GFR and hepatitis C co-infection are at increased risk.1 The potential nephrotoxicity induced by cART may considerably increase the risk of renal disease. Although previous studies of the longitudinal effects of cART on proteinuria are limited, certain frequently used antiretroviral medications such as tenofovir have been associated with acute renal failure. Moreover, there is increasing evidence that HIV-infected patients have hypertension requiring pharmacological treatment, which also represents an important risk factor for kidney disease.

The choice of antihypertensive therapy for HIV-infected cART-treated patients must be made carefully. The classes of antihypertensive drugs that block the RAS, such as ACE-Is and ARBs, may be ideal. Several studies have reported beneficial effects of dual RAS blockade on kidney disease progression and proteinuria reduction in the general population. A more recent trial (IMPROVE)5 has shown the effectiveness of fixed-dose combination ARB/ACE-I therapy in reducing albuminuria in non-HIV-infected hypertensive subjects. It is therefore advisable to use combination ARB/ACE-I therapy in more complex cases to obtain a greater nephroprotective effect. Data on ACE-I and ARB use in HIV-infected patients are anecdotal,6 and there have been no well-designed studies on this subject to date.

Our patient’s race was an additional problem in selecting effective antihypertensive therapy, because antihypertensive regimens that inhibit the RAS may be ineffective in black patients. In the African-American non-infected population, responsiveness to monotherapy with ACE-Is, ARBs and beta-blockers may be poorer than responsiveness to diuretics and calcium channel blockers (CCBs).7 In our patient dual RAS blockade therapy did not have substantial effects on BP control, while the main antihypertensive effect was achieved with the use of the CCB lercanidipine, in the absence of important interactions with cART. Lercanidipine did not improve proteinuria in our patient. This may indicate that HIV-related kidney disease is not only correlated with hypertension levels. The use of combined therapy with 20 mg lisinopril plus 300 mg irbesartan, obtaining a dual RAS blockade, produced a marked improvement in kidney function, with a -88% decrease from the baseline urinary albumin level.

CONCLUSION

This case shows that dual blockade of the RAS with combined ACE-I and ARB therapy reduced albuminuria in an HIV-infected black African patient. Furthermore, it indicates that the lowering of protein excretion brought about by dual RAS blockade is independent of BP reduction. Available data suggest that the beneficial effect achieved with combination therapy derives from more prolonged and complete inhibition of the RAS rather than from a physiological interaction between the ACE-I and the ARB.4 This more extensive RAS inhibition may provide incremental end-organ protection through its effects on chronic vascular responses to injury.

There are no conflicts of interest. No financial support was given for the study.

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The South African public sector antiretroviral treatment (ART) guidelines have recently been changed to include tenofovir in the first-line regimen. Injectable drugs from the aminoglycoside class are part of the intensive phase of regimen 2 tuberculosis (TB) treatment and the multidrug-resistant (MDR) TB treatment regimen in the South African TB programme. We wish to draw the attention of clinicians managing patients with HIV-associated TB to the potential dangers of concurrent administration of these drugs. We present two illustrative cases.

**CASE 1**

We recently admitted a 47-year-old man with a background of hypertension who had a serum creatinine level of 131 µmol/l prior to ART. He was diagnosed with pulmonary tuberculosis (Mycobacterium tuberculosis was cultured from his sputum). Because he had had a fully treated episode of pulmonary tuberculosis in 2007, he was commenced on regimen 2 TB treatment (including streptomycin during the intensive phase) in March 2010. At this time he tested HIV positive, and because he had a CD4 count of 61 cells/µl he was commenced on tenofovir, lamivudine and efavirenz in May 2010, while still receiving streptomycin. He was referred to our hospital 3 weeks later with a 1-week history of weakness, vomiting and confusion. The creatinine level was now 1 902 µmol/l and the urea level 59 mmol/l. He was admitted, tenofovir was switched to stavudine, streptomycin was stopped, and he received intravenous rehydration and a broad-spectrum antibiotic. His blood culture was negative and urine microscopy showed no evidence of urinary tract infection. His creatinine level steadily decreased and within 3 weeks was 160 µmol/l.

**CASE 2**

A 28-year-old HIV-infected man was on a tenofovir-based ART regimen when he was diagnosed with MDR TB. He was started on MDR TB treatment including kanamycin and remained on tenofovir. His creatinine level rose from 64 µmol/l to 180 µmol/l within 1 month of starting MDR treatment. He was then referred to our hospital. Tenofovir was changed to stavudine and the kanamycin was stopped, yet his creatinine remained elevated 3 months later (125 µmol/l), suggesting that chronic renal damage may have resulted. He will continue to be followed up.

**DISCUSSION**

The aminoglycosides are potent nephrotoxins, in part because of the high concentrations they attain in the proximal tubular cells (PTCs) – up to 10% of the total parenteral dose may be concentrated in these cells. Here they undergo retrograde transport through the endoplasmic reticulum, where they can interfere with protein sorting and synthesis, and are then transported into the nucleus and mitochondria where they can inhibit mitochondrial ribosomes (in a way that is analogous to their bactericidal effect on the small ribosomal unit of bacteria). It is thought that one mechanism through which they cause acute tubular necrosis (and Fanconi’s syndrome) is tubular mitochondrial toxicity.

Like the aminoglycosides, tenofovir attains high concentrations in the PTCs as a result of active uptake into these cells. A substantial proportion of patients taking tenofovir may develop certain of the features of Fanconi’s syndrome (a proximal tubular wasting syndrome) as a result of PTC dysfunction. One study reported that 22% of patients on tenofovir developed at least 2 out of 6 features of proximal tubular dysfunction such as hyperaminoaciduria, glycosuria in the presence of normoglycaemia, and hyperphosphaturia. Tenofovir may also cause renal failure. There is evidence to suggest that tenofovir’s nephrotoxicity is related to tubular mitochondrial toxicity with abnormal mitochondria.
having been observed on electron microscopy of tubular cells in renal biopsies of patients on tenofovir. Acute tubular necrosis has been observed in patients who have had a renal biopsy after developing tenofovir-related acute renal failure.

When tenofovir was developed there were concerns that it would be nephrotoxic because other nucleotide reverse transcriptase inhibitors (adefovir used to treat hepatitis B and cidofovir used to treat herpes virus infections) are nephrotoxic. However, early clinical trials failed to demonstrate any excess risk of renal adverse events in participants receiving tenofovir. These clinical trials did, however, exclude patients with impaired renal function and those on other nephrotoxic drugs. Subsequent reports from HIV treatment cohorts showed that tenofovir is associated with mild decreases in glomerular filtration rate when compared with patients on other antiretrovirals. More importantly, a minority of patients on tenofovir develop acute or chronic renal failure. In a review of studies from developed world settings it was estimated that <1% will develop clinically significant renal impairment. In 2006, Zimmermann et al. published 5 cases of acute renal failure related to tenofovir and reviewed a further 22 cases that had been reported in the literature to that date. In 5 of these 27 patients the renal impairment did not fully resolve after stopping tenofovir. In a recent analysis of the EuroSIDA cohort, increasing exposure to tenofovir was associated with a higher incidence of chronic kidney disease. A recently published systematic review and meta-analysis found that there was a modest but statistically significant increase in the risk of acute renal failure in patients on tenofovir compared with other antiretrovirals (risk difference 0.7%, 95% confidence interval (CI) 0.2 - 1.2). Importantly, in 11 of the 17 studies in the meta-analysis patients with abnormal renal function at baseline were excluded, and the majority of the studies reviewed were clinical trials from which patients on other nephrotoxic medications were likely to have been excluded. These studies may therefore have underestimated the risk of tenofovir nephrotoxicity by excluding patients at higher risk.

There is concern that in sub-Saharan Africa the risks of tenofovir nephrotoxicity may be greater because of the high background prevalence of renal disease, including HIV-associated nephropathy, and lack of capacity to monitor renal function regularly. An analysis of renal outcomes of the DART study, conducted in Uganda and Zimbabwe, showed no difference in the incidence of severe reductions in estimated glomerular filtration rate in patients started on tenofovir-based regimens compared with other regimens, but all the patients who died of renal failure (N=11) were on tenofovir. Contributing co-morbidities were identified in most of these 11 patients. In one of these patients it was thought that the combination of gentamicin and tenofovir was responsible. An additional issue to consider in our setting is that if patients do develop severe renal failure, access to dialysis facilities, especially in rural areas, is limited.

It is biologically plausible that the toxicities of aminoglycosides and tenofovir may be additive in the mitochondria of PTCs. Analysis of data from the tenofovir expanded-access programme revealed that being on concomitant nephrotoxic medications was an independent risk factor for elevations in serum creatinine during follow-up.17 In a case-control study conducted in a US HIV clinic, concurrent nephrotoxic medication (such as high-dose or chronic non-steroidal anti-inflammatory drugs (NSAIDs), amphotericin B and aminoglycosides) was shown to independently increase the risk of tenofovir-associated nephrotoxicity (odds ratio 6.4, 95% CI 2.2 - 18.4). Indeed, the package insert for tenofovir states that it ‘should be avoided with concurrent or recent use of a nephrotoxic agent’. A particular concern is that aminoglycosides for treating TB are prescribed for between 2 and 6 months. It is likely that the risk of nephrotoxicity with tenofovir and aminoglycoside will be greater if co-administered for this long duration. One approach that has been suggested is that the combination could be used, but with close monitoring of serum creatinine. However, given that drug-induced nephrotoxicity may result in acute renal failure within 1 - 2 weeks this would necessitate a frequency of monitoring and follow-up of results that is not practical in busy HIV and TB programmes.

While the new national ART guidelines do not address the risks of co-administration of tenofovir and aminoglycosides, we think that there is sufficient evidence to concur with a recent recommendation to avoid the co-administration of tenofovir and aminoglycosides whenever possible.20 When considering what to do in the light of this co-toxicity, it is important to recall that the aminoglycosides (kanamycin or amikacin) used in the treatment of MDR TB and the cyclic polypeptide, capreomycin, used in the treatment of extensively drug-resistant (XDR) TB, are essential components of these treatment regimens. On the other hand, streptomycin is not a critical component of regimen 2 TB treatment, particularly now that rapid drug susceptibility testing is available to appropriately direct therapy in patients being retreated for TB. We therefore recommend the following:

■ During the intensive phase of MDR TB treatment (while the patient is on amikacin or kanamycin), do not prescribe tenofovir. In place of tenofovir use zidovudine, stavudine or abacavir. After completing the aminoglycoside component of MDR TB treatment, patients could be switched to tenofovir provided the estimated creatinine clearance is >50 ml/min. This switch to tenofovir is particularly important in patients with hepatitis B co-infection.

■ The same approach should be used in patients on capreomycin during the intensive phase of XDR TB treatment. Capreomycin is also nephrotoxic.

■ In patients on tenofovir who require regimen 2 TB treatment, omit streptomycin from regimen 2. In
patients starting tenofovir-containing ART while on regimen 2 TB treatment, omit the streptomycin from regimen 2 from when they start the tenofovir. In all other respects regimen 2 TB treatment should remain unchanged.

Our first case highlights another important point: that it is critically important to calculate the estimated creatinine clearance in patients before starting tenofovir, and if it is <50 ml/min, tenofovir should not be used.1 This patient had an estimated clearance of 32 ml/min prior to ART (this was probably related to HIV-associated nephropathy and/or hypertensive nephropathy). This patient should therefore not have received tenofovir or streptomycin. It is likely that in this case underlying renal impairment and treatment with two nephrotoxins all contributed to the development of severe acute renal failure.

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To the Editor: We refer to the article by Parkhurst and Whiteside in the April 2010 issue of the *Southern African Journal of HIV Medicine.* 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, particularly among individuals with acute HIV infection (AHI).

Evidence is mounting that a large proportion of HIV transmission may be attributed to individuals who are in the acute phase of HIV infection, best described as the time period during which HIV can be detected in blood serum and plasma but before the formation of antibodies, as measured by standard assays. The viral burden in blood and genital secretions is particularly high during this brief period, resulting in individuals with AHI being highly infectious. They are often unaware of their status or believe themselves to be HIV negative.

We conducted formative research with individuals with AHI from October 2007 to June 2008 in Lilongwe, Malawi, and Johannesburg, South Africa. Under the auspices of CHAVI (the Center for HIV/AIDS Vaccine Immunology) the research aimed to gain a better understanding of the sexual risk behaviours of individuals with AHI at the time of infection and immediately thereafter to assist with recruitment of such individuals into a formative cohort (CHAVI 001) and begin investigation into potential interventions for this period of high infectivity.

Our sample included 37 individuals identified with AHI during this time period. During in-depth interviews participants were asked to comment on topics to include in a potential intervention for individuals with AHI and intervention delivery strategies. We explicitly asked about the feasibility and acceptability of two potential interventions to interrupt HIV transmission during the acute period: 100% condom use or abstinence for 3 months.

More detailed information from this study on sexual behaviour at the time of infection and responses to proposed intervention activities is available elsewhere.

An intervention to reduce risk behaviours during AHI is currently being developed in Lilongwe, Malawi. The HPTN 062 study is evaluating the acceptability and feasibility of an enhanced, individual-level counselling intervention for individuals in the acute and early phase of HIV infection. Data collected will provide further understanding of the feasibility of abstaining during the acute period. Results are expected in 2012.

While a limited period of abstinence might theoretically be effective for limiting HIV transmission, the realities of implementation are likely to be challenging. Support for such a strategy was limited in this population of individuals with known HIV infection, despite their ongoing participation and support in an observational study. There is likely to be even less support from individuals who do not know their status or who do not perceive themselves to be at risk of infection.

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In this context, a contemplative book like *Parental Trust and Pocket Money* should be mandatory. Social activism, which like South Africa, an annual parliamentary debate on AIDS as a political issue. In high-prevalence countries in sub-Saharan Africa, the book also highlights a need to institutionalise income countries should be encouraged to finance their low-income/high-prevalence countries, while middle-income countries where affordability and availability of second-line drugs are particularly challenging. The resource countries where affordability and availability of first-line treatment. This is particularly important if we are to prevent resistance from developing, particularly in low-resource countries where affordability and availability of second-line drugs are particularly challenging. The authors also suggest that donor funding must focus on low-income/high-prevalence countries, while middle-income countries should be encouraged to finance their HIV/AIDS services using national resources.

The key argument is that the AIDS community needs to shift from its current short-term thinking to a longer-term action plan. Unlike the global campaign against climate change, which has always adopted a long-term view, the reaction to the HIV epidemic was initially framed as an emergency response. From the start, HIV was portrayed as a catastrophe waiting to happen; its complex social and behavioural determinants, which could only be addressed in the long run, were not deemed as crucial as the here-and-now. It is no coincidence, for instance, that the HIV/AIDS co-ordinating body for Swaziland, a country with one of the highest HIV prevalence rates in the world, was named the National Emergency Response Council on HIV and AIDS (NERCHA).

Part of the HIV community’s success in mobilising unprecedented amounts of funds in such a limited time is no doubt due to this approach. Nevertheless, this strategy is now back-firing. Millions of people have been placed on ARVs and thousands of new programmes have sprung up as a result of PEPFAR and Global Fund money, but now that the tide has changed and future funding is uncertain, sustainability poses a massive challenge.

The book brings together the work of nine working groups focusing on modelling, social drivers, programmes, financing and leadership, among other things. It compiles the current consensus – arrived at following a long and serious consultative process – on all the key aspects of the epidemic into a single document. In so doing, the book does not actually tell us anything new. As the authors suggest, we should focus on prevention, and improve the efficiency of spending on HIV. We must ensure greater donor co-ordination and come up with innovative financing mechanisms and incentive schemes such as advance market commitments, in order to encourage research and investments in the right places.

We must devote ourselves to finding and funding more easily administered and longer-lasting first-line treatment. This is particularly important if we are to prevent resistance from developing, particularly in low-resource countries where affordability and availability of second-line drugs are particularly challenging. The authors also suggest that donor funding must focus on low-income/high-prevalence countries, while middle-income countries should be encouraged to finance their HIV/AIDS services using national resources.

Given the extent of the HIV problem in sub-Saharan Africa, the book also highlights a need to institutionalise AIDS as a political issue. In high-prevalence countries like South Africa, an annual parliamentary debate on AIDS should be mandatory. Social activism, which

Imagine a small gathering. Gradually, word spreads and the intimate affair turns into a fulcrum of activity. From a handful of friends, hundreds of people join, bringing strobe lights, powerful loudspeakers and copious amounts of food. The party, one of the most successful ever held, lasts through the night. Then the lights are turned on, the cops arrive and the party grinds to a halt. No more parties are allowed, ever again.

It is perhaps crude to depict the struggle to get HIV/AIDS on the global agenda as a successful party being busted. The HIV/AIDS ‘community’ – for lack of a better word to describe a disjointed group of people focusing on a common challenge – is, however, a victim of its own success. In the 2000s it managed to rally immense political support and mobilise unprecedented financial and human resources. Nowadays, the luxury of that precious capital is no longer there. New priorities are occupying the global community, and HIV/AIDS is being treated like a scolded child who has squandered both parental trust and pocket money.

In this context, a contemplative book like *AIDS: Taking a Long-Term View* is particularly necessary. The short, easy-to-read monograph takes a critical look at the field of HIV/AIDS policy from 1981 until today, 30 years after the virus was first reported. It explains and summarises, in layman’s terms, what the road ahead for HIV looks like. It serves as a useful resource for students of health policy as well as engaged policy makers.

‘It is fair to ask whether the global AIDS effort has always achieved good value for its money,’ suggests one of the chapters. ‘Despite a more than 53-fold increase in AIDS funding in barely over a decade, the epidemic continues to outpace the rate at which programs are delivering.’ These are indeed sobering estimates. Not only are such mind-boggling increases in funding unlikely to recur, but needs for such funds will certainly keep escalating. In light of this, a healthy degree of soul-searching is needed, and the book provides just that.

The book succinctly takes stock of what the world of HIV has achieved, what it could have done differently, and what it should do today to ensure that 2031, the anniversary marking 50 years since AIDS was first reported, will be a party and not a funeral. In so doing, the group of academics and high-level practitioners that authored it – the aids2031 Consortium – provides a much-needed vision going forward.
was instrumental in obtaining public provision of ARVs in the country, needs to play its role in ensuring that HIV remains at the forefront of political debate. The monograph also places the fight against HIV in historical perspective; the past teaches us that HIV must be tackled from all angles at once in order for it to be defeated. ‘Virtually every major public health success has been built on a combination of behavioral, biomedical, social and structural approaches,’ point out the authors, citing the campaign against smoking as a key example. In the absence of game-changers – such as the discovery of an effective vaccine, new drugs, or even a cure – our efforts to steer clear of ‘business as usual’ must be strengthened.

In sum, none of these recommendations is revolutionary, and that is exactly what is most significant about the book. It tells us what we know we should be doing but aren’t doing. The greatest challenge in 2011 will be to ensure that these recommendations don’t fall on deaf ears. If they do, in 2031 we will find ourselves the victims of a bad hangover at the end of another busted party.

Ilaria Regondi
Alan Whiteside
Concerning paediatric palliative care and infant mortality:
1. True (A) or false (B) – click on the correct answer: In South Africa most deaths of children under 5 are due to trauma.
2. True (A) or false (B) – click on the correct answer: Most AIDS-related palliative care in South Africa is rendered by unskilled home-based carers.
3. True (A) or false (B) – click on the correct answer: Antenatal zidovudine may reduce intra-uterine vertical transmission.
4. True (A) or false (B) – click on the correct answer: Postpartum transmission contributes relatively more to infant mortality than intra-uterine transmission.

Concerning ART and HIV testing programmes:
5. True (A) or false (B) – click on the correct answer: Less stavudine and more protease inhibitors are prescribed as first-line therapy in private sector patients.
6. True (A) or false (B) – click on the correct answer: Stavudine is a cause of peripheral neuropathy.
7. True (A) or false (B) – click on the correct answer: Providing VCT in the workplace is stigmatising and leads to boycott of testing.

Concerning HIV and the lungs, nerves and kidneys:
8. True (A) or false (B) – click on the correct answer: Cytomegalovirus (CMV) infection usually occurs in patients with well-preserved immunity.
9. True (A) or false (B) – click on the correct answer: In transbronchial biopsy specimens, CMV is identified by viewing ring forms.
10. True (A) or false (B) – click on the correct answer: HIV plus smoking predisposes to emphysematous lung disease in an additive way.
11. True (A) or false (B) – click on the correct answer: Bilateral facial palsy is reported and may be a result of an inflammatory radiculopathy similar to Guillain-Barré syndrome.

Concerning hepatitis B infection in HIV:
12. True (A) or false (B) – click on the correct answer: HIV-related renal disease manifests as proteinuria or elevated creatinine clearance.
13. True (A) or false (B) – click on the correct answer: Ninety per cent of children with perinatally acquired HBV from mothers who are HBeAg positive will go on to have chronic disease.
14. True (A) or false (B) – click on the correct answer: HIV decreases the rate of spontaneous HBsAg seroconversion.
15. True (A) or false (B) – click on the correct answer: Patients who are eligible for HBV vaccination but have CD4 counts <200 cells/µl mount poor antibody responses to HBV vaccine.
16. True (A) or false (B) – click on the correct answer: Vaccinate patients with hepatitis B vaccine regardless of CD4 count.

Concerning management of hepatitis B/HIV co-infection:
17. True (A) or false (B) – click on the correct answer: HIV-HBV co-infected patients with ALT ≥2 times the upper limit of normal are at an increased risk of HBV disease progression.
18. True (A) or false (B) – click on the correct answer: ART is contraindicated for any co-infected patient with CD4 counts >350 cells/µl who has symptomatic liver disease.
19. True (A) or false (B) – click on the correct answer: A hepatitis flare may occur in a patient who has been on a lamivudine-containing regimen and develops hepatitis B resistance to lamivudine.
20. True (A) or false (B) – click on the correct answer: Only newborn babies of mothers infected with HBV who are co-infected with HIV should receive hepatitis B immunoglobulin (HBIG) plus the first dose of the hepatitis B vaccine within the first 12 hours after delivery.