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FROM THE EDITOR

The article by Professor Robin Wood in this issue highlights the dilemma surrounding antiretroviral first-line regimens. We do have an effective, cheap, first-line therapy: however it contains d4T, which has toxicities. These have been noted and vary in prevalence in South Africa. The efficacy and cost of the current first-line therapy has to be balanced against the decreased toxicity and increased expense of a first-line therapy containing tenofovir (expected to be registered in South Africa in about 12 months). The increased costs of a tenofovir-containing regimen will include the higher cost of monitoring, this time for renal toxicities.

On the one hand the public health viewpoint would support increasing access to antiretroviral therapy, but increased numbers of treated people would mean having to deal with an increase in disabling side-effects, which include neuropathies, hepatotoxicities, lipoadenopathies, and sometimes serious and even fatal toxicities such as lactic acidosis. It will be interesting to see how the debate regarding proposed new first- and second-line regimens recommended by the World Health Organization unfolds.

It is indeed heartening to see increased access to antiretroviral therapy in a number of under-resourced rural communities as a result of the energy and dedication of informed HIV clinicians. This issue of the journal highlights two examples, the KOSH Branch of the HIV Clinicians Society (Klerksdorp, Orkney, Stilfontein and Hartebeesfontein, also known as the Matlosana district of the southern region of North West Province (NWP)) and Madwaleni Hospital, which is over 100 km away from its referral centre, the Nelson Mandela Hospital Complex in Mthatha.

In the NWP the southern and Bojonala regions have the highest HIV prevalence rates (31.1% and 30.4% respectively). The KOSH Branch was recently launched by a dedicated and energetic team led by Ms Tanya Nielson and Dr Bramie Variava. Three branch meetings have been held so far at which experts have given talks and difficult cases have been discussed. These CME meetings facilitate local networking and offer additional support to health care professionals involved in the rollout of private, corporate and public sector ART programmes.

Madwaleni hospital, a 220-bed district hospital serving a population of approximately 256 000, was initially built as a missionary hospital in the early fifties. At the end of 2005 it had only a rudimentary HIV service, but with the enthusiasm and hard work of Dr Richard Cooke and Ms Lynne Wilkinson it now has well over 200 patients on ARV treatment and only one patient has been lost to follow-up!

The focus on HIV/AIDS is often on treatment, but prevention strategies should not be minimised as they are so important in the fight against the spread of HIV. Methods include microbicides, condom use, circumcision, delaying of sexual activity, monogamous relationships and so on, discussed eloquently by Dr Linda-Gail Bekker *et al.*

The Society wishes the southern African delegates attending the Toronto conference in August a safe journey and a stimulating and informative conference.

DES MARTIN

Editor, Southern African Journal of HIV Medicine

MESSAGE FROM THE EXECUTIVE

The Society executive is very excited to report that we have secured funding to significantly expand our support to HIV care programmes in Southern Africa. We will be looking at improving existing treatment and other guidelines. We will also be looking at new guidelines in areas that have been raised by clinicians on the ground, as well as establish several 'think tanks' to give people space to start throwing around new ideas in the field of HIV prevention and treatment. We will be expanding access to the Journal and Transcript wherever possible, and providing more support to our advocacy arm to organisations involved with access to HIV care. The Society has recently been instrumental in several high-profile court cases promoting the scientific and rational approach to HIV chronic treatment. I hope that by the time you read this our new website will be functioning, as this will allow access to back issues of the Journal, a resource on which our members seem to place huge value. I hope that you will continue to support us in all these initiatives. The central office will grow to accommodate these expanded programmes, and we hope we will be able to continually improve the service to our members.

Giving quality HIV care to huge numbers of people is an unbelievably massive challenge. We need creative and brave thinking. Our respective governments and our patients are relying on us to step up and give calm, professional advice on the best way forward. The Society needs to take this responsibility very seriously, and we will be asking for your help at every turn.

FRANCOIS VENTER

President, Southern African HIV Clinicians Society

THE ROLE OF STAVUDINE IN THE SOUTH AFRICAN PUBLIC SECTOR ANTIRETROVIRAL PROGRAMME: SHOULD THE PERFECT BE THE ENEMY OF THE GOOD?

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Stavudine (d4T) was one of the first nucleoside analogues developed as an HIV antiretroviral (ARV). An early monotherapy trial demonstrated similar antiviral activity to zidovudine (AZT),[1] and a comparative study of d4T and AZT in combination with lamivudine (3TC) and a protease inhibitor(PI) reported similar therapeutic outcome in each randomised treatment arm.[2]

Since registration in 1993 by the US Federal Drug Agency, d4T has been used extensively in combination therapy and was one of the first ARVs to become available in South Africa as a generic formulation. There is recently published evidence that its use is associated with higher CD4 cell count responses than other nucleoside analogues.[3] The generic formulation with 3TC and nevirapine (NVP) is currently the cheapest ARV combination therapy available worldwide. With the development of a necessary public health approach to expanded access to ARVs in resource-poor settings the World Health Organization (WHO) included d4T in its recommended first-line ARV regimens.[4] Following widespread use of d4T, adverse events including lipodystrophy, neuropathy and lactic acidosis associated with long-term therapy have been increasingly recognised. Despite the proven utility of d4T in more than a decade of use and its very low cost there has been an increasing swing of medical opinion against use of d4T and a search for alternatives.

MECHANISM OF ACTION

Stavudine is a nucleoside analogue of thymidine, which is a pro-drug requiring phosphorylation by cellular kinases to the active metabolite stavudine triphosphate. The triphosphorylated molecule inhibits HIV reverse transcriptase by competing with the natural substrate deoxythymidine triphosphate and by incorporation into the viral cDNA causing chain termination.[5] Resistance genotypes generated during d4T use show much overlap with those generated by AZT, another thymidine analogue. D4T also inhibits human cellular DNA polymerases beta and gamma resulting in a marked reduction in the synthesis of mitochondrial DNA. This cross-inhibition of human DNA polymerases may constitute the causative mechanism of the more serious toxicities associated with d4T use.

TOXICITY

The toxicity of d4T is exacerbated when the drug is used in combination with other dideoxy nucleoside analogues and the combination with didanosine (ddI) is now discouraged in most treatment guidelines. Impairment of mitochondrial function is postulated to be the cause of increased lactate production and/or decreased clearance. The clinical sequelae vary from asymptomatic hyperlactataemia to fatal lactic acidosis, and from hepatomegaly with steatosis to hepatic failure. Recognised risk factors for lactic acidosis include female gender, increased body mass index, and prolonged use of d4T. Monitoring for elevated lactate is indicated in patients on d4T when hepatic transaminases rise, or there is unexplained weight loss or gastrointestinal symptoms. Peripheral neuropathy is also considered to result from mitochondrial dysfunction and symptoms are related to the dose of d4T. Neuropathy is more frequently reported in patients with advanced HIV disease and those with a prior history of neuropathy and when other neurotoxic drugs such as isoniazid and ddI are coadministered.

EXPERIENCE WITH d4T IN SOUTH AFRICAN PUBLIC SECTOR PROGRAMMES

The Cape Town Gugulethu treatment programme[6] was the first public sector ARV programme to initiate therapy in September 2002 with d4T/3TC and a non-nucleoside reverse transcriptase inhibitor (NNRTI) using a treatment protocol based on the WHO 2002 expanded access recommendations.[4] A second regimen of AZT, ddI and ritonavir-boosted lopinavir (Kaletra) is available to those who fail first-line therapy. Mortality early in this programme showed that 66% of deaths

occurred in patients awaiting ART and the majority of deaths on ART occurred in the first 6 months of treatment due to causes associated with the advanced stage of HIV infection of those accessing treatment.[7] Of the 68 programme deaths only 2 were ARV drug-related, a nevirapine rash with septicaemia and a d4T-associated lactic acidosis.[7] By April 2006 over 2 000 patients had received ARVs in this clinic. D4T substitution has been required in 206 individuals in the treatment programme, in 158 cases as a direct result of drug toxicity. The median time on d4T before switching was 403 days (IQR 280 - 569). Causes of drug-related switches were, in descending frequency, lipodystrophy (76 cases, 48%), peripheral neuropathy (57, 36%), hyperlactataemia (16, with 8 cases of acidosis – 10% and 5% respectively), elevated hepatic transaminases (5, 3%), unspecified causes (3, 2%) and pancreatitis (1, 1%). Another large HIV treatment programme in Khayelitsha, Cape Town, which began using d4T as a first-line regimen in 2003, has reported approximately 10% of patients switching from both AZT and d4T by 12 months.[8] Nucleoside reverse transcriptase inhibitor (NRTI) switches due to AZT toxicity were mainly the result of anaemia (82%), which occurred early, while d4T switches were reported later in therapy and appeared to be increasing with longer use of d4T in the programme. These cohort data indicate a higher rate of switching due to d4T toxicity than is reflected in published randomised trial data. A multinational comparative 3-year study of 602 drug-naïve individuals (26% female and 20% black) randomised to d4T or tenofovir in combination with 3TC and efavirenz had identical discontinuation rates (6%) due to adverse events in each drug allocation arm, and a sub-analysis of women in the study also showed similar regimen discontinuation rates in both arms.[9] Lactic acidaemia was reported in 1 patient who had been randomised to the d4T arm. If similar dosages and formulations of d4T are used in Gugulethu and Khayelitsha, there are two possible explanations for this apparent increased switching due to toxicity: firstly that the South African population is more susceptible to adverse effects of d4T than the randomised study population, or that there is significant ascertainment bias in the cohort data due to over-diagnosis of possible d4T-related clinical events. It is particularly important to establish if there is an increased population susceptibility to adverse effects of d4T, which may in turn be due to genetic or exposure to environmental cofactors.

ROLE OF (d4T) IN TREATMENT PROGRAMMES

d4T has been used successfully in the public health ARV programmes because it is cheap and initially very well tolerated. Toxicities accumulate after prolonged therapy and pose significant challenges to programme staff, who must maintain a high vigilance for potentially serious metabolic complications. The inability to monitor serum lactate easily together with the serious consequences that can result makes management of lactate metabolic derangements particularly problematic.

However, the major challenge facing the South African ARV programme is to reduce HIV-related deaths by increasing coverage of the existing programme to the 800 000 individuals currently in immediate need of therapy. The public health approach is epitomised by national tuberculosis control programmes, where treatment regimens are cheap, simple and effective and co-formulations are used where possible. Treatment options are limited, so that medical officers and nurses can be well acquainted with a small number of agents. First-line ARV therapy should be well tolerated and side-effects should be predictable and require minimal toxicity monitoring. Within such a public health framework it is important to establish whether any changes to existing regimens or use of alternative therapies will help or impede the necessary wider access to ARV therapy.

POSSIBLE ALTERNATIVE REGIMENS

Standard ARV therapy is based on a nucleoside backbone of two NRTIs together with either an NNRTI or a PI. There are 6 NRTIs registered in South Africa, stavudine (d4T), zidovudine (AZT), lamivudine (3TC), didanosine (ddI), zalcitabine (ddC) and abacavir (ABC). Of these only ddC and ABC are not already included in standard first- and second-line regimens. Currently the cost of ABC and the neurotoxicity of ddC would exclude them as substitutes for d4T in a first-line regimen. With the present choice of registered NRTIs, substitution of AZT for d4T in the initial first-line regimen would necessitate the subsequent use of d4T with ddI in the second-line regimen, a combination that is discouraged due to co-toxicity.[4] The present use of AZT in second-line following initial d4T failure in first-line therapy is not ideal, as both drugs have shared HIV resistance mutation profiles.

The choice of available NRTIs will be increased if tenofovir (TNF), a nucleotide analogue of adenosine 5'-monophosphate, is registered for use in South Africa. The drug has been licensed since 2001 in the USA and is under review for registration by the South African Medicines Control Council. Its US labelled use was initially for patients failing previous therapies and more recently extended to use in first-line therapy. It is generally well tolerated with some gastrointestinal adverse events and increased bioavailability when administered with food (40%). The prolonged elimination half-life allows once-daily administration, with the major route of elimination being both renal glomerular filtration and active tubular secretion. It has adverse pharmacokinetic interactions with ddI and has activity against hepatitis B virus which may precipitate severe acute exacerbations of hepatitis B in patients who have discontinued the drug.[10] The use of TNF, which will require additional renal function monitoring, will increase the programme costs of safety monitoring. TNF is also co-formulated with emitricitabine (FTC) into a single daily tablet (Truvada), which offers a reduced pill burden.

If TNF became available for use in the national ARV programme in South Africa, how could it be utilised? Substitution of d4T with TNF would increase the cost of the first-line regimen and increase monitoring requirements and therefore impede increased access to therapy. The cost

effectiveness of an ARV programme is very sensitive to the costs of the first-line therapy.[11] A direct substitution of the AZT in the second-line regimen would not be possible as coadministration with ddI is discouraged. Replacement of both AZT and ddI with TNF and 3TC or FTC would not increase costs and would provide a more rational second-line NRTI backbone. This strategy, although it would require the recycling of 3TC/FTC, would release AZT to be used as a switch alternative for d4T within the first-line regimen. The toxicity profiles of AZT and d4T differ in both spectrum and timing (Table I). Anaemia related to AZT occurs early after initiation of treatment in approximately 6 - 10% of African patients, while d4T is initially well tolerated. D4T and AZT could be used in a similar fashion to efavirenz and nevirapine, which have different toxicity profiles but are susceptible to similar genetic mutations of HIV. The use of low-cost d4T/3TC/NVP could be maintained in the initial first-line regimen if either those identified at high risk or those with early d4T toxicity could be switched to AZT.

TABLE I. COMPARISON OF RAND COSTS PER MONTH (PUBLIC SECTOR TENDER PRICES MAY 2006), TOXICITIES, AVAILABLE CO-FORMULATIONS AND PILL BURDEN OF STAVUDINE, ZIDOVUDINE, ABACAVIR AND TENOFOVIR

	Stavudine (d4T)	Zidovudine (AZT)	Abacavir (ABC)	Tenofovir (TNF)
Cost/ month *(generic)*	R42.59 *(22.66)*	R 126.79 *(143.64)*	R527.92 *(NA)*	R123.05 *(NA)*
Toxicity timing	Late	Early	Early	Early
Main toxicities	Neuropathy Lactic acidosis Lipodystrophy	Anaemia	Hypersensitivity	Renal tubular
Available combina-tions	d4T/3TC/NVP	AZT/3TC; AZT/3TC/ABC	AZT/3TC/ABC	TNF/FTC
Pill burden/ day	2 tabs	2 tabs	2 tabs	1 tab

SUMMARY

The major challenge facing the ARV programme in South Africa is to expand access rapidly to very large numbers of individuals at high immediate risk of death. In order to achieve this, a public health approach to ARV therapy requires the use of cheap effective drugs in simply administered regimens. Currently the generic combination of d4T/3TC/NVP constitutes the cheapest available ARV regimen. Serious toxicities associated with long-term use of d4T have raised concerns about the continued use of this drug in the first-line regimen. The rate of drug switching due to d4T toxicity in South African cohorts appears higher than that reported in controlled randomised studies, and this may either be due to a real higher toxicity event rate in the South African population or be an apparent increase caused by ascertainment biases. Mortality in existing ARV programmes is overwhelmingly dominated by late access to programmes rather than deaths due to drug toxicity. Changes to present ARV regimens must therefore be judged within a public health framework, which should enable wider access to therapy for those in immediate need of treatment.

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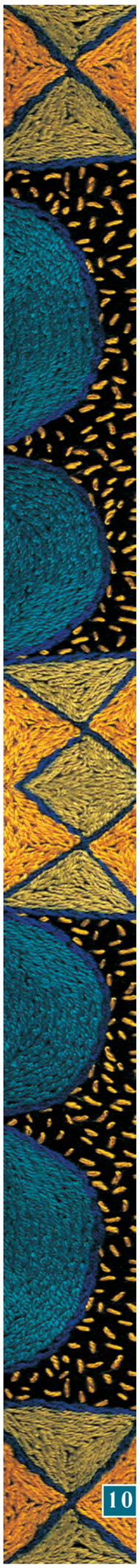

LABORATORY

ANTIRETROVIRAL THERAPEUTIC DRUG MONITORING

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Antiretroviral therapeutic drug monitoring (TDM) is an additional monitoring tool to assist in the management of HIV-infected patients. Antiretroviral TDM is frequently undertaken in Europe, but less often in the USA. This overview will assess the principles, current evidence for, and limitations of TDM. Lastly, the potential role of TDM in southern Africa will be discussed.

GENERAL PRINCIPLES OF TDM

The vast majority of drugs used in clinical practice do not require TDM. It is far easier for clinicians to adopt a 'one size fits all' approach to dosing. Alternatively doses may be modified according to response. However, with some drugs this will result in high rates of toxicity, or suboptimal efficacy.

The characteristics that make drugs suitable for TDM include:

- A narrow therapeutic window
- Good correlation between drug concentration and effect or toxicity
- Variable pharmacokinetics in different individuals
- The availability of a reliable assay.

Digoxin and the first-line anticonvulsants are examples of drugs where TDM plays an important role. However, even when all of these characteristics are present, TDM is seldom done as a routine part of management for every patient. Clinicians typically use TDM if there are clinical concerns such as toxicity, poor efficacy, drug interactions, or special groups at risk of altered levels. This use of TDM is rational and appropriate, as there are very few randomised controlled trials to support the routine use of TDM.

WHICH ANTIRETROVIRALS ARE SUITABLE FOR TDM?

The nucleoside reverse transcriptase inhibitors (NRTIs) are pro-drugs, which require activation by intracellular phosphorylation. There is a poor correlation between plasma NRTI levels and effect. Only a few laboratories are capable of measuring intracellular levels. NRTIs are therefore not suitable for TDM.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) display highly variable pharmacokinetics. The key cytochrome P450 isoenzyme responsible for metabolising efavirenz, CYP2B6, has a polymorphism that results in slower metabolism. This polymorphism occurs much more frequently in African Americans than Caucasians[1] – it is unclear whether this polymorphism will occur commonly in southern Africa. There is a correlation between higher plasma levels and neuropsychiatric adverse effects of efavirenz, and between lower levels and virological failure.[2] A population pharmacokinetic study has shown that Thai and South African patients have lower clearance of nevirapine, resulting in greater exposure, than patients in 'Western countries'.[3] This may account in part for high rates of nevirapine-induced hepatotoxicity, particularly among women with a lower body mass index, reported in a South African study.[4] Higher nevirapine levels are associated with a greater chance of virological success.[5]

The protease inhibitors (PIs) also have highly variable pharmacokinetics. Plasma concentrations of PIs have been shown to correlate with virological success.[6] High levels of certain PIs correlate with adverse drug reactions, notably nephrolithiasis with indinavir[7] and dyslipidaemia with lopinavir/ritonavir.[8]

Therefore both NNRTIs and PIs have many characteristics that make them potentially suitable candidates for TDM.

ARE RELIABLE ANTIRETROVIRAL ASSAYS AVAILABLE?

Currently there are no commercial kits to measure drug levels of antiretrovirals, though a few are in development, so antiretroviral TDM is conducted by laboratories that have developed their own in-house assays. It is therefore essential that laboratories participate in regular quality control to ensure that their assays are reliable. In a recent survey of laboratories conducting TDM, only 12 out of 31 had assays that were in the acceptable range for more than 90% of measurements.[9]

LIMITATIONS OF TDM

A number of randomised controlled trials have been conducted to assess the value of routine TDM. In these studies patients

were randomised to control or TDM arms, where the treating clinician was advised about the antiretroviral level and, if necessary, to adjust the dose. Two of these studies[10,11] showed higher rates of virological suppression in the TDM arms. However, a number of other studies have failed to show a benefit for routine TDM.[12,13] One problem encountered in these randomised trials is that clinicians often did not make the recommended dose adjustments. In some trials the follow-up was very short. Lastly, the trials were under-powered. Until a large trial is conducted to address the weaknesses of the existing studies, there does not appear to be a role for routine TDM for all patients treated with antiretrovirals.

A recent study[14] found that drug levels, particularly for PIs, were very variable in individual patients sampled at different times. This could partly be explained by the variability in the effect of dosing with food, which is important for the PIs studied. In addition, adherence can clearly affect drug levels; indeed, TDM is one tool to detect poor adherence. Controlling for adherence is difficult in clinical practice. This study[14] highlights the importance of not making major clinical decisions on the basis of a single TDM result.

PATIENTS AT HIGHER RISK OF DRUG LEVELS OUTSIDE REFERENCE RANGES

Given that current evidence does not support routine TDM, it makes sense to utilise TDM in patients at particular risk for either suboptimal or toxic levels.

CHILDREN

Several important physiological changes in childhood, particularly early childhood, affect the pharmacokinetics of drugs.[15] Firstly, the volume of distribution is affected as total body water is high in neonates and remains high in young children. Neonates have impaired drug absorption, metabolism and excretion, while in young children these parameters are enhanced compared with adults. Many authorities therefore recommend TDM in young children, especially as there are very limited data available for most antiretrovirals in children.

PREGNANCY

Many physiological changes in pregnancy affect pharmacokinetics:[16]

- Increased GIT motility
- Decreased protein binding
- Increased volume of distribution (fat and water)
- Mild hepatic enzyme induction
- Increased renal excretion.

Up to a third of pregnant epileptics experience an increased frequency of seizures owing to sub-therapeutic anticonvulsant levels, illustrating that these physiological changes of pregnancy are clinically relevant. A recent study showed lower lopinavir levels in pregnant women.[17] Despite this, the women still had good virological suppression. This change in PI levels induced by pregnancy is likely to be relevant when a degree of PI resistance is present – TDM should be considered in this setting.

DRUG INTERACTIONS

Many PIs are substrates of the important drug transporter, P glycoprotein. Their levels can be affected by drugs that inhibit or induce P glycoprotein. PIs and NNRTIs are metabolised by the cytochrome P450 system, and their levels can be affected by drugs that inhibit or induce this system. If a drug known to have such interactions has to be co-administered, TDM should be considered.

LIVER DISEASE

PIs and NNRTIs are metabolised by the cytochrome P450 system, which occurs primarily in the liver. Unlike renal disease, there is no accurate biochemical marker to indicate how much hepatic impairment is present. TDM should therefore be considered for patients with evidence of liver failure, as they may experience toxicity due to high levels.

INTEGRATING TDM AND PI RESISTANCE DATA – WHAT'S THE IQ?

PI resistance can to a certain extent be overcome by increasing the levels. It therefore makes sense to integrate the resistance data and the drug level. This is done using the inhibitory quotient (IQ), which is calculated by dividing the trough level by a factor, depending on the resistance test conducted. This is typically a genotypic test, and the trough level is divided by the number of major PI mutations. This genotypic IQ has been shown to correlate with virological success in PI-experienced patients.[18]

Note that this strategy cannot be used with the NNRTIs, as a single mutation generally confers very high-level resistance, which cannot be overcome by increasing the dose.

A ROLE FOR TDM IN SOUTHERN AFRICA?

Antiretroviral TDM could play an important adjunctive role in our area. Clearly this will be a limited resource, confined to high-risk patients or to those with some degree of PI resistance. There is a danger that laboratories will offer TDM without the necessary quality assurance. Until commercial kits become available, TDM should only be conducted by specialist pharmacology laboratories that participate in regular quality assurance.

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AIDS PREVENTION IN SOUTH AFRICA

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More individuals were newly infected with HIV in 2005 than any other year. Sub-Saharan Africa and especially southern Africa bears the brunt of this pandemic. Although the picture in sub-Saharan Africa is largely one of a 'stable' epidemic where AIDS-related mortality is matched by the incidence of new infections, some countries in the Southern regions have continued to see increasing HIV prevalence.[1] In this light, there is an urgent need for new approaches to HIV prevention. Here we review the current state of HIV prevention technologies, with particular emphasis on new approaches to HIV prevention that have particular promise in southern Africa. The focus here is on interventions that address sexually transmitted HIV, since the vast majority of new HIV infections in Africa are through heterosexual contact, and other important HIV prevention interventions (such as blood safety interventions and the prevention of mother-to-child transmission) are not included.

LESSONS FROM HIV EPIDEMIOLOGY IN AFRICA

Our understanding of prevention interventions can be framed by two general principles from infectious diseases epidemiology. First, the transmission dynamics of HIV can be described in terms of the basic reproductive number (Ro), which represents the number of secondary infections emanating from a singe infectious individual (i.e. a primary case) introduced into a population of susceptible individuals. The equation: Ro = ßc*D* shows how the basic reproduction number Ro is influenced by the probability of HIV transmission between individuals (ß, a function of both the infectiousness of the primary case and the susceptibility of uninfected individuals), as well as the number of sexual partners (c) and the duration of infectiousness (D) of the primary case.[2] Evidence from different parts of Africa suggests that variability in both the transmission probability and sexual partner changes are important in explaining the variable course of HIV epidemics in different regions.

The second key HIV prevention principle suggested by infectious diseases epidemiology is that reductions in transmission risk among the most sexually active members of the population can have a disproportionately large impact on the HIV epidemic. In other words, the most efficient and effective prevention strategies should be targeted at specific population groups where HIV acquisition risk is high.

Recent epidemiological research demonstrates how these principles may operate in sub-Saharan Africa. At a national level, Zimbabwe is one of the few countries that has seen a marked decrease in HIV prevalence that can be linked to changes in sexual behaviours (other notable examples include Uganda and Thailand). One recent analysis from Zimbabwe,[3] based on repeated studies of a rural Zimbabwean population between 1998 and 2003, shows a 23% reduction in HIV prevalence among men aged 17 - 29 years and 49% reduction among young women aged 15 - 24 years. These reductions have been attributed to proportional decline in sexual risk behaviours, namely delayed sexual debut, reduction in numbers of casual sexual partners and more condom use among females.

Further insights into the population spread of HIV in Africa come from the Four Cities study,[4] a cross-sectional study of HIV, other sexually transmitted infections, and sexual behaviours from Kisumu (Kenya), Ndola (Zambia), Cotonou (Benin) and Yaounde (Cameroon). This study suggested that high male circumcision rates in West Africa may have reduced the rate of HIV and other STIs, while genital ulcer disease, especially herpes simplex virus type 2 (HSV-2), may have contributed to higher rates in East and Southern Africa.

MALE CIRCUMCISION

The role of male circumcision in the prevention of HIV and STI acquisition became a hotly debated topic when a number of cross-sectional studies from different parts of Africa suggested that this intervention might have a protective effect,[5,6] and this finding has been supported by more recent data suggesting reductions in HIV transmission among HIV serodiscordant couples where the man is circumcised.[7] In addition to these epidemiological data, there are biologically plausible mechanisms for the observed reduction in HIV-1 acquisiton among circumcised males. The inner mucosa of the foreskin is rich in HIV-1 target cells, e.g. dendritic cells, CD4+ T cells, and macrophages that express relevant HIV-1 binding receptors such as chemokine receptors (CCR5) and DC-SIGN.[8] By contrast the external foreskin is keratinised and much less vulnerable to HIV infection. After circumcision, the only exposed mucosa is in the urethral meatus. Removal of the foreskin's target cells and receptors can represent a direct biological mechanism of protection.

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Three randomised controlled trials (RCTs) have recently been initiated in sub-Saharan Africa to explore the efficacy of male circumcision. The results of the RCT conducted in Orange Farm, South Africa, demonstrated a 60% reduction in the risk of acquiring HIV infection over 21 months of follow-up in newly circumcised, 18 - 24-year-old males. The incidence rate in the intervention group was 0.7 per 100 person years while in the control group it was 2.2 per 100 person years, a crude incidence rate ratio of 0.35 (95% CI: 0.20, 0.60). The other two RCTs (in Uganda and Kenya) are still to be completed. Should these randomised controlled trials also show the efficacy of male circumcision in reducing HIV acquisition risk, the implementation of this modality in the general population will still require further investigation of a range of issues including acceptability, rates and types of adverse events of the procedure, cost and logistics of introduction, and importantly the long-term effect of circumcision on behaviours such as partner reduction and condom use.[9]

VACCINES

An effective preventive HIV vaccine would provide the best method for controlling the HIV pandemic, especially in under-resourced countries, and so any successful vaccine will need to be applicable to all regions regardless of virus subtype and be licensed for use in all age groups including older children and adolescents. After almost 20 years of HIV vaccine clinical trials, and numerous phase 1 and 2 studies, there are a variety of vaccine products in the pipeline that look hopeful enough to be subjected to efficacy trials.[10]

VACCINE STRATEGIES

For a number of years the vaccine pipeline was limited to simple gp 120 or gp 160 proteins based on lab strains of the virus, synthetic peptides and simple poxvirus HIV-recombinant vectors. The constructs currently in the pipeline include gp 120 constructs based on clinical HIV isolates, bird virus vectors and other vectors such as modified vaccinia Ankara and Venezuelan equine encephalitis virus replicon expressing multiple HIV genes, and different constructs of naked DNA. The most promising candidates in the last few years have included live attenuated vectors containing a variety of HIV genes. These attenuated vectors include adenovirus, associated adenovirus and sindbis.[11,12]

CHALLENGES TO VACCINE DESIGN

The lack of an immune correlate of protection (clear type of immune response needed to provide protection against HIV) and the lack of an adequate animal model that can mimic human disease infection poses significant scientific challenges to developing a successful vaccine. In addition HIV-1 genetic diversity may complicate the development of a globally relevant HIV vaccine. Diversity may be addressed by the development of vaccine candidates comprised of cocktails of proteins of regional variants with the assumption that the immune responses elicited by a multiclade, multi-gene vaccine will be of sufficient cross-reactivity to protect against a range of wild-type strains.[13]

PROTECTION REQUIRED

Current HIV vaccine candidates elicit reasonably potent cellular immune responses, but very low levels of neutralising antibodies. Cytotoxic T-lymphocytes are part of the cellular immune response that controls viral replication. Vaccines that produce strong CTL responses are more likely to control viral replication and thus reduce viral load. Used as preventive vaccines they may then modify disease in an individual who has breakthrough infection, leading to less morbidity, longer time to AIDS and possibly less HIV transmission. Antibodies provide the first line to the immune system defence and neutralising antibodies inactivate or prevent the virus making contact with target cells, providing the best possibility to abort or prevent infection. Neutralising antibody stimulation would thus be a highly sought after characteristic in a preventive vaccine, but has to date been very difficult to achieve. The gp 160 protein on the outside of the virus is important for stimulating neutralising antibodies but is oligomeric and susceptible to glycosylation. Most HIV infections occur via the mucosal route and so it may be important to stimulate mucosal immunity in rectal and genital tracts as well as cellular and humoral responses in the blood to achieve protection.[10,14]

Prime-boosting is a new combination strategy that seeks to enhance vaccine responses by invoking various types of immunity. A typical strategy would involve priming with a naked DNA vaccine which would be expected to do little more than stimulate production of memory T cells, followed by boosting with a live vector/protein, which would then stimulate a strong cellular response as well as neutralising antibodies. So far early studies in humans have shown this to be safe.[12]

PROMISING CANDIDATES THAT ARE FURTHER ON IN HUMAN TESTING

A number of world-wide networks, e.g. the HIV Vaccine Trials Network (HVTN), the International AIDS Vaccine Initiative and the South African AIDS Vaccine Initiative, as well as pharmaceutical companies, are involved in the global effort to develop and test preventive vaccines. After 20 years of ongoing research and only one completed, albeit ineffective, phase 3 trial in AIDSVAX, a bivalent recombinant gp120 vaccine, the HIV vaccine development pipeline is full with a number of promising candidates that look good enough to move beyond phase 1 and 2 clinical trials into efficacy testing. The NIAID in collaboration with Merck and the HVTN have initiated a test of concept study (phase IIb) in North America and South America, the Carribean and Australia. This randomised placebo-controlled trial will test Merck's HIV vaccine, the MRK Ad5 HIV-1 gag/pol/nef vaccin, in a study that will enroll 3 000 participants. The trial is set to answer two questions: whether (*i*) pre-existing immunity to the adenovirus subtype 5 (Ad5), which is the vector used in this vaccine design, dampens the immune response to this vaccine; and (*ii*) the cellular immune response elicited by this vaccine is robust enough to protect against infection. This trial will also assess disease progression in those who become infected despite receiving the vaccine.

A sister trial, the HVTN 503, is scheduled to take place in South Africa later in 2006. Since South Africa is a subtype C region

where there is a high prevalence of pre-existing immunity to Ad5, this trial will answer the question regarding the importance of sub-type in vaccine design as well as the role of pre-existing immunity to Ad5. Three thousand adults, the majority of whom are likely to be women, will participate in this trial.

Shortly thereafter, a second large efficacy trial is planned to evaluate the VRC multiclade DNA vaccine and the VRC multiclade Ad5-based vaccine sequentially also in a prime-boost strategy.

SAAVI VACCINE DEVELOPMENT PROGRAMME

The South African AIDS Vaccine Initiative (SAAVI) is also contributing significantly to the global effort. Not only are there several community clinical trial sites being prepared around the country to ensure that there are large numbers of well-educated and carefully prepared healthy volunteers to participate in these imminent large-scale trials, but in collaboration with the University of Cape Town there are also two products that are about to enter into human testing. The SAAVI DNA-C2 is a multigene subtype-C DNA vaccine and the SAAVI MVA-C is a multigene HIV-1 subtype-C recombinant MVA vaccine. These two South African vaccine candidates will be tested in a 'prime-boost' phase I trial design in collaboration with the HVTN both in South Africa and the USA in 2007.

ADOLESCENT INVOLVEMENT IN VACCINE TRIALS

One of the most effective ways to curb the epidemic in the developing world would be to vaccinate older children and adolescents prior to their sexual debut. The use of an HIV vaccine in this population will require clinical trials in adolescents to determine the vaccine's safety and immunogenicity. A precise strategy for the involvement of adolescents in clinical trials is urgently required, and again SAAVI and South African researchers are leaders in the international dialogue on this topic.[15,16]

VACCINE MANUFACTURE, PROCUREMENT AND DISTRIBUTION

Previous vaccine history has shown that once an efficacious vaccine is developed the usual pattern of deployment is in the developed world first and the developing world later. A plan for the urgent procurement and distribution of a successful HIV vaccine when available needs to exist to make the vaccine available it is where needed most – namely in resource-poor settings – as quickly as possible. This includes mechanisms for pricing, global financing, demand estimates and preparedness for production capacity, appropriate delivery systems and strategies for high-risk populations. Harmonisation of African regulatory systems and guidelines for approval are urgent, not only for this later phase of vaccine deployment, but also during this current important phase of vaccine testing. The newly established HIV Vaccine Enterprise aims to co-ordinate global efforts around these issues.[17]

MICROBICIDES

In view of the problems associated with male condoms, developing HIV prevention technologies that are under the control of women is an important avenue for HIV prevention. One of the most promising technologies currently in large-scale human trials is vaginal microbicides. A microbicide is a substance formulated to significantly reduce transmission of HIV and other sexually transmitted infections (STIs) when applied topically to the vagina or rectum.[18,19] They can be formulated as gels, creams, films, suppositories, sponges or vaginal rings, or used in conjunction with other barrier methods such as the diaphragm or cervical cap. The mode of action of microbicides includes antiviral activities, barrier action between the pathogens and vaginal and rectal tissue, or modification of vaginal or rectal milieu which makes HIV infection less likely.[20] Compared with male or female condoms, microbicides are expected to interfere less with intimacy and sexual pleasure and be more discreet.[21]

Although microbicides are primarily being developed for use by women, it is possible that they may have a bidirectional protective effect for men as well. As women's reproductive intentions alter throughout their lives, both contraceptive and non- contraceptive microbicides are being developed. Another research agenda is to develop a microbicide that is protective for partners practising anal sex, as such a product could be used for both heterosexual and MSM sex. Importantly, a microbicide shown to be safe and effective should be easily available over the counter. Mathematical modelling of a microbicide assumed to be 60% efficacious and to have 20% uptake by women at risk of HIV suggests that 2.5 million new HIV infections could be averted in developing countries.

There are currently 16 candidate microbicides in clinical development including five products in advanced stages of clinical testing (phase IIB/III trials). All of these products are being tested in Africa, and most are being tested in South Africa specifically. More than 20 000 women will take part in the current trials over the next 5 years. Results of the first products are expected to be available in late 2008.[12,22]

BARRIER METHODS

Currently the most widely available tool for prevention of HIV infection during sexual intercourse is the male condom. Male condoms afford a high degree of protection: consistent and correct male condom use reduces HIV transmission by between 80% and 97%. However, in many parts of Africa condoms are not acceptable as they act as a contraceptive and may also interfere with sexual pleasure and reduce intimacy. Men predominantly control use of male condoms during sexual intercourse, and many women do not have the power to negotiate condom use in their relationships. As a result, there have been significant recent developments in other types of barrier methods to prevent the sexual transmission of HIV.[23]

THE FEMALE CONDOM

Numerous studies have shown that the female condom is an acceptable method for many women and men, and is a valuable alternative for women whose partners refuse to use male condoms. Unlike the male condom, the female condom can be inserted some time before sex, and does not depend on the same degree of male co-operation for its successful use. The female condom is a soft, loose-fitting polyurethane

sheath that covers the vagina, cervix and external genitalia. Laboratory studies have shown that the female condom is effective at preventing the transmission of viruses and bacteria. While there are less clinical data available than for the male condom, the WHO has agreed that the female condom is effective in preventing HIV and other sexually transmitted infections (STIs). However, despite the effectiveness and acceptability of the female condom, they are not widely distributed or available in South Africa. This is partly due to costs (more than 10 times that of a male condom) but also to a lack of commitment to this female-initiated technology by donors and governments. Nonetheless, the female condom represents an important HIV prevention option where it is available.[24,25]

CERVICAL BARRIER METHODS

In the last few years, interest has grown in cervical barrier methods as potential technologies for HIV prevention. The cervix is covered by a single cell layer of columnar epithelium, in contrast to the stratified squamous epithelium of the vagina. As a result cervical columnar epithelium is more friable than the stratified squamous epithelium of the vaginal walls, making it more susceptible to mechanical disruption. This anatomical vulnerability is compounded by the increased presence around the cervix of surface receptors targeted by HIV as well as inflammatory cytokines, both which may also facilitate HIV infection. Additional evidence from primate experiments has shown that cervical epithelium is the first site of infection after vaginal exposure to simian immuno-deficiency virus (SIV).

On the basis of this evidence, barrier methods that protect the cervix specifically (such as the diaphragm, the sponge and the cervical cap) may be useful tools for HIV prevention, and there are currently a number of trials of this topic underway in southern Africa. There is ample evidence that the different cervical barrier methods are safe, easy to use, inexpensive and highly acceptable to both women and men. New cervical barriers are in development, and the efficacy of these methods against pregnancy, STIs and HIV is being investigated. In addition, should an effective microbicide be identified, the combination of a cervical barrier and a microbicide may offer even greater potential for prevention of HIV transmission.[26]

HERPETIC GENITAL ULCER DISEASE CONTROL

The role of bacterial STIs (including syphilis, chlamydia infections and gonorrhoea) in increasing the risk of HIV infection is well established. More recently, HSV-2 has received attention as an important risk factor for heterosexually-transmitted HIV. HSV-2 is the most common sexually transmitted infection worldwide, typically causing recurrent episodes of genital ulcers, although a large proportion of infected individuals are asymptomatic.[27-29]

Recently, there have been growing concerns about the role of HSV-2 in HIV transmission given the fact that it is the most common cause of recurrent genital ulcer disease in a significant proportion of the adult population, which is also at risk for HIV. Genital ulcers act as a portal of entry or exit for HIV and activated lymphocytes, including CD4 cells, are frequently recruited to these sites of inflammation and are primed to receive or present HIV at the site of ulceration. A recent meta-analysis of 19 epidemiological studies showed that prevalent HSV-2 may increase the risk of HIV acquisition in men and in women by as much as 3-fold even after adjustment for sexual behaviour, and that HSV-2 may account for as many as 38 - 60% of new HIV infections in women, and 8 - 49% in men in the general populations.[30]

Controlling HSV-2 may have an important impact on HIV incidence, particularly in settings where HSV-2 prevalence is high. Currently the options for herpes control are limited to a few strategies: primary prevention through condom use and behavioural modification will be useful in uninfected populations, e.g. young people. Treatment of HSV-2, primarily with acyclovir, may also have an effect on HIV and randomised control trials are currently underway to investigate this. There is strong evidence that suppressive treatment for genital herpes reduces the levels of HIV in the genital secretions of infected women (a potential marker of infectiousness and therefore transmission). The results of trials to evaluate the effect of suppressive therapy on HIV acquisition and HIV transmission are likely to be available within 2 years.[31]

SOCIOBEHAVIOURAL INTERVENTIONS

In addition to the biomedically focused interventions discussed above, behavioural interventions remain a valuable strategy for reducing new infections. We know what specific behaviours contribute to the spread of HIV in South Africa (large numbers of new sexual partners and unprotected sexual contacts), and yet the virus continues to spread. Two theories have been used to explain and predict the spread of HIV and attempts to curb this spread.[32]

The first theory focuses on individual behaviour and behaviour change, and discusses the ways in which intentions, attitudes and beliefs affect health behaviour. The second theory involves understanding broader social issues which affect the epidemic. For example, it seems clear that an important part of what drives the epidemic is not individual intentions and behaviours but broader social, economic and cultural conditions. Women, for example, may find themselves in a situation in which they have little power or decision-making in their lives, and for reasons of immediate survival may be forced into transactional sexual relationships with men that will involve unprotected sex. A key challenge for those wishing to reduce the spread of HIV through behaviour change is to design interventions that bridge the divide between individual models of behaviour change and focus on broader social issues. Health practitioners, by virtue of their training, are often better at thinking about individual level issues and interventions than in intervening and assessing interventions at a broad social level.

The need for both levels does, however, remain. Successes in HIV prevention in African countries such as Uganda, furthermore, have similarly been attributed both to individual-level interventions and to the commitment of government as a whole to creating social conditions and relationships in which safe sex is not a taboo topic but an issue which is seen to concern everyone. Campbell[33] has discussed the importance of what she terms 'political will' in curbing and containing the epidemic.

At a practical level, voluntary counselling and testing (VCT) represents an important strategy for changing sexual behaviours. There is substantial evidence that appropriate risk reduction messages provided during VCT can have a significant impact in reducing high risk behaviours among individuals who wish to be tested for HIV. In one multicountry trial, including sites in Kenya and Tanzania, there was a more than 30% reduction in unprotected intercourse among individuals receiving VCT compared with individuals who received health promotion messages only. This study and related research has contributed to what some policy makers have called a 'serostatus approach' to addressing the HIV epidemic, in which HIV testing is a critical first step that can be used to target services for HIV prevention (for HIV-negative individuals) or care and treatment (for HIV-positive individuals).[34]

Within South Africa, a number of large, multifaceted behaviour change campaigns have been developed to reduce sexual risk behaviours, particularly among young people. Two of the best known of these are Soul City (a multimedia intervention including television, radio and magazines) and LoveLife (a media campaign linked to adolescent-focused health care services). It is difficult to examine the precise impacts of campaigns of this type, but preliminary evaluations have suggested that these interventions have played a valuable role in both increasing awareness and knowledge of HIV/AIDS among individuals, and in shifting popular perceptions of the disease in communities heavily affected by HIV. However the role that these interventions may play in altering the incidence of HIV infection remains unknown.[12]

CONCLUSION

While prevention efforts need to be redoubled in sub-Saharan Africa, where prevalence rates are so high, there is at least some hope for success.[1] The most recent UNAIDS report on the Global AIDS epidemic states: 'Among the notable new trends are the recent declines in national HIV prevalence in two sub-Saharan African countries (Kenya and Zimbabwe), urban areas of Burkina Faso, and similarly in Haiti, in the Caribbean, alongside indications of significant behavioural change – including increased condom use, fewer partners and delayed sexual debut.' However, perhaps even more spine-chilling are indications that in regions where HIV rates had declined, a resurgence in new infections particularly among specific risk groups such as young MSM populations, is occurring. A subject we have not covered here is the ultimate impact of antiretroviral treatment (ART) and the impact that the new drive to increase world access to ART will have on transmission and subsequently prevalence in many parts of the world. At the very least, in this new era of antiretroviral access, limiting numbers requiring antiretrovirals in the long term is good medicine and cost saving. This demands more research into efficacious prevention strategies and monitoring vigilance. It has been said that an ounce of prevention is worth a pound of cure ... but it takes a ton of work!

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COMMUNITY ARV SERVICES

THE MADWALENI HIV/ARV PROGRAMME

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Richard Cooke and Lynne Wilkinson sought out a deep rural hospital in the old Transkei area of the Eastern Cape to attempt to set up a holistic HIV programme including access to antiretrovirals (ARVs). They looked for a hospital difficult to access by road, where the majority of the people were unemployed and where HIV-positive people currently have minimal health and social support.

They identified Madwaleni hospital, a 220-bed district hospital built as a missionary hospital in the early fifties. It is approximately 30 km south-east of a small town called Elliotdale (approximately 80 km south-east of Mthatha). District statistics indicate that the hospital serves a population of approximately 256 000.

Madwaleni is approximately 110 km (including 30 km of dirt road) from its referral centre, Nelson Mandela Hospital Complex (NMH) in Mthatha. Madwaleni has a small operating theatre, an X-ray facility and a laboratory, and patients are referred to NMH for all specialist consultations, and for surgery other than minor operations and caesarean sections. By car or ambulance this route takes approximately $1\frac{1}{2}$ hours, but for patients who are referred and need to use public transport, it takes closer to $2\frac{1}{2}$ hours.

Madwaleni has a total of 5 doctors (including HIV/ARV programme doctors) and 117 nurses (including 46 professional nurses) at the time of writing in 2006. It has a small nursing college on site.

At the beginning of 2005 Madwaleni's HIV programme, as at many rural government hospitals, was run by a single nurse and included HIV voluntary counselling and testing (VCT) for people coming to the hospital and specifically requesting to be tested, a small HIV support group started the previous year, prophylactic treatment (when available) for those patients requesting assistance, prevention of mother-to-child transmission (PMTCT) counselling and provision of nevirapine to some of the HIV-positive women accessing the hospital's services, and provision of formula feed (when available) for mothers who chose to formula feed upon receiving PMTCT counselling.

MADWALENI'S HIV/ARV PROGRAMME

Madwaleni was accredited as an ARV site by the Eastern Cape Department of Health on 14 February 2005 on condition that a pharmacist was employed prior to rollout. Anemari Buitendach joined Madwaleni in May 2005 as both the hospital and HIV programme pharmacist. The ARV rollout began on 28 June 2005 after the first batch of ARV drugs was received on 27 June 2005.

The staff complement has increased dramatically from 3 staff members in January 2005 (site co-ordinator, doctor, nurse) to 22 staff members, including 2 doctors, 3 nurses, 1 site co-ordinator, 1 administrator, 1 data capturer, 1 hospital pharmacist, 1 hospital social worker, 5 community health workers, 6 peer educators and a driver. In addition, a community service physiotherapist has joined Madwaleni for the first time and also works with the HIV programme patients. Two more pharmacy assistants joined the programme in mid-May 2006.

Madwaleni's HIV/ARV programme centres around the support groups run by counsellors (community health workers and peer educators) and nurses at Madwaleni and 6 primary health care clinics. Based on support group attendance, patients join the HIV/ARV programme and receive regular and continuing counselling irrespective of their CD4 counts. Patients with CD4 counts lower than 200 cells/µl begin to prepare for ARV readiness and are put on ARV treatment.

Where is Madwaleni?

A VCT outreach programme was started in which counsellors do 'door to door' HIV awareness in the communities

surrounding the hospital. Thereafter nurses do HIV testing in the communities on days arranged with the local headman/chief, often coinciding with government grant collection days.

An infant follow-up clinic (IFC) for HIV-exposed infants and a paediatric HIV wellness and ARV programme for HIV-positive children is run on a Wednesday and is closely co-ordinated with the maternity ward in the hospital and the antenatal clinics at the primary health care clinics.

The most recent initiative has been the integration of tuberculosis (TB) inpatients into the HIV programme. This aims to fast-track inpatients diagnosed with tuberculosis into the HIV programme, and where applicable put them on ARV treatment (ART).

The Madwaleni HIV/ARV team.

DISEASE PROFILE IN THE HIV/ARV PROGRAMME

The most common presenting signs and symptoms are productive coughing, weight loss, dermatological conditions (especially papular pruritic eruptions, ringworm, fungal lesions and herpes zoster), and peripheral neuropathies. Chronic diarrhoea is common in AIDS patients and ARVs are now an option where management by repeated rehydration and antibiotics fails. Common diagnosis on clinical grounds include oral and vaginal candidiasis, genital condylomas and herpes simplex virus (HSV) 1 and 2. Tuberculosis is by far the most common disease affecting patients at Madwaleni and remains a major problem. Common WHO stage 4 conditions seen include cryptococcal meningitis and Kaposi's sarcoma, but relatively few cases of *Pneumocystis jiroveci* pneumonia (PJP) are seen.

Conditions such as cervical dysplasia diagnosed on pap smear and extrapulmonary tuberculosis (EPTB) are under-diagnosed. It is therefore necessary that HIV/AIDS patients are actively screened for these conditions, the latter when clinically indicated.

Neurological conditions are also under-diagnosed and patients often present on anticonvulsant medication with a longstanding 'epilepsy' diagnosis written in the OPD card. Neurocysticercosis is common in this part of South Africa and is frequently treated empirically. Owing to culture/language barriers faced by English-speaking doctors, counsellors are encouraged to recognise signs of confusion and mental deterioration through repeat counselling sessions. Counsellors can prove valuable in referring neurological cases that could be HIV encephalopathy or organic CNS pathology.

Early indications are that syphilis does not have a high prevalence in the current programme. Of 376 baseline serological tests, 28 (7.4%) tested positive for syphilis, but 24 were only weakly reactive (false positives occurring at low titres).

The first 90 patients started on ARVs at Madwaleni HIV clinic were staged according to the WHO classification as follows: stage 1 – 4%; stage 2 – 30%; stage 3 – 52%; stage 4 – 13%. A further 60 patients were staged on entry to the HIV Wellness programme: stage 1 – 43%; stage 2 – 20%; stage 3 – 30%; stage 4 – 7%.

SIDE-EFFECTS AND ADVERSE EVENTS

The majority of patients report initial dizziness on efavirenz which improves after a week. Two patients – a man and a woman – presenting with psychiatric symptoms were switched from efavirenz to nevirapine. While the man is doing well, the woman had a Stevens-Johnson drug reaction to co-trimoxazole/nevirapine progressing to toxic epidermal necrolysis (TEN), and died at the referral hospital.

Women of child-bearing age are encouraged to take the nevirapine-containing regimen, allthough more blood sampling for drug safety monitoring is required. Only one woman has fallen pregnant after starting ARVs, but this will increase as general health and quality of life continue to improve. Family planning is encouraged and every woman is counselled on injectable contraceptive options.

High alanine transaminase (ALT) levels are common (see Table I), but only one patient on nevirapine discontinued medication, owing to an isolated drug hepatitis. She is soon to commence regimen 2 ARV treatment.

Two patients on regimen 1b were screened for hyperlactaemia. Both are women, obese and with high CD4 counts. Both had lost weight . A handheld lactate meter indicated a lactate level of 8.2 mmol/l in in the first patient and 3 mmol/l in the second. Serial measurements were similar. The first was switched to zidovudine (AZT), and her condition appeared to settle. Unfortunately she was transferred to another site before the switch could be assessed properly, including haematological toxicity. The second settled on symptomatic treatment alone.

Known causes of death on ARVs include 1 case of TEN (see above), 1 case of proven multidrug-resistant (MDR) TB, 1 patient in whom a computed tomography (CT) scan of the brain revealed a pontine lesion (tuberculoma/lymphoma), 1 pulmonary tuberculosis (PTB) retreatment failure (sputum positive at 5 months), and 1 case of tuberculous meningitis (immune reconstitution). Four died of unknown causes – in each case the baseline CD4 count was below 50 cells/µl, including a 5-year-old child with a CD4% of 0.24%.

The first two patients with virological failure are soon to start on regimen 2.

TABLE I

At end March 06		Notes
Total people tested for HIV at Madwaleni (since Jan 05) and 6 clinics (since Oct 05)	4 119	The monthly average for the last 6 months is 445 (Madwaleni and clinics)
HIV prevalence rate	23.7%	Jan 05 - Mar 06
June 05 – April 06		
Total No. of adults on HIV/ARV programme	513	
% of adults with CD4 < 200 cells/µl	57.1%	
Total No. of children on HIV/ARV programme	42	
% of children with CD4% < 15%	51.7%	
Adults initiated on ARV treatment		
Male	63 (33%)	
Female	128 (67%)	
Total	191	
Children initiated on ARV treatment		
Male	6 (55%)	
Female	5 (45%)	
Total	11	
Average No. of patients initiated on ARV treatment per month	20	
% adults on regimen 1a	64.9%	
% adults on regimen 1b	28.2%	
Mean absolute CD4 in 'decision to treat' (DTT) group (cells/µl)	105.03	*N* = 178 (excludes children on ARV treatment and patients transferred in from other sites)
Mean CD4% in DDT group	8.9%	*N* = 178 (excludes children on ARV treatment and patients transferred in from other sites)
Adults on ARV treatment for 6 months that have not achieved undetectable viral loads (< 400/ml)	7 patients, of whom 3 patients have < 1 log decrease	*N* = 62 (excluding deaths before 6 months, transfers out before 6 months, patient stopped on ARV treatment, missed or still outstanding viral loads)
Adults on ARV treatment for 6 months – mean increase in absolute CD4 count (cells/µl)		*N* = 61 (excludes deaths before 6 months, transfers out before 6 months, patient stopped on ARV treatment, missed or still outstanding CD4 counts)
Baseline	118.52	
6 months	250.41	
Increase	131.89	
Adults on ARV treatment for 6 months – mean increase in absolute CD4%		*N* = 61 (excludes deaths before 6 months, transfers out before 6 months, patient stopped on ARV treatment, missed or still outstanding CD4 counts)
Baseline	8.89%	
6 months	16.51%	
Increase	7.62%	
Patients died on ARV treatment	9	Includes 1 child See notes
ARV patients lost to follow-up	1	
Patients in whom ARVs discontinued	2	
Hepatotoxicity related to nevirapine (*N* = 56)		
Any > ULN	44.6%	
ALT > 3 X ULN	10.7%	
ALT > 5 X ULN	3.6%	

ULN = upper limits of normal; ALT = alanine transaminase.

SUCCESSES

COMMUNITY INVOLVEMENT

Intensive community involvement has led to specific successes for the Madwaleni HIV/ARV programme. As stated above, there are 5 community health workers and 6 peer educators (HIV-positive members of the programme) who work permanently on the programme with the further assistance of certain community health workers at the clinics. This has allowed intimate access to patient attitudes, feelings and expectations. In addition, their contribution has been invaluable in lightening the workload of the remaining staff (especially nurses) without compromising patient relationships and care. The counsellors are involved at all levels of the programme, which also ensures their full participation, including running support groups (group counselling), individual ongoing counselling of HIV wellness programme patients, preparing patients for ARVs from an individual commitment perspective,

Certification of adherence counsellors.

Our pharmacist and nurse explain the complexities of ARV treatment to a patient.

The Madwaleni HIV support group in full swing.

assisting in the selection of patients ready for ARV treatment and doing ongoing adherence counselling. They also conduct home visits to prepare the patient's family for his/her ARV treatment, to report any socio-economic problems to the social worker. The counsellors are involved with the adult, child and pregnant women components of the programme.

In addition to the counsellors, the programme is supported by many 'HIV programme activist' support group members who assiduously attend the support group, get involved in every initiative that the programme presents, counsel people in their homes and villages and introduce new members to their support groups on a weekly basis. These people are key to spreading the programme's 'follow-up' net widely.

As a result, of over 200 patients on ARV treatment in the programme, only 1 has been lost to follow-up.

RURAL HOSPITAL STAFF MOTIVATION

Much criticism is levelled at public sector nurses in South Africa with regard to lack of motivation and work ethic. This is often unfair, as it is rarely the nurses themselves who are the root cause of the problem. Nurses are frustrated by years of isolation in rural district hospitals, unsupported by management and administrative functions, with few career development paths or remuneration incentives. Consequently they adopt attitudes of resignation and defeat. At Madwaleni patient and counsellor enthusiasm and participation in the programme have served as catalysts for renewed involvement of the nurses and improved performance.

CO-ORDINATION FUNCTION

Lynne Wilkinson (an attorney by profession) has taken on the role of project manager for the programme. Many rural programmes are left either to doctors or to nurses to set up and manage in addition to their many clinical duties. The programme has greatly benefited from having a dedicated person to set up administrative and data systems, staff management, funder reporting, government liaison and co-ordination of tasks within the programme. This system has allowed Dr Richard Cooke to head the clinical programme and cover general hospital responsibilities.

PRIVATE-PUBLIC PARTNERSHIPS

In the Eastern Cape, government budgets support employment, ARV drugs and laboratory costs. Operating budgets are small, however, and in many instances extremely difficult to utilise through general hospital procurement and payment systems. It was intended that the Madwaleni HIV/ARV programme would be set up as a government accredited and funded site for purposes of long-term sustainability and that private funding would be brought in only to facilitate and accelerate the building up of the programme. In addition to government funding, the Madwaleni HIV/ARV programme has been funded by the Rural Health Initiative (RHI), Difaem, a few private individuals, and since October 2005, the Aurum Institute for Health Research (PEPFAR funding). This has allowed us to accelerate the implementation of the programme.

CHALLENGES

HIV AND TB CO-INFECTION

While many opportunistic infections can be managed routinely, the TB epidemic is a challenge of huge proportions. Madwaleni's TB beds (80 of 220) are normally full to capacity. The DOTS system is ineffectively implemented and large numbers of patients needing retreatment are admitted to hospital for daily streptomycin injections. During 2005, 75 inpatients died. Multidrug-resistant (MDR) TB is an increasing problem: in 2005, 16 of 500 inpatients were identified as having MDR TB. Adult TB prophylaxis regimens are not provided by the central pharmacy depots.

Of the patients on ARVs, 103 (54%) have a history of TB (29% of these 103 are retreatment cases). Of the patients on ARVs 57 (30%) were on TB treatment at the time they started on ARVs (39% of these 57 were retreatment cases); 10 patients (9.7%) were started on TB treatment while on ARVs.

These figures support channelling of resources to diagnose TB as early as possible. If extending national guidelines on HIV/TB co-infection is not the answer, then district hospital staff must be in regular consultation with expert clinicians with respect to management of HIV/TB co-infections.

Strict monitoring of patient symptoms by counsellors, regular weight monitoring, regular sputum collection and a screening chest X-ray are helpful for diagnosing pulmonary/pleural TB. More TB cultures are now done routinely in smear-negative pulmonary tuberculosis diagnosed clinically and radio-

graphically, but the required 4 - 6-week waiting period is unhelpful. Extrapulmonary TB is under-diagnosed in this resource-limited setting. With the recent arrival of an ultrasound machine (supplied by government), doctors must now acquire skills to aid ultrasound diagnosis of abdominal TB in addition to the regular obstetric and gynaecological investigations. Unfortunately the high turnover of short-term community service doctors means that the benefit of this training is short lived.

To address the high HIV prevalence among TB inpatients, the HIV/ARV programme has been extended to the TB ward by fast-tracking patients assessed clinically and identified by the ward doctor. Counsellors then provide HIV education, assess individual commitment and provide adherence counselling so that patients can be started on ARV treatment while in the ward. Further emphasis is placed on education of all TB/HIV patients before discharge to ensure continued participation in the ARV programme on an outpatient basis.

Owing to the high prevalence of TB among the ARV programme members, adherence to TB medicine needs to be included in ARV adherence counselling, especially in view of the high pill burden for TB/ARV patients. However, this does not solve the problem of TB patients who do not form part of the programme, which needs to be addressed with TB ward staff and clinic staff. No ARV programme can be successful without an effective TB programme.

HIV education in our communities.

MEDICINE INTERACTIONS AND TOXICITY

Patients often present with multiple pathologies, but in resource-constrained hospitals too many conditions are treated empirically. Madwaleni is no exception. Faulty diagnostic tools (e.g. unavailability of X-rays or laboratory reagents out of stock), lost/delayed results, and lack of specialist guidance all contribute to this practice, which has the negative consequences of medication interactions, toxicities and high financial costs. Madwaleni is attempting to address this in part by outsourcing a specialist one day a month to guide junior doctors. Doctors are also increasingly trying to stop prophylactic co-trimoxazole as early as possible. While useful for 'adherence practice', co-trimoxazole is religiously swallowed (960 mg daily) to the extent that doctors struggle to convince patients to stop when their immune systems improve. The introduction of single-drug TB medicine formulations at district hospital level will go some way towards improving our management of TB drug toxicities.

INCREASED DIAGNOSIS DOES NOT ALWAYS INCREASE MANAGEMENT CAPABILITY

As a service is built up and more clinical diagnoses are made, it is frustrating when treatment/management capabilities do not increase in tandem. For example, the women's health clinic is identifying more genital condylomas and abnormal pap smears, but unreliable equipment and an imperfect referral system result in too few cauterisations and colposcopies. Similarly, our laboratory offers the full range of basic tests, as well as investigations such as liver function tests and cryptococcal/bacterial antigen tests. CD4 cell counts, polymerase chain reaction assays, viral loads, biochemistry and many others are done in Mthatha. Others including cytology investigations have to be done in East London (4 hours' drive away). Blood cultures are not routinely available at Madwaleni.

Mothers in the support group bring their children for testing.

ARV DRUG FORMULATIONS

While ARV drug supply has been good, it is maintained by programme staff fetching the orders. In addition, in the months of December and January limited numbers of new patients could be started on ARV treatment because the Mthatha depot had no electrical power and placement of new orders was therefore difficult.

Changes in dosage formulations causes frustration. Intensive adherence counselling is hampered by an abrupt change in pill colour. Lamivudine, for example, changed from white to red and stavudine from orange/brown to red/yellow. Similarly, unavailability of certain dosage formulations such as efavirenz 600 mg meant that Madwaleni was supplied with 200 mg tablets. A number of the ARV patients on the programme are illiterate, and changing colours and number of pills raises concerns about adherence and increased pill burdens. This problem was solved by selecting 10 highly adherent and focused patients to receive the 3 x 200 mg dosage of efavirenz until the stocks ran out, while other patients were kept on the simpler single-pill regimen. Similarly, 20 mg stavudine tablets have repeatedly been unavailable, resulting in paediatric patients having to take ridiculously large quantities of the liquid formulation.

INCREASING OUR KNOWLEDGE OF TRADITIONAL XHOSA MEDICINE

Counsellors encourage support group members not to use traditional Xhosa medicine without first consulting our clinical

staff rather than forbidding them to do so. The support group members themselves have adopted a negative attitude towards traditional medicine, often as a result of their own personal experiences, and convey these stories and attitudes to new support group members. As a result, clinicians are not currently experiencing problems on the HIV programme with Xhosa medicine interaction with ARV drugs. Staff, however, do not have a full understanding of the patients' opinions relating to Xhosa medicine and their interaction with their ARV drugs, and this needs to be studied further.

POOR ACCESS TO HEALTH CARE

Access to both the hospital and the primary health care clinics is hindered by many factors including impassable dirt roads, few ambulances and limited taxi routes. The direct impact on the programme is manifested by a low conversion rate of VCT-positive individuals onto the HIV/ARV programme through the support group 'gateway', as well as precious resources spent on ensuring patient follow-up: clinic visits by doctors, database monitoring of follow-up visits, a driver transporting counsellors on home visits and patient searches.

BUILDING A ONE-STOP SHOP

The intention is to provide a comprehensive primary ARV service. The programme will need to be adapted in the future when the breadth of service itself becomes a barrier to increasing the numbers on the programme. Currently new adult patients are initiated onto ARVs on only one day per week as a result of stretched resources. Other HIV/AIDS services provided by the hospital include a VCT service, an infant follow-up clinic, a paediatric ARV treatment clinic, peripheral clinic HIV wellness and ARV readiness programmes, (during which the doctor rotates through three clinics per day), a prenatal clinic, and a women's health clinic. Doctors are also involved in all areas of rural medicine, including ward rounds, OPD work and theatre time.

While this system is not currently limiting access to ARV treatment, in that the programme is coping with the demand for ARV treatment (no waiting list), this is likely to change in the future and a further day would then need to be considered. Increased nurse participation in clinical monitoring of ARV patients would also be of assistance.

A further difficulty to overcome is that a patient who falls into a number of categories (e.g. she is on ARV treatment, her child is part of the infant follow-up (IFC) and she requires a pap smear) cannot be expected to attend a number of different days in a week.

DECENTRALISING THE PROGRAMME

Decentralising the programme to the clinics, including the wellness and ARV programmes, improves health care access but more resources are needed to implement, monitor and maintain the programme at this level. At present patients join the HIV wellness programme and are prepared for ARVs at the clinics. They are, however, required to go to Madwaleni for their ARVs. The ARV patient follow-up and monitoring is only done by the largest of the clinics or at Madwaleni. The programme's aim is to ensure that this takes place at all clinics, and newly appointed pharmacy assistants are in the process of being trained to assist the nurses with dispensing repeat medication. When resources allow, it is envisaged that the initial ARV take up will also be done at the clinics with the assistance of the clinic doctor.

Egg-catching on Teambuilding Day.

PALLIATIVE AND HOME-BASED CARE: UNDER-PREPARED

The increasing numbers of patients accessing hospital treatment and the Madwaleni ARV programme may have two negative consequences in the long term: the hospital will not have the resources to cope, and the number of treatment failures will grow. Facilities to improve the palliative care of these chronically ill patients are urgently needed. Such a facility could provide intensive short-term step-up treatment and care. It could also serve as a training venue for relatives and counsellors, enabling early discharge into home care. The programme has motivated the Eastern Cape Health Department to include such a facility as part of the planned hospital revitalisation.

SUSTAINING HIV-POSITIVE SUPPORT GROUPS

Currently the main motivation for attendance at an HIV support group is gaining an understanding of HIV, living with HIV, and ARV treatment. This is crucial but will not provide experienced members with an incentive to continue attending on a weekly basis. Resources need to be found to support income generation and education or training opportunities to sustain the support groups.

CONCLUSION

The HIV/ARV team realises that success is ultimately dependant on sustaining the programme. With continued district, provincial, hospital and, most importantly, community support, this is an achievable goal.

The local countryside.

HIV-DISCORDANT COUPLES: AN EMERGING ISSUE IN PREVENTION AND TREATMENT

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An increasingly encountered phenomenon in research and clinical management of HIV is HIV discordance, the situation where one member of a sexual partnership is HIV infected, while the other is uninfected. This situation has wide clinical and research implications. In particular, seronegative partners within discordant relationships are a particularly high-risk group for HIV acquisition; a high proportion of new HIV infections in mature generalised epidemics is likely to occur within discordant couples.[1] In this overview we will examine some of the biological and socio-behavioural correlates of discordance. As identification of the joint serostatus of a couple poses particular challenges for counselling and testing, we will describe the model for couples counselling developed by the Centers for Disease Control and Prevention, which we use at our centre, and some of the lessons we have learned in conducting couples counselling since the establishment of a couples counselling centre at the Perinatal HIV Research Unit (PHRU) in April 2004. Lastly, we will also discuss two clinical issues that frequently arise, namely dealing with the desire for children and HIV prevention options.

THE TSWARISANANG COUPLES CENTRE

South Africa, with one of the highest HIV prevalence rates in the world, has a generalised heterosexual epidemic. Voluntary counselling and testing (VCT) is an important component of HIV prevention strategies. The traditional clinic-based VCT has been more accessible to women. In 2004, the PHRU established a couples HIV counselling centre (Tswarisanang Centre), possibly the first of its kind in South Africa. Between April 2004 and February 2006, 1 425 couples have received couples HIV counselling and testing (CHCT). The mean age of couples entering the service was 30.7 years. Only 238 (17%) of the couples were formally married. Of the couples 452 (32%) were discordant, 671 (47%) were concordant negative, and 302 (21%) were concordant positive. Of the 452 couples who were discordant, the male was positive in 326 cases (72%) and the female in 126 (28%). While these figures may not be representative of the broader Soweto community, given the self-selected nature of the couples presenting for CHCT, they are nonetheless instructive. CD4 counts were available for the positive partner in 210 of the discordant couples, the median CD4 count being 379/µl (interquartile range 230 - 566/µl). Of the HIV-positive partners in the discordant relationships 185 (87%) were also herpes simplex-2 (HSV-2) positive.

CORRELATES OF HIV DISCORDANCE

A number of biological factors have been described that appear to modify the chances of transmission within a couple. The chances of transmission have been shown to increase with increasing viral load in several studies.[2-4] The level of HIV in plasma has been noted to be lower in HIV-positive men in discordant relationships compared with men in HIV-concordant relationships.[2] The sex of the uninfected partner may modify the risk of transmission. In prior North American or European studies, the rate of male-to-female transmission has been noted to be greater than that of female-to-male transmission (reviewed in[5]). However, in developing countries this asymmetry is not noted, and the efficiency of female-to-male transmission appears far greater, in some instances exceeding male-to-female transmission.[6] Male susceptibility to infection appears to be attenuated by circumcision, which has been shown to be associated with an approximate halving of the odds of concordance among 221 couples participating in an observational study in four African cities.[7] The finding that circumcision can reduce the risk of male acquisition of HIV has since been confirmed in a randomised controlled trial.[8]

Prior sexually transmitted infections, in particular genital ulcer disease, and serological presence of infection with HSV-2 have also been shown to be highly associated with concordance.[3,9] In the four cities study, HSV-2 status of the couple was the only factor that remained significantly associated with concordancy. In couples where both members have serological evidence of HSV-2 infection, the odds of HIV concordance were 8.6-fold that of couples where neither partner was HSV-2 infected.[7]

A wide number of immunological and virological factors have been investigated for their role in efficiency of HIV transmission between partners, including viral subtype, stage

of HIV infection, sharing of human leukocyte antigen or HIV co-receptor gene alleles, and the presence of serum HIV-specific IgA.[3,6,10-14] However, the relative contribution of each of these multiple factors is unclear.

Social or behavioural factors may also influence the concordance of HIV results within couples. These may broadly be divided into factors that affect the transmissibility of HIV between couples per sex act and factors influencing the number of sex acts during which exposure may occur. Examples of the former include use of condoms or other barrier methods and certain sexual behaviours, such as sex during menstruation or 'dry sex' (use of vaginal drying agents). Examples of the latter include the frequency of intercourse and duration of the relationship. Sexual activity outside of the partnership is another critical aspect.

Partnership dynamics that may determine risk behaviour within partnerships include such concepts as emotional closeness, communication, power, duration, and concurrency.[15] The interaction between relationship dynamics and condom use or concurrent partnerships may be complex. Knowledge of HIV status, receipt of voluntary counselling and testing, and fertility desires are further considerations when approaching the social or behavioural aspects of HIV concordance. Condom use within the marriage has been associated with reductions in concordance in several studies.[2,7,16] However, as highlighted by several authors, condom use is unusual prior to HIV testing.[3,17] Importantly, condom use has been noted to increase substantially after CHCT, although correlation of self-reported rates of condom use with biological markers (such as sperm seen on a vaginal smear, pregnancy, or HIV transmission) indicates that substantial underreporting of unprotected intercourse persists.[18,19] Concurrent partnerships raise the chances that one or more members of a couple will be infected with HIV, or that the couple will have concordant positive results.[2,16,20]

COUPLES HIV COUNSELLING AND TESTING

The majority of South Africans living with HIV/AIDS do not know their status, as rates of testing are still very low owing to limited access. This leads to a common situation where one member of a couple will assume, in the absence of a test result, that their results are the same as their partner, a phenomenon known as 'testing by proxy'.[21] Clearly this position does not recognise the possibility of discordant results. Hence, one of the key features of CHCT is to explore communication around sexual activity by each member of the couple, and that partners support each other during CHCT, a notable difference to individual VCT. A key condition of CHCT is that partners test and receive their results together. All phases of CHCT are conducted with both members of the couple present. This avoids the dilemma faced by individuals learning they are HIV positive in individual VCT and having to disclose these results to a partner who may not be adequately prepared. Owning the results together may help reduce problem situations, blame and possible violence. CHCT also assists the couple to make decisions and to plan adequately for the future.

As a new strategy, CHCT presents its own challenges and advantages. CHCT uses a risk-reduction model, and the presentation of results to the couple together facilitates the introduction and planning of prevention, tailored to the joint serostatus. In South Africa the adoption of CHCT has been a recent event, much assisted by national campaigns such as the emphasis on CHCT by Khomanani (Fig. 1).

Our initial experience indicates that deciding to test together was a mutual decision for the majority of couples.[22] The most common reasons cited for attending CHCT were that the couple are planning a family, want to find out HIV status, or attend as a sign that they support each other. Our impression is that, to some extent, individuals may use CHCT as a means of disclosure of a prior test result to their partners. Our centre has provided training in CHCT to over 100 local counsellors. In that undertaking we have noted that, while couples generally do not express incorrect beliefs regarding discordance at the time of CHCT, dealing with 'myths' regarding discordance is an important aspect of counsellor training. Examples of these 'myths' include the concept of a hidden infection not detectable by HIV tests, that the negative partner may be in the 'window period', the thought that transmission is a consequence of 'rough sex' and that 'gentle sex' will protect HIV-negative partners, belief in protection by God, or simply denial that discordance as a phenomenon exists.[23]

CLINICAL ISSUES FOR HIV-DISCORDANT COUPLES

PREVENTION OPTIONS

Coping with discordance includes determining how best to implement prevention of infection of the uninfected partner. Many couples cope well with this stressful and challenging situation and arrive at a solution that best suits their circumstances. Perhaps the most common strategy is condom use.[18,19,23] Some studies have shown remarkable uptake following CHCT, from < 3% before CHCT to over 80% of sex acts afterwards being performed with the use of a condom.[18] The impact also seems to be particularly strong when the male partner is receiving counselling and testing for the first time.[19] Other strategies reported include separation, which seems to be an option adopted in particular by couples with relationships of shorter duration that did not include children, and particularly affects discordant relationships where the HIV-infected partner is a woman.[23, 24] Few couples appear to choose abstinence, although abstinence is apparently easier to negotiate if endorsed by an HIV-positive man.[23] The adoption of non-penetrative sex could also be considered as an option. Use of antiretrovirals by the uninfected partner, as either pre- or post-exposure prophylaxis, has not been prospectively evaluated in this setting, so efficacy and safety are undefined.

While still in the realm of clinical investigation, additional interventions are being tested that may provide further options for couples.[25] These include suppression of HIV shedding by the infected partner through treatment with antiretroviral agents. In addition, the antiviral drug acyclovir is being tested for its possible effect on reducing HIV transmission.

Fig. 1. Khomanani Campaign has highlighted the need for couples testing (images courtesy of Khomanani).

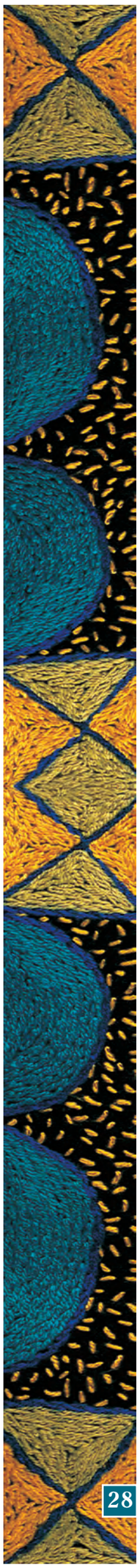
DESIRE FOR CHILDREN

One of the biggest challenges facing discordant couples is balancing the desire to have children with the risk of HIV transmission. Understanding of the couple's perspective of factors that influence the desire to have a child, as well as maintaining a non-judgemental and culturally sensitive approach by the service provider, can assist the couple in coming to terms with the complexities of HIV discordance and reproductive decision making. Ethical guidelines from professional bodies such as the American College of Obstetrics and Gynecology have noted that assisted reproductive technologies should not be withheld from HIV-infected infertile couples merely on the grounds of HIV serostatus.[26] However, ethical controversies in this area remain.

Adequate preconception counselling to establish the stability of the discordant couple is also important, because many couples separate after childbirth.[27] Fertility care of HIV-discordant couples should be optimised on the basis of the sex of the infected partner; clinical, immunological and virological status of the infected partner; and cost and accessibility of assisted reproductive technologies. The couple should be counselled and informed about risks involved and possible ways of reducing the risk of HIV transmission.

Where the infected partner is male, the main concern is the risk of transmission to the female partner; a range of possible interventions could be considered.[28] None of these have been subjected to clinical trials to fully evaluate the risk-benefit balance for each recommendation. These clinical interactions must therefore be preceded by a detailed discussion about the potential outcomes.

If the couple opt to practise unprotected intercourse, this should take place only during the fertile window period. It is important to adopt a holistic approach to optimise risk reduction and chances of conception. Fertility should be confirmed in both partners. The viral load should be suppressed. It is advisable to document suppression of both blood and seminal viral load when possible, acknowledging that most laboratories may not be equipped to handle genital tract samples.[29] Both partners should be investigated for genital infection and treated appropriately if it is present. All components of risk reduction behaviour counselling should be emphasised. These include unfaithfulness, risky sexual practices (e.g. anal sex, dry sex), use of vaginal irritants, etc. The couple should return to safe sex as soon as the fertile period is over, regardless of pregnancy status. The uninfected partner should also undergo routine HIV testing. Experimental



approaches using pre-exposure chemoprophylaxis to further reduce the susceptibility of the uninfected partner are another consideration. In the event of conception, the couple should continue to practise safe sex to prevent perinatal infection. HIV testing should also be done during pregnancy to detect maternal infection and provide interventions to prevent mother-to-child transmission.

In some specialised centres, semen processing and intrauterine insemination have been adopted. Several techniques are available.[30,31] The first involves 'sperm washing', in which sperm are separated from seminal fluid through repeated cycles of centrifugation and resuspension in fresh medium, with the supernatant being discarded after each round. The 'swim up' technique is similar, but includes an additional step in which the preparation is incubated for a period and the motile sperm swim into the medium, from where they are collected. A third technique uses density gradient purification. These techniques has been available since 1992 but are not widely available even in developed countries; accessibility therefore still remains a problem.[28] Also, the cost of PCR testing of the final sperm aliquot and intensive medical supervision makes it an expensive undertaking, unaffordable to the general population. The procedure might have to be repeated a number of times before pregnancy is achieved, further raising the cost. It is also known that some couples lose patience and try to conceive spontaneously through unprotected intercourse.

Where the infected partner is female, the aim is to reduce the risk of transmission to the uninfected male partner and the unborn child. The comprehensive approach when practising unprotected sex during the fertile period is as described above. The prevalence of pregnancy is generally low among HIV-infected women owing to lower rates of conception and increased rates of pregnancy loss.[32] The couple should be provided with this information at preconception counselling because fertility problems create anxiety and stress even among concordant-negative couples. In these cases, artificial insemination could be considered.

In conclusion, discordant couples need to be encouraged to make informed reproductive decisions. Ideally there should be no coercion; both the infected and the uninfected individuals in the discordant relationship need to be comfortable with the decision to have a child, regardless of the sex of the infected/uninfected partner. The role of the health provider is to provide adequate information and to help guide the whole process, including through the postpartum period if pregnancy is achieved. Existing programmes need to be strengthened in dealing with this, and research programmes and multidisciplinary guidelines to define the safest and most effective therapy possible in South Africa need to be established.

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ANTIRETROVIRAL TREATMENT AND THE PROBLEM OF POLITICAL WILL IN SOUTH AFRICA

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South African AIDS policy has long been characterised by suspicion on the part of President Mbeki and his Health Ministers towards antiretroviral therapy.[1,2] The Minister of Health, Manto Tshabalala-Msimang, resisted the introduction of antiretrovirals for mother-to-child transmission prevention (MTCTP) until forced to do by a Constitutional Court ruling – and she resisted the introduction of highly active antiretroviral therapy (HAART) for AIDS-sick people until a cabinet revolt in late 2003 forced her to back down on this too. Since then, the public sector rollout of HAART has gained momentum, but it has been uneven across the provinces and continues to be constrained by a marked absence of political will at high levels.

South Africa's premier demographic model (the ASSA2003 model) predicts that only in 2008 will HAART coverage reach 50% (see Fig. 1). This does not reflect well on South Africa. Recent comparative analysis shows that South Africa's HAART coverage is below par given its economic, institutional and epidemiological characterists.[3] As illustrated in Fig. 2, South Africa is among those countries whose HAART coverage is less than expected given international norms. Although South Africa comprises a large share (25%) of the total number of sub-Saharan Africans on HAART (whether in the public, private or not-for-profit sectors), this comparative analysis indicates that South Africa should be doing a lot better. Furthermore, South Africa has performed poorly with regard to its own domestic targets set by the 2003 Operational Plan. As can be seen in Fig. 3, by the end of 2005, the numbers of people on HAART in the public sector was still less than 30% of the original planned total.

Part of the problem has to do with procrastination by the Health Minister with regard to drug procurement. On 2 March 2004, she unveiled her drug procurement timetable to the parliamentary portfolio committee on health showing that the earliest that drugs would be available for a public sector rollout was July 2004 (and in the end, the tender was only finalised in March 2005). It was only after the Treatment Action Campaign (TAC) threatened legal action that the provinces were allowed to obtain drug supplies through an interim tender process.

South Africa's public sector HAART rollout is strongly underpinned by external funding and support – especially in the Western Cape and KwaZulu-Natal. Of the total number of public sector HAART patients (111 786), 54% were part funded by external donors (the largest being PEPFAR) working in partnership with the public sector. The contribution that

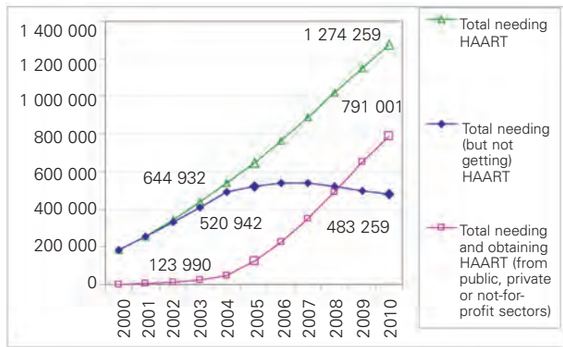

Fig. 1. Numbers of people needing and obtaining HAART (mid-points for each year) whether from the public or the private sectors (source: ASSA2003 demographic model).

donors make to public sector patients varies between donors, across projects (with some treatment sites being fully funded by donors, and others simply obtaining targeted support) and over time. For example, the first public sector donor project, which was between Médecins Sans Frontières (MSF) and the Western Cape government, was initially almost entirely funded and managed by MSF, but over the past few years, the province has assumed a greater role, with the plan being that as of 2007 the sites will be run entirely by the public sector.[6] The Western Cape government also received funding from the Global Fund (which was disbursed in October 2004) for six HAART sites including the sites it was operating in partnership with MSF. This makes it impossible to disentangle precisely the relative contribution of government and donor agencies to the HAART rollout.

BUDGETING FOR THE PUBLIC SECTOR ROLLOUT

National financial data on the HAART rollout are similarly opaque, with the available information being limited to the

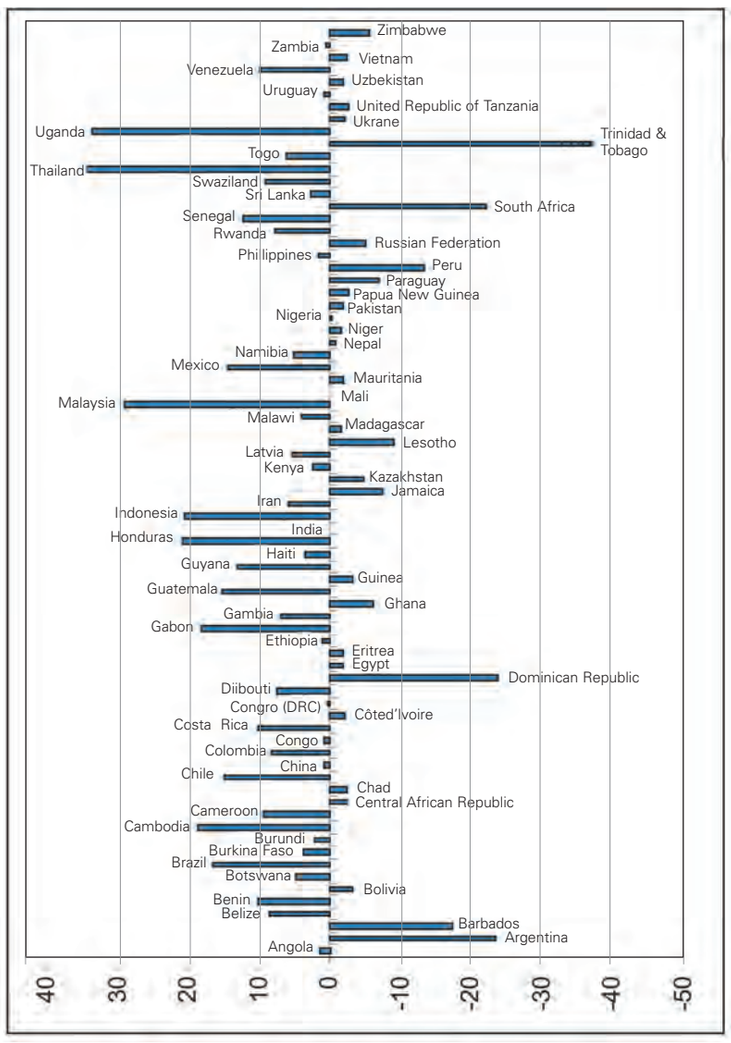

Fig. 2. The difference between actual HAART coverage and predicted HAART coverage in December 2004 (using regression model 4.5 reported in reference 3).

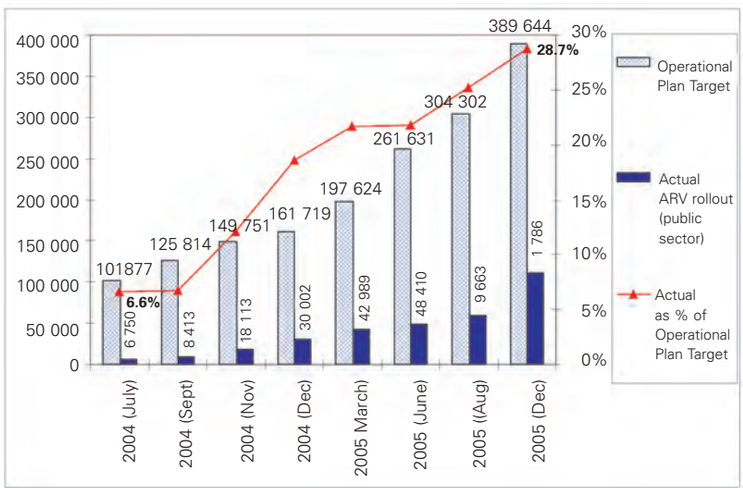

Fig. 3. Planned and actual growth in the provision of antiretroviral treatment (sources: ASSA2003 demographic model and references 4 and 5).

occasional cryptic remark in various general budget documents. However, judging from an August 2004 Treasury document reviewing government finances,[7] sufficient finances were allocated by the national Treasury to provincial governments to fund the Operational Plan. The report states that a sum of R300 million had been allocated to the 'comprehensive HIV and AIDS programme, ARV rollout in particular' for 2004/5. At this stage, the Treasury would have been working in terms of the budget provided by the Operational Plan which proposed to have 54 000 people on treatment by March 2004 at a total cost of R296 million.[4] This included budgeting for additional staff, laboratory testing, antiretroviral drugs, nutritional supplements, health systems up-grading, programme management, capital investment and research. Of course by late 2004 (when Treasury finalised its medium-term expenditure framework) it would have been clear that the rollout was proceeding far more slowly and at best was only going to achieve its March 2004 target a year later (as had indeed been announced by President Mbeki in his 2004 State of the Nation address[8]). This, together with the fact that HAART prices had fallen further since the operational plan was budgeted, meant that the allocation of R300 million for the 2004/5 financial year was more than sufficient to fund the (delayed-by-one-year) planned comprehensive rollout.

Yet, by the time March 2005 came along, the rollout was still only at about 80% of the original first year's treatment target (i.e. at about 43 000 people). In other words, more money had been allocated by the national Treasury for the comprehensive rollout in 2004/5 than had been used by the national and provincial health departments for that purpose. Despite this poor showing, the Treasury continued to be optimistic and supportive, and allocated enough in 2005/6 to have 150 000 people on HAART by March 2006,[9] while making the commitment to allocate further budget to the rollout as it progressed.

The Treasury's target of 150 000 HAART patients in the public sector by March 2006 appears to be spot-on with the achieved level of 111 786 by the end of December 2005. The national Treasury had, in other words, allocated sufficient resources to fund all of these patients. Yet as it turned out, the Global Fund, PEPFAR and various other NGO

partnerships took the pressure off the South African state to such an extent that only 51 494 HAART patients needed to be fully covered by the government budget. If we assume that the average contribution of donors to public sector projects is 50% of the total costs (which is probably an underestimate given that the Global Fund contributes substantially more to the Western Cape by paying for drugs, personnel, diagnostic testing and infrastructure[6]), then at least a quarter of the budget allocated by the national treasury for the HAART rollout was not used for that purpose.

THE PROBLEM OF POLITICAL WILL

According to a recent assessment by the International Treatment Preparedness Coalition (ITPC) of South Africa's HAART rollout,[10] the major constraint is political leadership. The economic analysis presented here supports the ITPC's contention. It suggests very strongly that the overall public sector rollout in South Africa is not constrained by budgetary allocations but is instead constrained by ineffective leadership in the national Department of Health. While it is true that a rapid and sustained HAART rollout requires additional investment in, and upgrading of, the public health sector, it is important to note that this was all budgeted for in the Operational Plan, and as argued above, existing subsequent allocations for the rollout by the national Treasury are consistent with that Operational Plan (although revised downwards to account for the slow initial pace of the rollout).

Put bluntly, if the national Health Minister had prioritised upgrading the health system and rolling out treatment, the Minister of Finance would have provided her with the funds and a further 30 000 people (at least) would be on HAART in the public sector. If the Ministry of Health had managed to roll out treatment in line with the original planned targets (which were initially budgeted for by the National Treasury) then an additional 278 000 people would be on HAART. Instead, the Health Minister has yet to chart a way forward to address the human resources crisis in the health sector,[11] and has undermined the HAART rollout yet further by sending out confusing messages about the relative benefits of HAART, nutrition and unproven alternative remedies.[2,12] She has also undermined attempts by provinces to access Global Fund grants[6] and has yet to use her powers under the Patents Act to issue compulsory licences to enable the local production or importation of generic versions of the patented drugs which compromise over half of the value of the March 2005 tender.[13]

There are strong grounds for concluding that South Africa could have achieved a much higher HAART coverage than it has, and that the major constraint on the rollout is political will. The national Treasury has made resources available to the Health Minister to facilitate a HAART rollout, yet a significant proportion of these have not been used for this purpose. The Health Minister appears to be undermining rather than energising the rollout. A large part of South Africa's failure to achieve a higher HAART coverage must be placed at her door – and that of President Mbeki, who at the very least is complicit in so far as keeping her in her post is concerned.

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TAKING STOCK OF THE NATIONAL ARV PROGRAMME: WHAT EXACTLY HAVE WE DONE?

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On 8 August 2003, the government of South Africa (SA) made a commitment to provide antiretroviral (ARV) treatment in the public health sector. On 19 November 2003, it published the Operational Plan on Comprehensive HIV and AIDS Care, Management and Treatment for South Africa (the Operational Plan). Some $2\frac{1}{2}$ years later, let us take stock of what is happening.

In June this year, world leaders met in New York at the United Nations General Assembly Special Session (UNGASS) on HIV/AIDS to review whether member states have met certain obligations agreed in the 2001 Declaration of Commitment on HIV and AIDS. While the meeting is politically important, it is bound to offer very little hope to millions of people living with HIV in Africa, South America and Asia who continue to wait for access to treatment. This is because even though there seems to be an international commitment to expand AIDS treatment access, the global rate of access is short of the internationally endorsed universal access goal for 2010, leaving millions without lifesaving care and hundreds of thousands of people with HIV/AIDS facing the prospect of imminent death. According to the World Health Organization (WHO), about 600 000 more people gained treatment access in 2005. At that rate, fewer than half of those who need AIDS treatment will have access in 2010.[1]

This is why an international alliance of civil society advocates has called for setting a new global AIDS treatment target of '10 by 10' – 10 million people accessing treatment by 2010. But the international community seems to have gone out of its way to avoid setting explicit global treatment targets that would focus attention on specific outcomes, acknowledge the responsibilities of global institutions as well as countries, and drive accountability. Current negotiations on the 2006 UNGASS Political Declaration suggest that the treatment section is weak, particularly on setting explicit treatment targets.

In SA, the national Department of Health submitted its final Progress Report on the Declaration of Commitment on HIV and AIDS (Progress Report) to the UN for the purposes of this meeting.[2] But it did so unilaterally and without any significant consultation with stakeholders. The Department excluded the views of civil society, private bodies and health academics, and it has been accused of failing to confer adequately with many partners that have assisted it with implementing the Operational Plan. For example, at a public meeting of the Joint Civil Society Monitoring Forum (JCSMF) held in March 2006, participants and members of the JCSMF were informed of one consultative meeting hastily convened by the national Department of Health on 2 March 2006 to discuss SA's report to UNGASS on progress with the implementation of the UNGASS Declaration of Commitment (2001). At that meeting, civil society and other stakeholders were told to submit comments on the draft Progress Report within a week. But even though some organisations managed to submit short recommendations within a week, those recommendations were subsequently ignored in the final report. The Progress Report has been criticised by many organisations in SA for glaring inaccuracies as well as its attempt to gloss over key shortcomings of SA's AIDS policies.[3,4] Significantly, the Progress Report fails to include information, data and statistics relating to HIV mortality, prevalence, TB and HIV incidence, ARV patient numbers and ARV treatment targets.

Globally and locally, targets are important. For example, the WHO committed to treating 3 million people in the developing world by the end of 2005. Even though these targets were not met by then, it created the momentum to scale up treatment access in many parts of the world – including in SA and countries that until then did not have domestic capacity to start ART.

The world's leaders have now committed themselves to achieving universal access by 2010. Will they fail? A lot depends on whether this commitment is vigorously pursued by member states at a local level. So far the picture does not look promising. In November last year the International Treatment Preparedness Coalition (ITPC)* issued *Missing the Target: A Report on HIV/AIDS Treatment Access from the Frontlines.* The report detailed specific barriers and potential solutions to AIDS

* The International Treatment Preparedness Coalition (ITPC) was born at the International Treatment Preparedness Summit that took place in Cape Town, South Africa, in March 2003. That meeting brought together for the first time community-based treatment activists and educators from over 60 countries. Since the Summit, ITPC has grown to include over 700 activists from around the world and has emerged as a leading civil society coalition on treatment preparedness and access issues.

treatment delivery in six countries heavily affected by the epidemic (including South Africa) and made recommendations for national governments and multilateral institutions. Six months after the publication of *Missing the Target*, the ITPC has found progress on several of the barriers to scale-up identified in November. However, deficient national leadership, and slow implementation of reforms remain critical roadblocks to treatment delivery and are costing lives every day in each of the six countries reviewed.[1]

With regard to SA, the ITPC identified the lack of proper leadership coupled with AIDS denialism as the main obstacles to increasing the number of patients on treatment. Other barriers include an acute shortage of health workers, mainly nurses and pharmacists, lack of proper infrastructure, and insufficient access to and promotion of VCT. The report noted that too few children were on treatment.

On a global level, the ITPC called for a new and more effective Global Fund for AIDS TB and Malaria (GFATM) Country Coordinating Mechanism (CCM) as well as sustainable funding for the GFATM, fewer restrictions and more collaboration from the PEPFAR programme including using generics registered by individual states and providing reproductive health services including condom distribution, increased visibility and leadership from UNAIDS and WHO, and greater involvement from civil society in treatment expansion.

WHAT HAS HAPPENED?

So let us look at what has happened since. In SA, by January 2006, the total number of people on ARV treatment in both the public and private sector was estimated to be about 200 000 - 220 000. About 110 000 - 120 000 people were purportedly accessing ARVs in the public sector, with an additional 90 000 - 100 000 receiving it in the private and not-for-profit sectors. (F Hassan and D Bosch – unpublished data, 2006, and F Hassan – unpublished data, 2006. See also Social Cluster briefing, Parliamentary Media 10 February 2006,[5] where the Minister stated that there were 229 sites treating 117 897 patients on ARVs at the end of December 2005. For a more detailed analysis of the Operational Plan see Hassan F, forthcoming publication by Equinet, 'The Provision of ARV Treatment in SA', **www.equinetafrica.org**). The majority of the approximately 110 000 - 120 000 patients (both adults and children) receiving public sector care are concentrated in three provinces (Gauteng, Western Cape, and KwaZulu-Natal). Most of the patients in the public sector are women, averaging at about 60% of all patients. Without the significant contribution of donors such as ARK, MSF and PEPFAR the public sector numbers would be even lower.

At the end of 2005, about 245 000 - 300 000 children were estimated to be living with HIV. Some experts suggest that on the basis of these figures, about 50 - 60% need immediate access to ARVs. At present we estimate that only about 10 000 - 15 000 children are receiving ARV treatment, that is about 10% of the total patients on treatment, while others argue that this figure is substantially lower. In particular, in many smaller and less resourced provinces the number of children on treatment is far below 10%.[6] Children therefore continue to be neglected during the planning for the provision of ARVs and HIV care. And the same trend is merging in other developing countries.

In addition, very few men are accessing treatment in the public sector in SA. But in the private sector, men outnumber women on treatment. This is because workplace treatment programmes are generally more available to male workers. Most patients on ARV treatment in the public sector are still receiving care at academic hospitals and so-called hospital 'main sites', with very few patients accessing ARV treatment at non-hospital, rural and remote sites.

What all of this tells us is that accurate numbers are hard to come by. This is because there is no proper Monitoring and Evaluation System (M&E) in SA. (Clinicians have warned that accurate data are absent on the number of patients on ARVs. For example, there are two separate systems (pharmacy and clinical) for capturing key data, and they rarely agree.) The national Department of Health has confirmed this.[7] It has admitted that the total number of people receiving ARV treatment is 'not yet known, as the patient monitoring system is not yet able to collect information to this level of detail in a reliable manner'[7] (p. 26) – this some $2\frac{1}{2}$ years *after* the Operational Plan was adopted.

Public health experts advise that the failure to have a proper M&E system has resulted in provinces being entrenched in a range of different data collection solutions and approaches. According to them even though revised indicators for the HIV programme are available, many of these are not feasible without a facility-based system through which data can be aggregated. The indicators themselves are often confusing and do not follow principles of collecting limited but necessary information (see Hassan F, forthcoming publication by Equinet, 'The Provision of ARV Treatment in SA').

BARRIERS TO IMPLEMENTATION

As in most other developing countries, human resources are a major barrier to the speedy implementation of prevention and treatment programmes in SA. Even though the national Department of Health has finally released its Country Plan for Human Resources in Health (HRH Plan) it remains to be seen how the plan will address real shortages in the short, medium and long term.[8,9]

Notwithstanding an initial forecast made to Parliament by the national Department of Health in February 2004 that the process of drug procurement would be completed by June 2004, the award of the drug tender was only announced on 2 March 2005, some 13 months after the drug procurement process commenced and more than 16 months after the Operational Plan was adopted.[10] The tender is worth over R3.7 billion and expires in 2007. But serious problems may arise with drug supplies. This is because, unlike the Brazilian government, the SA government is not planning ahead. For

example, it is not taking steps to ensure a sustainable supply of a range of key drugs. There appears to be very little government concern that there is only one supplier of Kaletra. The same is true of efavirenz (marketed by MSD as Stocrin) – even though a licence has been issued to Aspen Pharmacare to manufacture a generic version, it is still not yet registered for commercial use. If more competition truly existed, we would also witness a downward pressure on prices. This is important given that in terms of value, two pharmaceutical companies, Abbott Pharmaceuticals and MSD, have secured a substantial percentage of the tender (more than 50% jointly). Therefore, if the prices of key drugs are not brought down through generic competition, government will continue to waste valuable resources. In addition, without multiple suppliers sustainable supplies of key drugs will be jeopardised. For example, since the inception of the Operational Plan there have been several reports regarding problems with drug availability in various parts of the country (Gauteng, KwaZulu-Natal and Mpumalanga in particular). The supply of efavirenz has been beset with problems of repeated stock-outs.

On treatment regimens, while there is consensus among HIV clinicians in the private sector that d4t should be removed from the first-line treatment regimen and replaced with tenofovir (which has fewer side-effects), this has not happened because tenofovir is not yet registered by the Medicines Control Council (MCC). It is unclear when it is likely to be registered or why the fast-track process that it has been subject to has not materialised. Clinicians have warned that this delay is undermining the possibility of using optimal treatment regimens in the public sector.

In order to achieve universal access by 2010, SA and other developing countries will therefore have to step up their efforts. If ineffective national leadership and AIDS denialism continue, these targets will be undermined locally and globally. And it is worrying that there are no signs of these problems abating. For example, in legal papers filed by the national Department of Health this year in the Cape High Court in a case brought by the Treatment Action Campaign (TAC) against *inter alia* Matthias Rath, his associates and the Government of SA for making widespread false and exaggerated claims about the medical utility of high dosages of multivitamins (claiming that multivitamins are substitutes for ARVs), the Director General of Health has reported finding no wrongdoing by Rath or his associates, and has therefore defended not taking any steps to end the widespread distribution of false information by Rath suggesting that vitamins are a substitute for ARVs.[11]

Therefore, despite having some of the best HIV/AIDS policies on paper and a strong legal framework for protection against unfair discrimination, confusion and ambiguity has characterised our government's response to AIDS.

While members of parliament (MPs) and senior ANC officials have privately berated such a response, none, save for two prominent ANC members, Kader Asmal (former Minister of Education and ANC MP) and Ben Turok (ANC MP), have publicly drawn themselves (albeit unwittingly) into the debate. International donors and institutions such as the WHO, GFATM, and UNAIDS have also shied away from publicly doing so. The one exception has been Stephen Lewis in his capacity as Special UN Envoy for HIV/AIDS in Africa. Lewis has repeatedly declared that the lack of leadership and political commitment in SA is undermining the regional and international struggle against HIV/AIDS. For this the Ministry of Health has unfairly attacked and attempted to marginalise him.

Regionally and internationally, SA's response is not only embarrassing but dangerous as well. This is because many developing countries look to SA for solutions and leadership.

Therefore, in my view, the ARV programme has become a comfortable hiding zone for government and in particular the denialist views of certain senior officials. Because government is paying for ARVs, no one dare criticise the pace of implementation. But we must. You see, our government may be paying for ARVs but it is doing so slowly, reluctantly and without any great vigour or creativity. In fact, it is deliberately stalling on its own programme.

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PROFILE: HIV IN NORTH WEST PROVINCE, SOUTH AFRICA

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North West Province (NWP) has one of the highest HIV prevalences in South Africa. It is further challenged by severe poverty, a huge surface area housing a scattered community, and limited human resources. Despite this, it is one of the provinces that have successfully initiated large-scale ARV access in South Africa. This article describes the challenges and solutions that the province has grappled with to improve access to care for people with HIV.

Matlosana is a district of the Southern Region of the NWP and was previously referred to as KOSH (Klerksdorp, Orkney, Stilfontein and Hartebeesfontein). The Southern and Bojonala regions have the highest HIV ANC prevalence rates in the province (31.1% and 30.4% respectively, the provincial rate being 26.7%) (Fig. 1).

Possible reasons for these figures include a highly mobile population:

- Klerksdorp is located along the N12, a major truck route to the Northern Cape, Namibia and Botswana.
- Klerksdorp is a major trading post for surrounding areas that lack services such as retail, health, academic and training institutions.
- There is a high proportion of migrant workers (goldminers who are often not unionised contract workers and hence have no mine medical cover).

Klerksdorp-Tshepong Hospital Complex (KTC) resembles most secondary-level hospitals in South Africa in that it provides primary hospital care for those living in the immediate vicinity (Matlosana), secondary care for patients from all primary care hospitals in the Southern and Bophirima regions, limited tertiary services for the entire NWP (renal unit, MDR TB unit, oncology unit, burns unit) and on occasion quaternary care (highly infectious unit for outbreaks of viral haemorrhagic fevers such as Congo fever).

Large numbers of public secondary-level institutions are seeing increased numbers of patients, have severe budgetary constraints, face shortages of skilled personnel, particularly senior clinical and auxiliary staff (senior medical officers, general specialists, psychologists, social workers, senior nurses, senior pharmacists, etc.) and lack diagnostic and therapeutic tools. Junior staff, mainly interns and community service doctors, are often called upon to provide a wide range of services as these institutions are inundated with complicated and difficult cases referred from their primary referral sites.

The rollout of the South African government's Plan for Comprehensive Care for HIV/AIDS in the Public Health Sector has created new challenges that have shaken the practice of medicine. An old cliché that not only defines health as a physical state of wellness but also includes social, psychological and economic sufficiency can best be realised by the goal of the Comprehensive Care package. 'HIV medicine' is no longer a clinical entity. It forces us to consider other pertinent issues in relation to the growing pandemic, which include a study of interpersonal relations, sexuality in diverse cultures, death and dying and being culturally sensitive, the right to and access to disability/support grants, early identification of families in dire need, orphans and their support, food security, home-based care availability, and a host of other no less important local issues (informal settlements, water, sanitation, etc.).

Not only do 'HIV clinicians' have to deal with 'non-medical' issues, HIV as a disease also confounds the most astute of pure clinicians because of its multi-system manifestations. These include autoimmune phenomena (idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, haemolysis, etc.), opportunistic infections (TB, *Mycobacterium avium* complex, cryptococcal meningitis, pneumocystis pneumonia, etc.), malignancy (Kaposi's sarcoma, lymphoma, etc.) and antiretroviral therapy (ART) with its complications. Furthermore HIV can be a coincidental finding in patients with other diseases (hypertension, diabetes, cardiac, pulmonary, renal, etc.), often leading to diagnostic and therapeutic dilemmas. Often extensive (expensive, difficult and time-consuming) investigations and procedures are undertaken to diagnose a patient's presenting condition. These range from radiological (X-rays, ultrasound, computed tomography scans) and laboratory (histology for biopsies, cultures of material/specimens, serology, etc.) to invasive procedures (bronchoscopy, endoscopy). Doctors who work in high HIV prevalence areas become familiar with HIV-associated illnesses that were previously rare or uncommon (PCP/Crypto), or common diseases (such as extrapulmonary tuberculosis or

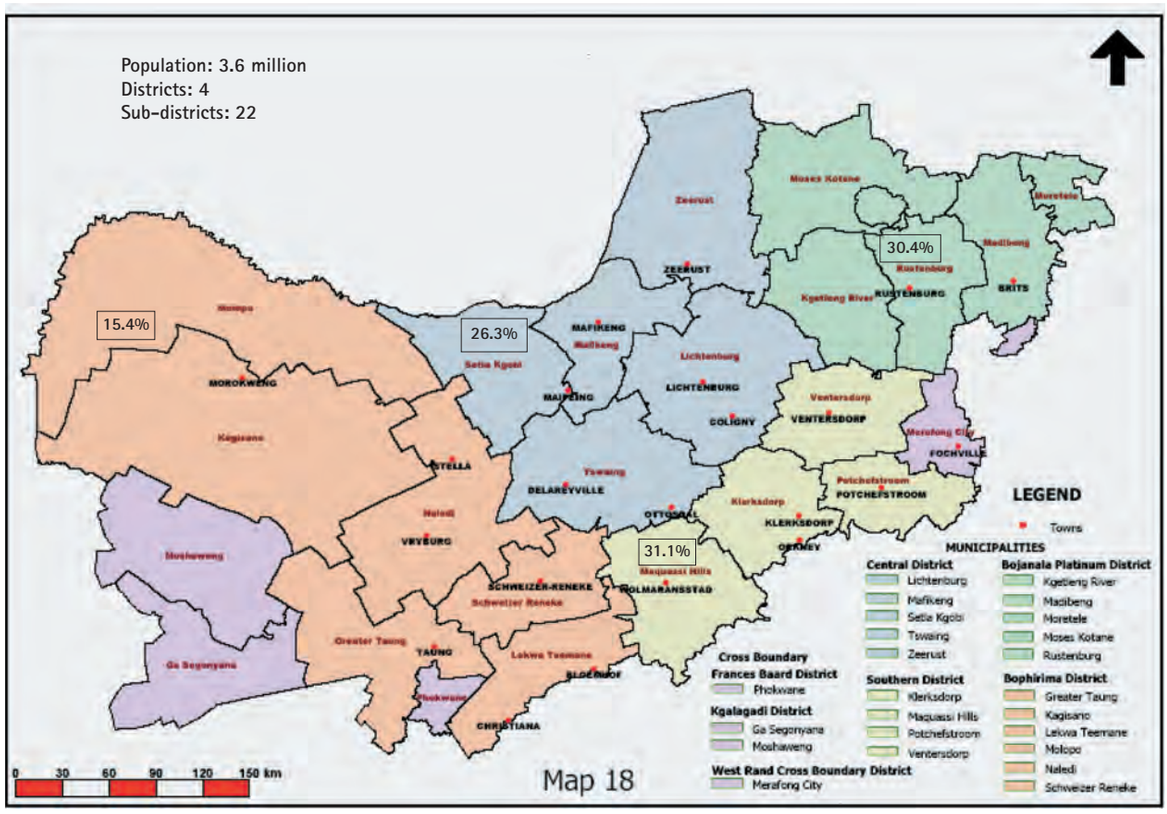

Fig. 1. North West Province: district and local municipalities (source: Municipal Demarcation Board, 2002).

pneumonias) presenting differently. Sub-specialist support for diagnosis and therapy is lacking at most secondary hospitals, and this further frustrates the clinician.

With increasing access to antiretrovirals (ARVs), a more endemic/chronic form of HIV now coexists leading to newer disease entities including multidrug-resistant or mutant HIV, lactic acidosis, lipoatrophy, lipodystrophy, metabolic syndromes, reconstitution disease (tuberculosis, crypto, hepatitis, MAI, etc.) and other toxicities induced by ART.

Clinicians working in areas where the prevalence of HIV is high, specialist support is scarce and ARV rollout is expanding require ongoing training, as a patient can incidentally be found to be HIV positive (asymptomatic or on therapy) and present with a non-HIV-related ailment or with various 'sub-specialist complaints' (pericardial TB, spinal TB, renal failure, etc.) directly attributable to HIV or its related opportunistic diseases or effects of therapy.

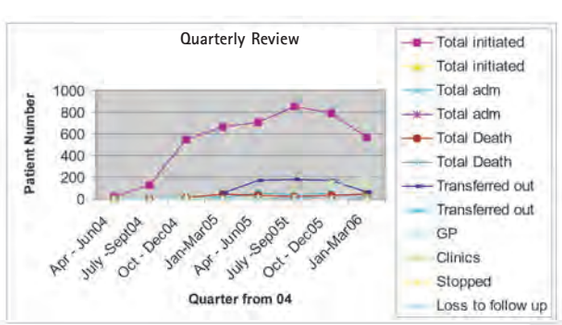

Fig. 2. Quarterly review, April 2004 – March 2006.

Tshepong Hospital is located in a high HIV prevalence region (31.1%) (NWP ANC seroprevalence study, 2004) and the Department of Medicine deals with large numbers of acutely ill HIV-infected individuals (accounting for 60% of admissions). An average of 250 new cases of HIV are diagnosed each month (local hospital statistics), many present with advanced (stage III/IV) disease and CD4 counts of < 200/µl, and many are malnourished. Our crude fatality rate averages 16% (3 - 5 deaths a day), and HIV-related disease was found to be a major contributor. An audit presented at the 2005 AIDS Congress in Durban showed that 45% of deaths were confirmed as HIV positive, another 20% were clinically positive, in 30% HIV status was unknown, and only 5% were confirmed HIV negative (mortality analysis in the Department of Medicine, Klerksdorp/Tshepong Hospital Complex, July 2003 – June 2004).

The Department of Medicine is responsible for 160 acute medical beds and 80 step-down beds with a bed occupancy rate of 80% and an average length of stay of 8 days. The step-down unit provides palliative, recuperative and rehabilitative care. While the Department of Health in NWP prepared its rollout plan in October 2003, KTC began setting up a Wellness Unit. With help from local business, renovations to the site were undertaken and the site was officially opened by our previous MEC for Health (Dr Sefularo). Partnerships with NGOs including Hospice, Lifeline and Seboka facilitated recruitment and training of lay counsellors. Faith-based organisations assisted with provision of food security for the destitute. Provincial support for a local HIV seminar in 2003 provided the original impetus for the training of doctors and nurses. RHRU

TABLE I. SUMMARY OF QUARTERLY STATS FOR THE WELLNESS UNIT, PRESENTED AT KTC QUARTERLY REVIEWS

	Apr – Jun 04	July – Sept 04	Oct – Dec 04	Jan– Mar 05	Apr – Jun 05	July – Sep 05	Oct – Dec 05	Jan – Mar 06	Total
Total initiated	25	124	548	667	704	851	785	566	4 270
Total adm.	0	4	26	6	50	47	50		183
Total deaths	4	2	14	41	31	23	27	40	182
Transferred out				48	168	183	168	67	634
GP							110	214	324
Clinics						100	138	127	365
Stopped ART	0	0	6	3	6	9	5	8	37
Lost to follow-up	0	0	1	0	2	13	0	6	22
Total follow-up									2 706

and later AURUM consolidated the training. Partnering with our district primary care team enabled us to develop staging sites at local clinic level and strengthened the referral process.

Provincial will and support led to the Wellness Unit with its multidisciplinary team being fully established at the point of official accreditation in July 2004.

In line with the Provincial Plan, KTC assisted other sites with their programme implementation by assisting with staff training, accreditation and treatment of patients from these sites. Taung, Vryburg, Ganyesa and Potch have all been accredited and patients from these areas were successfully referred back.

As the programme is rapidly growing (initiating ARVs in an average of 240 patients per month) (Wellness Unit stats, KTC quarterly reviews – Table I) the need to refer stable patients (with good immunological and clinical response) to their local clinics has become more apparent. Clinics that were originally staging sites are now seeing and distributing medication for the down-referred patients (pre-packed for each patient and delivered to the clinic by the hospital pharmacy). A pilot programme for down-referral is referring stable patients to a local GP network (funded by Broadreach) where the GPs receive a capitation fee for following up these patients. Down-referred patients return to hospital 6-monthly for ongoing tests. As a result more space at the Wellness Centre has been created, enabling us to continue with initiating newer patients on ARVs. There are also cases in which earlier initiation or hospital-based initiation of ARVs needs to be considered. The logical next phase would be the initiation of ARVs in stable patients at the PHC level. Plans are being developed and it is hoped that by 2007 selected clinics may begin initiating ARVs provided they meet requirements for accreditation.

The complexities of HIV and a rapidly expanding HIV programme mean a growing need to form strategic partnerships. With this in mind we at KTC have pursued partnerships with RHRU, AURUM, Broadreach, Hospice, Lifeline, Seboka, primary care clinics, the local GP network and other care providers in Matlosana. The formation of the HIV Clinicians Society has given us a means of disseminating medical information to caregivers in our areas.

Thanks to the persistent Tanya Nielson, an enthusiastic pharmacist who worked hard in setting up our branch, our inaugural launch (attended by 100 care providers) was a success. Attendees included doctors, pharmacists, dieticians, primary care nurses, social workers and home-based care groups, all part of a multidisciplinary team needing to understand HIV from authorities in their field. Dr Francois Venter presented an overview of the rollout programme and the challenges posed by ARV provision. Professor Churchyard presented a talk on TB and HIV and how ARV will impact on the TB epidemic.

A second meeting was held in May and again this was enthusiastically supported, encouraging us to continue.

The North West Provincial Department of Health, KTC management, and the staff of the Wellness Unit all need to be thanked for the success of the unit.

HIV AND HEPATITIS B COINFECTION IN SOUTHERN AFRICA: A REVIEW FOR GENERAL PRACTITIONERS

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Sub-Saharan Africa is facing serious HIV and hepatitis B epidemics, with coinfection becoming a major public health problem. In addition, the prevention and treatment of concurrent illnesses such as hepatitis B in HIV-infected people is becoming increasingly important as their life expectancy lengthens due to treatment with highly active antiretroviral therapy (HAART). Despite the important epidemiological burden and clinical consequences of coinfection, there is a paucity of research to inform practice that derives from studies conducted in highly endemic regions. This article reviews the current status and limitations of knowledge on coinfection with the hepatitis B virus (HBV) and HIV. It will examine the basic epidemiology of coinfection; the implications for disease progression of each condition; the therapeutic implications including drug toxicities; and current evidence and guidelines for the use of vaccine-based prevention strategies. In addition the article highlights critical areas for future research on coinfection in sub-Saharan Africa.

his article aims to review important aspects of and recent developments in coinfection with HIV and hepatitis B for general practitioners. Our review starts by briefly reviewing aspects such as the prevalence, transmission, prevention, complications and treatment of hepatitis B disease. The subsequent sections deal in more detail with the various aspects of coinfection, including the prevalence, natural history, serological diagnoses, disease progression, outcome of HAART, and HBV vaccination in HIV-positive patients. Coinfection with these two viruses is a complicated topic and most currently available research is from developed settings where predominant transmission modes are different to most African countries, in particular horizontal spread dynamics. In addition, disease prevalence differs markedly, as does vaccine administration and timing, and the feasibility of therapeutics in developing compared with developed countries.

On the African continent 25.4 million individuals are infected with HIV, and in South Africa 5.6 million people were infected with HIV by the end of 2003.[1] Globally, more than 2 billion people have serological evidence of HBV infection and between 350 and 400 million people, representing over 5% of the world's population, are chronically infected.[2] Sub-Saharan Africa is estimated to have approximately 50 million chronic HBV carriers and around 2.5 million of these live in South Africa.[3] Research from sub-Saharan countries has shown the prevalence of chronic HBV in the general population to vary between 9% and 20%.[4] Based on seroprevalence studies, the estimated HBsAg carrier rate in the South Africa is approximately 9%,[5] with a marked difference in prevalence rates between rural and urban populations. This is demonstrated by prevalence rates in the rural Eastern Cape of 15.5% (in the 0 - 60-month age group), compared with 1% in Soweto in the 1980s.[4] Some of these studies are dated and predate universal HBV infant immunisation, but still no explanation currently exists for the geographical variability of HBV infection in South Africa.

Furthermore, even the basic epidemiology of HBV transmission in sub-Saharan Africa is poorly understood. Transmission is thought to be predominantly horizontal, though the details of transmission and marked urban-rural variation are not well understood. The vast majority of the region's population has been exposed to HBV by the age of 5 years. Thereafter HBV prevalence rates increase slightly when children first attend school, and again when they become sexually active.[6] The exact mechanism of HBV transmission has not been established, but the major risk factors associated with HBV infection include scarification, poor sterilisation techniques, re-use of needles, and close personal contact.[7, 8] This is in contrast to developed countries, where the majority of HBV transmission takes place in adulthood when sexual transmission and intravenous drug use form the predominant modes of transmission. Vertical (*in utero*) HBV transmission is not thought to play a major role in sub-Saharan Africa.[9]

Currently the most effective way to reduce the acquisition of HBV in sub-Saharan African countries is through early childhood HBV vaccination. In line with this the South African Department of Health added a vaccine against hepatitis B virus (HBV) into the Expanded Programme on Immunisation (EPI) in April 1995.[10] The World Health Organization (WHO) also recommended the inclusion of the HBV vaccine into their Expanded Programme on Immunisation (EPI) and by the year 2000 more than 100 followed this recommendation.[11] Although the oldest of the South African immunised cohort are only 11 years old now, follow-up studies have shown that small cohorts of immunised children were protected against clinical HBV infections,[12] and that that even at low coverage, reductions in indicator diseases such as HBV nephropathies have been recorded.[13] However, more extensive data on the field effectiveness of the current EPI HBV vaccination programme are still outstanding.

A successful HBV vaccination programme could therefore reduce the prevalence of chronic HBV disease and the high mortality rate (20 - 30%) due to hepatic complications. These include liver cirrhosis and hepatocellular carcinoma (HCC),[14] the latter having a 3-year survival rate of less than 20%.[8] The current morbidity and mortality resulting from chronic HBV infection in sub-Saharan Africa is high, with 20% of cirrhosis cases and 70% of all liver cancer cases in the region thought to be due to HBV infection.[5, 6]

In addition to vaccination, antiviral treatment for HBV is available for most patients with chronic HBV in developed countries. Sadly, access to HBV treatments in developing countries has lagged behind that of antiretrovirals (ARVs). The aim of treatment of hepatitis B is sustained viral suppression to a level associated with no or minimal liver damage.[15] The currently approved treatments in developed countries include standard interferon, lamivudine, adefovir dipivoxil, and entecavir. Decisions regarding treatment should balance the benefits (severity of liver disease) against the risks (adverse effects and costs).[15, 16] In most patients, careful monitoring over a 3 - 12-month period is needed to correctly determine the phase of chronic HBV infection and the severity of liver disease before starting treatment. Current guidelines[15] do not recommend treatment for hepatitis B envelope antigen (HBeAg)-positive patients with persistently normal alanine aminotransferase (ALT) but do for patients with ALT > 2 × upper limit of normal or moderate/severe hepatic inflammation if spontaneous HBeAg seroconversion does not take place after 3 - 6 months of observation (Table I). Patients with hepatic flares or decompensation should receive immediate treatment.

TABLE I. ANTIVIRAL TREATMENT GUIDELINES FOR HBV DISEASE

ALT	HBV DNA	Treatment recommendations
HBeAg positive		
<2 × ULN	> 5 $\log_{10}$	No treatment, monitor Treat if ALT 1 - 2 × ULN and moderate/severe inflammation or advanced fibrosis on liver biopsy
>2 × ULN	> 5 $\log_{10}$	Observe 3 - 6 months, treat if no spontaneous HBeAg seroconversion
HBeAg negative		
<2 × ULN	< 5 $\log_{10}$	No treatment, monitor Treat if ALT 1 - 2 X ULN or HBV DNA 4 - 5 $\log_{10}$ with moderate/ severe inflammation or advanced fibrosis on liver biopsy
>2 × ULN	> 5 $\log_{10}$	Treatment

ULN = upper limit of normal.

PREVALENCE OF COINFECTION WITH HBV AND HIV IN SUB-SAHARAN AFRICAN COUNTRIES

Early epidemiological studies did not show an increased prevalence of HBV among HIV-positive individuals. However, it was conducted when HIV prevalence was low, and was limited by small sample sizes.[6] Recently the prevalence of HBV in HIV-infected adults in sub-Saharan Africa was found to be nearly two times that of HIV-negative patients.[6, 17-26] This higher risk is not as great as that in developed countries, where the prevalence of HBV infection is increased by as much as 10 times in HIV-positive patients, possibly owing to different epidemiologies and modes of spread (such as intravenous drug use). Nonetheless, a high proportion of HIV-positive patients will be HBV coinfected in sub-Saharan Africa and more research is needed to allow an accurate estimation of the extent of the problem and to provide more information regarding differences in prevalence between various groups of patients including rural and urban populations, males and females, and children and adults.

THE NATURAL HISTORY OF HBV DISEASE IN HIV COINFECTED PATIENTS

The natural history of both HIV and hepatitis B infection appears to be influenced by the other, but depends on which infection was acquired first.[7] The more common scenario in sub-Saharan Africa is where children are first infected with HBV and subsequently infected with HIV as adults. In this setting HIV-positive patients with previous cleared HBV infections may lose their protective HBV antibodies due to HIV immunosuppression,[23, 27] and may therefore be at an increased risk of reinfection with HBV.[22, 27] In addition HIV-induced immunosuppression may cause reactivation of recovered (previously anti-HBs positive) as well as 'silent' chronic infections.[21, 27]

In sub-Saharan countries, the minority of patients are HIV-infected by the time they are exposed to HBV for the first time. Most of this sub-group would be children who acquired HIV vertically and are subsequently infected by HBV. HIV-negative children infected with HBV are more prone to develop chronic HBV disease; as many as 90% of those infected as infants and 50% of those infected as young children may become chronic carriers of the virus and are at high risk of liver disease later in life.[28] The effects of HIV infection in these children are unknown at present and require further study.

Research from developing countries suggests that HIV-positive adults who are subsequently infected with HBV are at a higher risk of becoming HBV carriers,[8, 19, 21, 23, 24] are more likely to have high HBV replication rates,[21, 24, 29] and are more likely to be HBeAg-positive for a longer time[21] than HIV-negative patients. All these factors could increase the risk of HBV transmission.

Almost all research looking at the natural history of coinfected patients has been conducted in developed countries, and research documenting disease progression in endemic African populations is needed as transmission dynamics of HBV and HIV differ significantly in these populations.

ISOLATED ANTI-HBc ANTIBODY AND SEROLOGICAL SCREENING STRATEGIES FOR HBV IN HIV-INFECTED PATIENTS

For a reminder of the interpretation of HBV serology, see Table II.[30]

TABLE II. INTERPRETATION OF HBV SEROLOGY

Serological markers	Clinical significance
HbsAG +	Acute or chronic infection
Anti-HBc IgM +	Acute infection; chronic disease with poor prognosis
Anti-HBc IgG and HBsAg +	Chronic infection
Anti-HBc IgG and Anti HBs +	Resolved infection
Anti-HBc only +	Exposure; low-level carrier; senescence of anti-HBs; false positive
Anti-HBs only +	Immunity (natural or vaccine)

Historically, screening strategies for HBV infection test for the presence of HBsAg and anti-HBs only. This strategy overlooks individuals with isolated anti-HBc antibodies. This pattern may represent resolved HBV infection, with loss of antibody to hepatitis B surface antigen (anti-HBs) or occult chronic HBV infection, with levels of the hepatitis B surface antigen (HBsAg) below the limits of detection.[31] Although isolated anti-HBc antibodies are less commonly seen in HIV-negative patients[32] they have increasingly been detected in HIV-positive individuals throughout the world.[33] This has been well researched in regions of low HIV/HBV endemnicity, particularly Europe and the USA.[34, 35] In these settings, it has been estimated that 10 - 20% of all individuals who are serologically positive for HBV have an 'anti-HBc alone' serological pattern. Of these, about 10% are HBV DNA positive.[34]

In areas of high endemnicity such as sub-Saharan Africa, mechanisms resulting in 'occult' HBV infection and the burden of these infections are less well understood.[36] The importance of this sub-group of patients is demonstrated by the finding that as many as 85% of these 'anti-HBc alone' HIV-positive patients have been found to be positive for HBV DNA.[25] Work from South Africa's Limpopo province suggests that 33.3% of HIV-positive adults with an 'anti-HBc alone' serological pattern were also HBV viraemic, compared with 0% of HIV-negative controls.[37]

No associated increased risk for mortality or progression of HIV infection in patients with isolated anti-HBc has been documented, either before or after the introduction of HAART.[38] Research suggests that the prevalence of isolated anti-HBc will vary with the epidemiological characteristics of the patients enrolled and the background seroprevalence of HBV infection. In addition it is proposed that the prevalence of isolated anti-HBc will be high among patients at a late stage of HIV infection, in areas of hyper-endemnicity of HBV infection.[25]

In conclusion, these findings strongly support the concept that HIV infection is a risk factor for occult HBV infections, and the clinical importance of HBc only is still to be studied. In the future, screening for HBc only may be recommended as standard of care for HIV-infected patients. In addition more research, documenting how HIV-1 infection alters the serological response to HBV infection and the frequency of and factors associated with isolated anti-HBc in endemic patient populations, are needed to increase our understanding of this complex interaction.[31]

IS HIV DISEASE PROGRESSION ACCELERATED BY HBV COINFECTION?

Several studies looking at HIV and HBV interactions have been published recently. Findings are conflicting. Some show no impact of HBV coinfection on HIV disease progression,[39-42] while others suggest that HBV co-infection was associated with reduced survival in patients with clinical AIDS.[43] More recently several studies have shown no convincing evidence that HBV hastens progression to AIDS.[19, 23, 24, 33, 44-45] A reason for these conflicting results could be that the majority of clinical studies conducted have only considered HBsAg as a marker of chronic HBV disease,[33, 44] and many of these studies suffer from a number of limitations such as small sample sizes, lack of standardisation of important variables, and confounding variables such as the introduction of HAART.[17] While most available evidence does not show a significant impact of HBV on HIV disease progression, further research is required. In particular, HBsAG-positive patients should be stratified into subgroups according to other variables such HBV DNA levels to determine whether their HIV disease progresses differently.

IS HBV LIVER DISEASE PROGRESSION ACCELERATED BY HIV COINFECTION?

Several studies from developing countries show evidence that coinfection with HIV alters progression of HBV infection. This includes an increased progression of HBV towards chronicity,[8, 46-48] higher levels of HBV replication,[8, 23, 44, 48-50] and a reduced rate of spontaneous loss of HBeAg and/or HBsAg and seroconversion to anti-HBe and anti-HBs.[48] Individuals

who are HBeAg positive and/or have high HBV replication rates generally have more rapid liver disease progression and are more infectious.[30]

Conflicting data exist regarding the degree of liver inflammation in coinfected patients. The pathogenesis of hepatic damage in chronic HBV disease is predominantly immune mediated, with CD8 cells targeting HBV antigens on infected hepatocytes, resulting in inflammation and necrosis.[51] Immune deterioration due to HIV leads to reduced necro-inflammatory activity and reduced ALT levels.[51] Research involving men who have sex with men from developed countries supports the hypothesis for a reduction in liver inflammation in HIV-coinfected patients.[49, 52] Thus, despite higher HBV DNA viral levels in coinfected patients, liver inflammation appears less[39] and may be undetected by routine transaminase screening. Reasons for this could be that HIV immunosuppression may reduce liver damage as a result of a less aggressive HBV-specific immune response.[21] In contrast, other research involving mostly injecting drugs users in developed countries shows increased inflammatory activity.[53, 54]

There are contradictory data regarding the impact of HIV on progression towards cirrhosis and hepatocellular carcinoma in coinfected patients. Some studies from developed countries failed to show any negative impact of HIV coinfection on hepatitis B disease progression.[8, 49, 55] However, numerous studies have shown that HIV infection exacerbates liver disease in patients with HBV co-infection.[29, 39, 43-45, 50, 54, 56-64] In addition, several clinical reports have shown that the risk of end-stage liver disease is significantly increased in HIV-infected patients with chronic HBV.[43, 56, 58, 62, 65-71] The MACS cohort study found that the liver-related mortality rate was higher in men with HIV-1 and HBsAg than in those with only HIV-1 infection or only HBsAg. They further found that the liver-related mortality rate in coinfected individuals was highest in those with lower nadir CD4+ cell counts.[56] This increased risk of HBV disease progression should be considered in any HIV/HBV-co-infected patient with detectable HBV-DNA.[48] South Africa would be an ideal country to perform well-designed and well-funded studies to evaluate this issue.

Some patients with coinfection therefore seem to have more aggressive liver disease (i.e. progression to cirrhosis or liver failure), while other patients have minimally active liver disease with little or no evidence of progressive liver disease.[72] The reason for this discrepancy is unclear and no correlation has been found with any specific clinical factor or laboratory tes.[63] Mechanisms to explain the progressive liver disease despite less liver inflammation are unknown at present, but include potential direct toxicity of high HBV viral levels on hepatocytes[73] or the fact that liver cirrhosis and cancer take years to develop and might be masked by the premature death of patients with HIV/AIDS in the absence of HAART.[74] Other possible explanations to explain these differences include the variety of infecting HBV genotypes in different geographical areas; differences in the degree of HIV immune suppression; and confounding by other factors related to liver damage, such as alcohol use and other infective agents e.g. HCV and HDV. In addition further research needs to be done to clarify the current uncertainty regarding HBc-only patients, the role of HBeAg and HBV DNA levels and whether they carry a similar prognosis among coinfected patients.

ANTIVIRAL TREATMENT OF HIV AND HBV IN COINFECTED PATIENTS

Lamivudine, adefovir, entecavir and alpha-interferon are antiviral drugs used for the treatment of chronic HBV infection in developed countries.[75] Of these, only lamivudine, which is active against both HBV and HIV, is readily available in sub-Saharan Africa. Most countries in the sub-Saharan region use antiretroviral regimens that include lamivudine, and some recommend lamivudine as the drug of choice in HIV/HBV coinfection.[21] Unfortunately HBV resistance to lamivudine occurs in up to 20% of cases per year[56] with long-term use.[21, 45, 76] This has potentially serious implications in HIV-endemic areas, where the majority of HBV chronic carriers are likely to be HIV-positive. Others advocate against the use of lamivudine in coinfected patients, because of the development of resistance that is often signaled by late occurring hepatic flares.[39] As an alternative, it has been suggested that in HBe antigen-positive coinfected patients, lamivudine should be reserved for those who develop clinical hepatitis.[77] This recommendation was based on the finding that the risk for long-term lamivudine resistance is greater in HBeAg-positive patients.[77] Long-term studies in areas with high levels of coinfection are necessary to understand the optimal timing of lamivudine introduction to HAART regimens better.

Tenofovir and emtricitabine also have dual antiviral activity against HIV and HBV and it is hoped that they will soon become available in southern Africa, broadening the armamentarium against HBV in coinfected patients. The nucleotide analogues (adefovir and tenofovir) have the advantage of a higher genetic barrier to the development of HBV resistance than the nucleoside analogues (lamivudine and emtricitabine). As these drugs do not share the same resistance profile, they can be used for salvage therapy.

Sadly, access to HBV treatments in developing countries has lagged behind that of ARVs, but once more drugs become readily available the best option may be to ensure that combination antiviral therapy for HBV is administered in conjunction with antiretroviral therapy, thus avoiding the selection of resistant viral species for either or both viruses.[78] Such a combination could be tenofovir and lamivudine as part of HAART,[74] which could be used for patients with liver cirrhosis, HBsAg-positive patients, patients with active HBV disease with HBV viral replication, and possibly even for all coinfected patients.[77, 79]

HAART TOXICITIES IN COINFECTED PATIENTS

The most common drug-related toxicity in HIV/HBV-coinfected patients on HAART remains hepatotoxicity.[39, 56, 61, 78, 80-86] The

development of severe hepatitis has been reported with HAART regimens containing nevirapine, efavirenz and ritonavir at full doses.[61] Liver damage is thought to result indirectly from immune restitution after the commencement of HAART,[56] or directly from liver toxicity caused by protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs).[61, 73, 78] Problems with regulation of restored immune system in the first 6 months of HAART can lead to atypical presentations of various infections including hepatitis B and may occur in 30 - 40% of individuals that initiate HAART at low CD4 counts.[85] Regimens containing NNRTIs or full-dose ritonavir, should be used cautiously in coinfected patients and discontinued if symptoms or grade 4 increases in aminotransferase levels (>10 × upper limit of normal) develop. Close monitoring of coinfected patients initiating HAART during the first few weeks of therapy is recommended. Despite the increased incidence of hepatotoxicity most of these patients tend to experience a progressive resolution of liver abnormalities without interruption of treatment.[58, 61, 78, 80, 84-87]

As progression to liver cirrhosis in coinfected patients takes 20 years on average,[71] the prevention of death from opportunistic illness in patients treated with HAART increases the likelihood of sequelae of HBV coinfection. In the EuroSIDA cohort, longer exposure to HAART was associated with an increased death rate from liver-related disease in patients with similar CD4 counts. This could be a consequence of direct liver toxicity of HAART or due to progression of HBV/HBC disease.[71] In addition HAART could possibly potentiate the flare-up of HBV directly or indirectly because of mutations resulting from immune pressure,[61, 62, 88] explaining reactivation that develops independent of lamivudine resistance or withdrawal of lamivudine.[62] Little evidence is available regarding the efficacy of HAART in coinfected patients. A cohort study from Thailand reported a delayed CD4 count recovery after coinfected patients were initiated onto HAART, but this was not sustained and there was no associated increased progression of HIV disease.[40]

As discussed previously, the studies highlighted above were conducted in developed countries with significant differences in the profile of HIV and HBV disease. Additional research from developing countries to establish the outcome and toxicities of HAART in coinfected patients is needed to shed light on these important questions.

HBV VACCINATION IN HIV-POSITIVE PATIENTS

T-cell-dependent and independent antigens are affected by HIV immune suppression, and worsen as HIV disease progresses. Owing to this deterioration in immune response, studies of HBV vaccination in HIV-infected infants suggest reduced vaccine efficacy.[89] This reduced immune response pertains both to the antibody titre and its durability.[33, 90-96] Fortunately, in the HAART era evidence suggests that individuals' immune responses to vaccines can be restored to those of HIV-uninfected persons.[97] High CD4 cell counts and low levels of HIV viraemia improve the immunological response to the HBV vaccine.[90, 98] Guidelines from developing countries recommend HBV immunisation for all HIV-positive individuals who have not been exposed to HBV.[90, 98] Strategies to improve response rates include increased dosages of vaccine, prolonging the vaccination schedule, or both.[33, 90, 99, 100] In general there is no harm in vaccinating HIV-infected patients with inactivated HBV vaccines despite the transient increase in HIV viraemia immediately following HBV immunisation.[99, 101, 102] Most guidelines recommend monitoring anti-HBs every 6 - 12 months, after completion of HBV vaccination schedules, to establish efficacy and the need for booster doses.[103]

SUMMARY OF IMPORTANT POINTS

- Coinfection with HIV and hepatitis B is a becoming a major public health problem in sub-Saharan Africa.
- Recent evidence from sub-Saharan Africa shows the prevalence of HBV in HIV-infected adults to be nearly two times that of HIV-negative patients.
- The natural history of both HIV and hepatitis infections is influenced by the other, but this complex interaction is not well understood at present.
- HIV infection is a risk factor for occult HBV infections and it is therefore recommended that anti-HBc antibody testing be included in HBV screening for all HIV-positive patients.
- Available evidence from developed countries does not show a significant impact of HBV on HIV disease progression. Further research is required.
- HIV reduces the immune response to HBV infection, but there is evidence of a paradoxical acceleration of HBV disease progression.
- Future treatment options for coinfected patients could include combination antiviral therapy such as tenofovir and lamivudine, which are active against HBV as well as HIV, thus avoiding the selection of resistant viral species for either of the viruses.
- Close monitoring of coinfected patients initiating HAART is recommended, as these patients have an increased incidence of hepatotoxicity.
- Guidelines for developing countries recommend HBV immunisation for all HIV-positive individuals who have not been exposed to HBV.
- Most research on coinfection has been done in developed countries where HIV and hepatitis disease prevalence, transmission modes and therapeutic options differ markedly and more research from developing countries is urgently needed.

CONCLUSION

HIV and HBV infection are two of the most prevalent infectious disease currently affecting the sub-Saharan region, and coinfection with these two viruses is a common occurrence. The effects that coinfection with these two viruses have on the transmission, natural history, diagnosis and treatment of both diseases are not clearly defined in this setting. Most research has been conducted in developed countries with very different transmission modes, disease prevalence, vaccine administration timing, and availability of certain therapeutics. Data from these settings are therefore difficult to extrapolate to developing countries with endemic

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CASE STUDY

EVALUATION OF FEVER OF UNKNOWN ORIGIN BEFORE STARTING ANTIRETROVIRAL THERAPY

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A 34-year-old woman tested HIV-positive in December 2005, and was referred to a specialist HIV unit in mid-January 2006. She had presented to her general practitioner with oesophageal candidiasis and a history of a cough and occasional loose stools since November 2005, with an 8 kg weight loss over the past 6 months. She had no history of other opportunistic infections or HIV-related conditions. On examination her temperature was 38.5°C and she had sinus tachycardia. Wasting, pallor and severe oral thrush were noted. There was no lymphadenopathy, hepatomegaly or splenomegaly, and the findings on respiratory examination were normal.

The patient refused admission and results of the following investigations were obtained as an outpatient: haemoglobin 6.9 g/dl (normocytic, normochromic), white cell count 5.56×10^9/l and platelet count 88×10^{11}/l. The CD4 count was 27 cells/µl (4.32%) and the viral load > 750 000 copies/ml. The serum albumin level was 22 g/l and the lactate dehydrogenase (LDH) level 3 116 U/l; levels of alanine aminotransferase (ALT), alkaline leucocyte phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) were within normal limits. Aerobic, anaerobic and mycobacterial blood cultures were negative. A bone marrow aspirate and trephine showed disordered erythropoiesis in keeping with retroviral disease. Histological examination of the trephine biopsy specimen showed no granulomas or signs of malignancy. The Coombs test was negative and the haptoglobin level was in the normal range. The chest radiograph was normal. The patient was given a blood transfusion which brought the haemoglobin level to 9.2 g/dl, and was treated with fluconazole.

Antiretroviral therapy (ART) was commenced with stavudine, lamivudine and efavirenz. Symptomatic peripheral neuropathy was detected 2 weeks later and the stavudine was replaced with tenofovir. Four weeks after starting ART the patient's condition deteriorated and she was found to be mildly confused, apyrexial and pale. A right-sided pleural effusion had developed. Aspiration of the effusion returned bloodstained fluid, cytological examination of which showed a high-grade plasma blastic non-Hodgkin's lymphoma. The patient was assessed by an oncologist but refused further treatment and subsequently died.

COMMENT

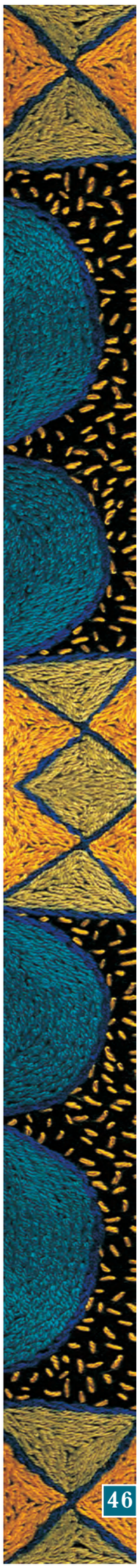
This case study encapsulates a clinical dilemma frequently encountered by South African HIV clinicians: a patient with advanced HIV disease presents for the first time with prominent constitutional symptoms; a careful evaluation for opportunistic infections is unrevealing; and ART is commenced. Within a few weeks of initiating ART a focal (and in this case fatal) disease process becomes apparent.

At issue here is how far the evaluation should be taken before ART is begun. The question becomes especially relevant in resource-constrained environments.

Diagnosing and treating opportunistic infections before starting ART is essential in order to reduce the possibility of immune reconstitution disease, and the likelihood of significant drug interactions.

Advanced HIV infection can cause fever and weight loss (constitutional symptoms) without underlying opportunistic infection. This is, however, a diagnosis of exclusion. The evaluation is best approached by considering the patient under the diagnostic label of fever of unknown origin (FUO). Typically, FUO is diagnosed using Durack's and Street's criteria:[1] temperature of 38.3°C or higher on multiple occasions over 3 days for inpatients or for more than 4 weeks for outpatients; failure to identify infectious organisms after at least 2 days of incubation of microbiological cultures; and a diagnosis that remains uncertain after 3 days despite appropriate investigation. In the South African context repeated temperature measurements can be difficult to obtain, and a history of fevers and chills or drenching night sweats persisting for more than 2 - 4 weeks is highly suggestive of FUO. Acute bacterial infections are unlikely to be confused with FUO owing to the abrupt onset of symptoms, presence of focal pain, and body fluids containing a predominance of neutrophils.

Various forms of tuberculosis are probably the most common cause of FUO in HIV-infected adults.[2] If cough is a prominent symptom at least 2 - 3 sputum specimens should be sent for staining for acid-fast bacilli.[3,4] The yield can be improved by



inducing sputum using an ultrasonic nebuliser and hypertonic saline[5,6] – if at all possible this specimen should be sent for mycobacterial culture. Other appropriate initial investigations would include a full blood count and white cell differential count, measurement of liver enzymes and C-reactive protein, urine analysis and a chest radiograph. Ultrasound of the abdomen and pericardial space is a useful technique with the potential to identify pericardial effusions, intra-abdominal lymph nodes, hepatic and splenic lesions, ascites and pelvic masses. The aim of the initial set of investigations is to detect a focal process that could potentially be the site of an opportunistic infection. Tuberculosis is compatible with pulmonary infiltrates (including micronodular, interstitial and airspace disease), pleural or ascetic exudates, pericardial effusion, mediastinal or intra-abdominal lymph nodes, or hypoechoic splenic lesions. Unfortunately, other infections and malignancies can present in a similar manner.

Mycobacterial blood culture is highly desirable if resources permit[7] (for example using the Bactec Myco/F Lytic bottle), as the technique has the potential to isolate bacteria, fungi and *Nocardia* as well as *Mycobacterium tuberculosis* and *M. avium* complex. However, the yield from urine culture in the context of advanced HIV can be as good as mycobacterial blood culture, and is less expensive.[6] If a blood or urine culture is requested the laboratory should be asked to use standard tuberculosis culture techniques for up to 6 weeks and to discuss all positive cultures with the clinician as 'contaminants' may be significant. The cryptococcal latex agglutination test performed on serum or cerebrospinal fluid rapidly confirms the diagnosis of *Cryptococcus neoformans* infection. Bone marrow biopsy is appropriate if a full blood count reveals bicytopenia or pancytopenia[8] and liver biopsy is appropriate if the cannalicular enzymes (ALP and GGT) are elevated. Biopsy of enlarged peripheral lymph nodes using either fine-needle aspiration or needle core can be helpful.[9] Biopsy specimens should be divided equally between normal saline for culture and formalin for histology.

It may be necessary to commence antituberculosis therapy without a definitive diagnosis being made. If this route is chosen a focal disease process compatible with tuberculosis must have been clearly identified and every effort should be made to send mycobacterial cultures before commencing therapy. Should the patient not show an objective response to therapy by 8 weeks an alternative diagnosis should be sought.[6]

The case study illustrates the propensity of ART-induced immune reconstitution to provoke diseases mediated by viral infections. Shingles (varicella zoster virus), condyloma accuminata (human papillomavirus), hepatitis due to the hepatitis B virus, and Kaposi's sarcoma (human herpes virus 8) can flare up in the months following successful initiation of ART.[10-12] In HIV-infected patients non-Hodgkin's lymphoma is closely associated with the Epstein-Barr virus and diagnosis shortly after ART has been initiated has been described.[13] Lymphoma-related B symptoms may have contributed to the patient's weight loss and fever. The management of HIV-associated malignancies differs from that of opportunistic infections as ART should be initiated as soon as the diagnosis is made in order to allow significant immune recovery before chemotherapy is started.

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ETHICS

MEDICAL ETHICS AND THE POLITICS OF THE SOUTH AFRICAN HIV/AIDS EPIDEMIC

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'Who among us shall dwell with the devouring fire? Who among us shall dwell with everlasting burnings?' He who walks righteously and speaks uprightly. He who despises the gain of oppression, who gestures with his hands refusing bribes. Who stops his ears from hearing of bloodshed and shuts his eyes from seeing evil.'[1]

Politics has been defined as the 'art and science of government' and ethics as 'moral principles, the science of morals in human conduct, rules of conduct'.[2, 3] The reader would know politics by its public face – its leaders, their words, their actions: 'levelling the playing fields', 'quiet diplomacy', 'kill the farmer, kill the boer', 'shifting the goal posts', 'redressing the imbalances', 'playing the race card'. Ethical issues in health are familiar too: triaging survivors, prioritising limited budgets, maintaining confidentiality, obtaining informed consent, deciding upon ventilator/dialysis access, euthanasia and embryo research. Making choices has never been easy.

Writing from prison in 1945, Bonhoeffer commented upon ethics: 'Rarely has any generation shown so little interest in any kind of theoretical or systematic ethics. Our period of history is oppressed by an abundance of ethical problems. Today, there are once more villains and saints. These emerge from the primeval depths to open the infernal or divine abyss and allow us to see briefly into mysteries of which we had never dreamed. What is worse than doing evil is being evil. It is worse for a liar to tell the truth than for a lover of the truth to lie. A falling away is of infinitely greater weight than a falling down. One is distressed by the failure of *reasonable* people to perceive the depths of evil or the depths of the holy. With the best of intentions they believe that a little reason will clamp together the parting timbers of their house...'[4]

Twelve years have passed since the establishment of South Africa's new democracy. Over this period the country's HIV prevalence has grown from 3% to 11 - 17%. Maternal prevalence rates and those of several provinces are higher.[5, 6] A recent report detailing the HIV prevalence among 17 088 South African teachers indicated that 12.7% were infected and that 52% of these had CD4 cell counts below 350 µl and 22% counts below 200/µl.[7] Most governments are ill prepared to cope with disasters of the magnitude of the AIDS epidemic. The new South African government has fortunately enjoyed the support of the international community and has had two decades of scientific knowledge upon which to draw. With fewer resources, Uganda reduced HIV prevalence from over 20% in 1993 to 5 - 8% currently. Thailand, like South Africa a 'middle-income' country, has maintained its 3% prevalence over the same period.[8-10] Despite the goodwill of scientists locally and abroad, the South African government has frequently chosen to follow an independent route with regard to public discussion and the management of the epidemic.

Dissidents who dispute the science of HIV have openly advised government and continue to do so.[11, 12] Mr Mbeki has at times based his remarks upon insights from the Internet, a source of unregulated data, opinion and bias.[12,13] Cabinet advocacy for the play 'Sarafina II' and the so-called AIDS cure, virodene, was premature and inappropriate: 'Instead of emerging victorious with a new African miracle cure, the government's reputation was harmed by the strong aroma of sleaze which permeated the virodene episode and by the fact that it ignored scientific checks and balances. Instead of accepting the recommendations of the Medicines Control Council (MCC), the government undermined the body by removing the chairperson and replacing him and others with more compliant members.'[13]

Herbs, vegetables, so-called 'immune boosters', various 'diets' and vitamin concoctions have been advanced as benefiting the infected.[14, 15] Evidence-based support for these assertions is largely absent, anecdotal, speculative or simply misinformation. Scientific data promoting the use of vitamins and trace elements in the HIV patient is limited. Where deemed to be indicated, vitamins and trace elements are not viewed as alternatives to the antiretroviral (ARV) drugs.[16, 17] Nutritionists and researchers agree that patients require access to healthy diets, and that where nutrition is needed this ought to be provided in the form of food.[18, 19] Support by public figures of homespun 'remedies' has led to general confusion and in some cases to patients refusing life-saving therapy with consequent loss of life.[20]

ETHICS IN THE CONTEXT OF GOVERNMENT

Moral principles should govern behaviour in government and in health care. We use ethical language when addressing political and health matters: '*primum non nocere*' (first do no harm), autonomy, beneficence, non-maleficence, justice and futility, and we contrast altruism with self-interest. The application of these ideas to society underlies the day-to-day running of government: utilitarianism – 'the greatest happiness of the greatest number' (Jeremy Bentham, 1748-1832), human rights (individual v. community rights), communitarianism – the building of a good and just society.[38, 39]

The ANC government of 1994 inherited an imperfect health care system.[30] Regional health has deteriorated for years: life expectancy in South Africa has fallen for the past 40 years and current levels are below those of 1960.[40] The AIDS epidemic has played a part in this, but one must also acknowledge the persistence of poverty, inadequate education, poor rural and urban living conditions and the fractured health infrastructure that grew out of the apartheid system. 'History', says Roberts, 'has many examples of people who sought to impose their vision of a good society by force – from the Crusades to the Khymer Rouge to the Taliban. Moving from coercion to coexistence, tolerance, and mutual learning requires a degree of openness that many find inconsistent with the certainty of their own vision.'[38]

DO GOVERNMENTS HARM THE HEALTH OF THEIR CITIZENS?

Sadly, many do. Living in South Africa before 1994 ensured unequal access to health care. We live with this legacy. 'The Nazi doctors made hell', is Elie Wiesel's commentary on life in Europe during the 1930s and 1940s.[41] Lenin wrote of 'purging the Russian soil of all kinds of harmful insects.'[42] Mao, according to the authors of a recent biography, 'was responsible for well over 70 million deaths in peacetime'.[43] Zimbabwe: 'its ambulance fleet includes *nine ox-drawn carts*, introduced in July (2004) as part of the struggle against climbing maternal mortality rates. Life expectancy at birth – according to the UNDP Human Development Report for 2004, is 33.9 years.'[44] South Africa: 'Between 1995 and 2000 the public health sector in the Western Cape was downsized by 3 601 hospital beds (24.4%) and by 9 282 health and support personnel (27.9%), while the local population grew by 8%.' Benatar continues, 'Public tertiary health services have been severely eroded... The failure of the (South African) government to promote a prevention campaign over the past decade and an initial focus on ineffective treatments have contributed to sustained and pervasive denial of the existence of the HIV pandemic as well as perpetuation of the stigma associated with HIV and AIDS.'[30]

Politicians are salaried public servants and are answerable to the community they serve. Our government has been re-elected twice and tasked with the provision of equable care to all its citizens – including those who carry the HI virus. 'Unemployment insurance, old age pensions, workmen's liability acts and other similar legislation represent the effort of political society to mitigate the inequalities which are created by the process of economic development ... The economic system heaps up profits in the hands of the owners of property and the state uses the power of taxation to reduce these profits and to assist the worker...'[45] But as Niebuhr observes, even democratically elected governments have their own agendas: 'The creeds and institutions of democracy have never become fully divorced from the special interests of the commercial classes who conceived and developed them.'[46] 1994 ushered into power those who were once the objects of the abuse of power. Has such a perspective resulted in better government? Is the altruism demanded of the newly qualified health worker who is obliged to complete community service matched by a similar altruism of the politician? How ought the South African public to view 'floor-crossing', the failure of municipalities to deliver basic services, unspent budgets, scandals – 'armsgate', 'oilgate', 'travelgate'? Is this altruism or self-service?

Who audits government? Where political opposition is weak most governments are left to audit themselves. 'The moral attitudes of the dominant and privileged classes are characterized by self-deception and hypocrisy... The most common form of hypocrisy among the privileged classes is to assume that their privileges are the just payments with which society rewards specially useful and meritorious functions.'[47] Governments and most human beings lack the moral clarity to judge themselves without bias.

WHAT OF THE HEALTH WORKERS THEMSELVES?

A recent review of nursing care in two Eastern Cape hospitals reported serious irregularities. The nurses and doctors had been trained in the management of severe malnutrition in children. Their performance was studied from April 2000 to April 2001. The authors comment: 'Despite the shortcomings in care, most aspects of the World Health Organization (WHO) guidelines were feasible, even with scarce resources ... The researchers visited each hospital about 6 times per month. Visits were unannounced and unobtrusive. A high proportion of deaths were due to doctor error ... but weaknesses in support and supervision from local and central management gave rise to a lax environment, exemplified by nurses fabricating pulse and respiration rates and some night nurses giving antibiotics hours ahead of schedule.'[48]

The training of health workers is not enough to ensure good medical care. Researchers note that 'for decades it was assumed that poor performance was due to a lack of knowledge and skill. The use of oral rehydration salts greatly increased during the 1980s and 1990s. However after more than 2 000 training courses on the management of diarrhoea and the provision of supervision from 1988-93 in more than 120 countries, the median percentage of children *correctly* rehydrated by health workers as assessed in 22 surveys, was only 20%.'[49] These researchers draw the conclusion that poor

health worker practices contribute to the low use of health facilities by vulnerable populations. Among reasons cited by poor Kenyans for failure to access health facilities were 'lack of money' and 'the belief that hospital staff have insufficient understanding of and tolerance for the patient's social and economic circumstances and language, and that facilities and drugs might be inadequate to assist their sick child.[50]

This perception seems to be held by the South African public too: 'Ms *N.M.* had been at the Helen Joseph Hospital in Johannesburg, since 6.30am. She had resigned herself to spending the day at the hospital. "I travel from Soweto to come here and get my pills because the service is better than at Baragwanath. There, the nurses scold us and will not help you if you don't have money to pay. The nurses go out for lunch and tea breaks, leaving us sitting here and when they come back they shout at us. I don't know why. And there is nothing we can do because we are poor."'[51] The South African Minister of Health after a recent visit to Chris Hani Baragwanath Hospital is quoted as saying, 'judging by what I have seen, I would not encourage people to use public health facilities.'[52]

WHAT OUGHT TO BE DONE?

What ought to be done to respond to the ethical and political issues surrounding the provision of care to the HIV-infected community of South Africa?

ACTIVISM

AIDS activism in North America and Europe resulted in an expanded access to ARVs, price reduction and the promotion of research: 'Decisions about the allocation of resources are inherently political and are thus amenable to effective lobbying'.[53] Locally, the Treatment Action Campaign has garnered support from city and township dwellers and rural communities. In so doing it has become a legitimate voice of the people.[54, 55] How might the ordinary health worker respond to perceived inadequacies or injustice? Withholding their vote or voting for an alternative party, drafting and supporting petitions, joining NGOs and activist groups or forming new groups – it was particularly the mass movements of the 1980s that led to the demise of the apartheid regime. There are issues that need to be addressed: speeding the process of new drug registration, enhancing access of indigent patients to ARVs, addressing the low morale of health workers in ARV rollout programmes, assisting in projects that aim to build the numbers and competency of staff employed in rollout centres. Those health care facilities that persist in rendering inadequate service must be identified and pressured to change. Corrupt health workers and disinterested officials must be weeded out of the system. The promises of government and local authorities must be matched by performance. Allocated budgets must be spent. Concerned bodies such as the HIV Clinicians Society might consider closer links with activist groups and networking with the Trade Union Movement and with grassroots communities across the country.

DEALING WITH DENIAL

Preventive strategies were defined decades ago. Universally acceptable treatment guidelines have been in the public domain for many years. Yet both transmission and mortality continue to increase. Denial has fed this situation. 'AIDS is here to stay. It is like the day after Hiroshima (or after 9/11!). The world has changed and will never be the same again. The new virus will be a fact of life for our children's children; much can be done to moderate its force, but it cannot be made to disappear.'[56] Asked about the value of garlic, olive oil, etc., the health minister commented, 'no one said these diets cure HIV. However they boost the immune system. I have met over 100 patients who 'got-up-and-walked' after following this dietary advice.'[57, 20] A truthful understanding of the epidemic has been scuttled by a belief in non-science, folklore and dissident opinions. Where truth is muddied and denied, society will not find solutions to the epidemic. Has this denial been deliberate? Do the politicians really believe what they say? Are politicians able to envision alternatives to the situations they are tasked to deal with? Can they work outside the box of their own value system and world view? 'It is the vocation of the prophet to keep alive the ministry of imagination, to keep on conjuring and proposing alternative futures.'[58] Few would credit the religious community of our day as having the status to provide such leadership. Prophets appear largely to have passed into the realm of antiquity and obscurity. Nevertheless we need them. 'Any justice which is only justice soon degenerates into something less than justice. It must be saved by something which is more than justice. The realistic wisdom of the statesman is reduced to foolishness if it is not under the influence of the moral seer.'[59] Politicians need ethics and the ethical scholar to guide them. Opposition to apartheid drew strength from tough religious people and those communities that refused to accept the status quo. We need such people today. The issue of denial needs to be faced both at the level of government and by the community. Infection with the HIV virus is perceived as shameful and evokes disgust, revulsion and rejection by many in the community. Exposure in the early days of the epidemic led to censure, harassment and in some cases the death of the infected person.[60] Only openness and honesty will deal with these inappropriate attitudes. Several political leaders have spoken of their sorrow concerning the loss of family members from this disease. But those who are themselves infected and enjoy prominence within our society need to become role models for society: seen to be taking medication, living well, dealing with life in a humble but challenging manner. We lack these heroes.

WHY DO GOVERNMENTS FAIL TO CONFRONT AIDS ADEQUATELY?

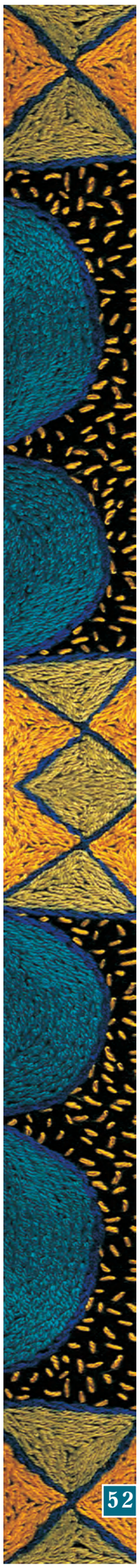
Sexual transmission is the dominant vehicle of spread in Africa. 'Safe sex' means abstinence, or being persistently faithful to one's spouse/partner, and using condoms to prevent exposure to body fluids. A core responsibility of government is to ensure that those most likely to spread disease adopt preventive behaviour.[61] Recent data suggest that some young people influenced by the 'loveLife' campaign

may be altering lifestyles. However, there is little evidence that viral transmission in the southern African region as a whole is diminishing. Can a nation or a continent change its culture? At the core of this epidemic is the vulnerability of our youth, particularly adolescent girls between the ages of 15 and 19 years. The HIV prevalence among this group far outnumbers that of boys of the same age. Older males transmit the virus to these teenagers. This culture of abuse clearly needs to change.[62, 63] But some customs are part of everyday life in Africa: long engagement periods necessitated by inflated bride prices, premarital sex to confirm fertility, conjugal rights of widows to males within the extended family or tribe. To these add poverty and sex for money, poor acceptability of condoms, single-parent homes, fathers and husbands who work long distances from their families and seldom return home. If this epidemic will be heard, it is saying that society has to change in significant ways. This perhaps is the central 'meaning' of this epidemic. What politician has shown any determination to confront this Goliath? 'The man with a conscience fights a lonely battle against overwhelming forces of inescapable situations which demand decisions. Evil comes upon him in countless respectable and seductive guises so that his conscience becomes timid and unsure of itself, till in the end he is satisfied if instead of a clear conscience he has a salved one, and lies to his own conscience in order to avoid despair. A man whose only support is his conscience can never understand that a bad conscience may be healthier and stronger than a conscience which is deceived.'[64] Ron Bayer: 'There are no simple answers that address the needs both for trust and candor in intimate relationships and for security in the era of AIDS. Systematic behavioral research is essential, as is searching inquiry into the ethical and psychological underpinnings of intimate relationships. Nonetheless, these questions make it clear that matters of sexual ethics are not moralistic diversions. They are at the heart of AIDS prevention.'[65]

Case isolation, quarantine, contact identification, notification and the provision of treatment underpin the effective public health response to a serious communicable disease.[8] With regard to the prevention of HIV, South Africa took its lead from Europe and North America where so-called HIV 'exceptionalism' had taken root.[66] Notification and identification were deemed to be an infringement of the individual's rights and likely to drive the epidemic underground. Perhaps the memory of the 'Pass Laws' and the abuse of personal freedom prompted this position, or the fact that in its earliest days the South African epidemic was focused on the white, middle-class gay community and thus not unlike that of Europe and the USA. Without notification, the South African government has been able to query prevalence data and contradict research findings.[67, 68] 'Governments', say Ainsworth and Teokul, 'will do those things that are not viewed as controversial and that can be expected to have widespread support.'[61] Would the 'public health' model of disease prevention be appropriate to South Africa? Can a government police its entire population? Cuba's approach has been dramatically successful: the HIV prevalence in Cuba is currently 0.03%, only 4 000 infected in a population of more than 13 million.[69, 70] It took a traditional public health approach incorporating isolation, quarantine and notification of exposed partners. How would one quarantine 6 million infected South Africans?

Is it not time to end this HIV exceptionalism? Several experts suggest that it may be.[8,66,71] De Kock argues for performing mandatory, voluntary and routine testing and testing where patients present with specific HIV-related illnesses such as TB and sexually transmitted diseases (STDs). It is stressed that such testing must be done in an open manner while maintaining strict confidentiality. In support of this approach he argues, 'What if the HIV prevalence were 30% in Geneva or New York?'[8] He notes that AIDS awareness is now huge in most of sub-Saharan Africa and that evidence of benefit from extensive pre-test counselling for HIV in this region 'is lacking'. Other researchers remind their readers that the political costs of *promoting a public health approach* include 'offending both sides of the political establishment'. They continue, 'Controlling epidemics is a fundamental responsibility of government, working in concert with physicians, patients and communities. Until we implement prevention programs with proven efficacy more widely, make voluntary screening and linkage to care *a normal part of medical care and expand screening* in community settings, and improve treatment, risk reduction, monitoring, and partner notification, we will continue to miss opportunities to reduce the spread of HIV infection.'[71] While the South African government and society fail to address the underlying cultural and ethical issues that orbit around this epidemic there is little likelihood that we in South Africa will follow these recommendations.

What of the health worker whose conduct is unprofessional? How does one change the low morale of our nurses and doctors? Denial and disinformation – untruth – have perpetuated the spirit of futility that has characterized much of the government's response to this epidemic. Health workers, we are told, are 'burnt-out and demoralised'.[72] But the epidemic is not yet over. Indeed the virus is likely to remain with us for many generations. Arthur Frank speaks of the rebuilding of Czech society in the 1990s: 'Vaclav Havel realized that the success of any institutional reform in post-communist Czechoslovakia depended on individual moral work.'[73] The principles are no different in Africa. 'Individual moral work'. Ethics and the practice of health care are inseparable. Ethics and the practice of good governance are inseparable. The control of the epidemic with vaccines and various 'magic bullets' are unrealistic dreams at this time. A cure is not around the corner. Hard work and difficult choices lie ahead. Inadequacies in the prevention of transmission need to be reviewed. The debate over appropriate public health strategies requires further thought. Cultural mores and norms that do the nation a disservice must be openly debated and change embraced where appropriate. Clear-thinking leadership, truthfulness and humility on the part of our politicians and goodwill on the part of our scientists may help to bring the country out of the dark tunnel it is in. The



plundering of this nation's life will only be halted when citizens and government listen to the lessons the epidemic is teaching.

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