SOUTHERN AFRICAN
JOURNAL
OF HIV MEDICINE

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Cover: *The 'Future Fighters' are a group of youth advocates in Cape Town, South Africa, who recognise the need to be more actively involved in prevention options and strategies for youth. The name of the group is inspired by their parents' generation – their parents fought for justice and equality, but with the threat of HIV they see a need to fight for their futures. The cover collage includes photos of the group relaxing at a retreat camp in Hout Bay, taken by group co-ordinator Nosiphiwo Soka of the Desmond Tutu HIV Foundation. Other photographs in the issue show these and other adolescents engaging in advocacy work.*

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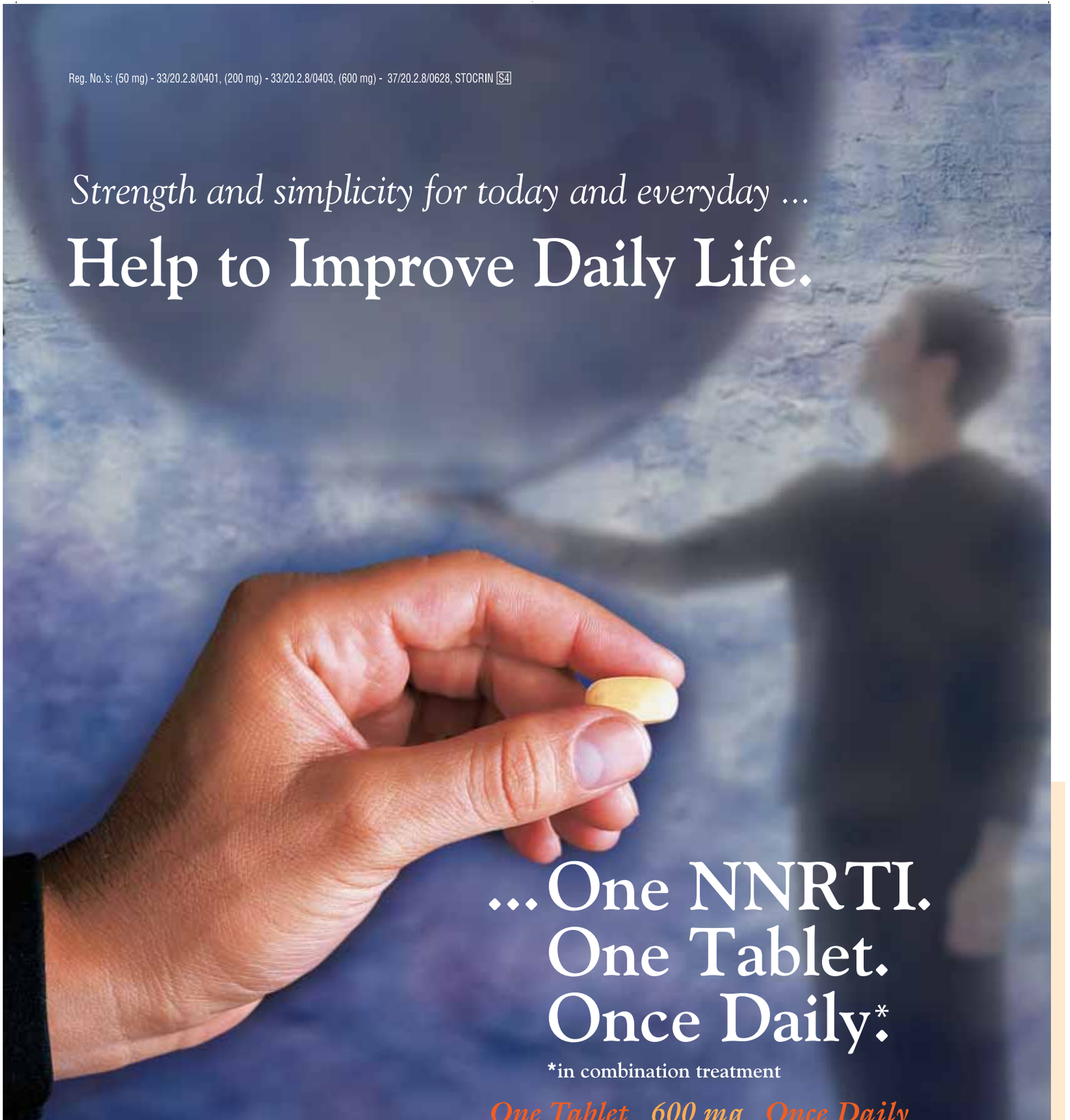

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FROM THE EDITOR

The *Journal* this quarter is, as usual, jam packed with relevant and valuable information. Among others, we have a description of the ethical and legal difficulties of involving adolescents in prevention research from Slack *et al*., a timely consideration as we assimilate the implications of the newly promulgated Child Bill and Sexual Offences Bill. Meyer-Rath gives a hard-to-ignore cost-effectiveness argument for rolling out treatment and prevention. Wanless and the Secure the Future group again highlight the good work being done by this charitable funding and the importance of community involvement. The Society President alludes to the excellent quality of information disseminated at the recently held South African HIV Conference. I was impressed at how practitioners and caregivers have progressed in terms of knowledge and understanding of the complexities of HIV care. In this issue we showcase a series of South African abstracts accepted and presented at the very competitive Conference on Retroviruses and Opportunistic Infections held earlier this year in Los Angeles. In each case we have asked the authors to describe the relevance and implications for the South African epidemic. In the next issue we will highlight presentations from the South African Conference, and include a summary of Wood's state-of-the-art review of diagnostics for tuberculosis at a symposium hosted by Roche at this conference. Finally, as has become our tradition, we have guidelines for you in the centre pages. In this edition, Spencer and the Nutrition Focus Group have outlined the first two chapters of the nutritional guidelines – more to follow. In addition, Venter has summarised the National Strategic Plan and the exciting partnership between the Clinicians Society and Soul City is described.

Well done to Francois and the team who have also recently launched the new and exciting website. We are working hard to have articles from this journal online as soon as possible after the distribution of the hard copy. Finally, we are happy to announce that articles can now be submitted to the journal online: go to www.sajhivmed.org.za and follow the instructions. You will be able to track the progress of your submission and we will be able to more efficiently keep track of all the incoming copy. Please get writing!

LINDA-GAIL BEKKER

Editor

MESSAGE FROM THE EXECUTIVE

The South African AIDS Conference has just finished as I'm writing this, amidst a new dawn for the rejuvenated South African National AIDS Council, the release of the ambitious National Strategic Plan, and a provocative World Health Organization document on provider-initiated HIV testing. The Conference, held every 2 years, had a very strong scientific programme with some excellent presentations. The Society had a strong presence, and we ran several highly successful skills workshops during the Conference as well as a hugely entertaining debate on circumcision. We were delighted that sponsorship from Cipla-Medpro enabled us to send a large number of rural doctors to the Conference, and hope that we can continue to support attendance in this way. I would like to congratulate Linda-Gail Bekker for two reasons – she is our new *Journal* editor, and she will be chair of the Conference in 2009. Moreover, her home town, Cape Town, will host the prestigious 2009 International AIDS Society Conference. Add to this the highly anticipated Botswana AIDS Conference next year, and no one need leave our shores in the near future to access the best scientific presentations and debates.

FRANCOIS VENTER

President

Fatima Hassan of the AIDS Law Project and Francois Venter of the Society get tested at New Start, after debating provider-initiated HIV testing at the 3rd South African AIDS Conference.

Olive Shisana, head of the Human Sciences Research Council, takes an HIV test at the 3rd South African AIDS Conference as part of the Sunday Times *campaign to get more people to do an HIV test.*

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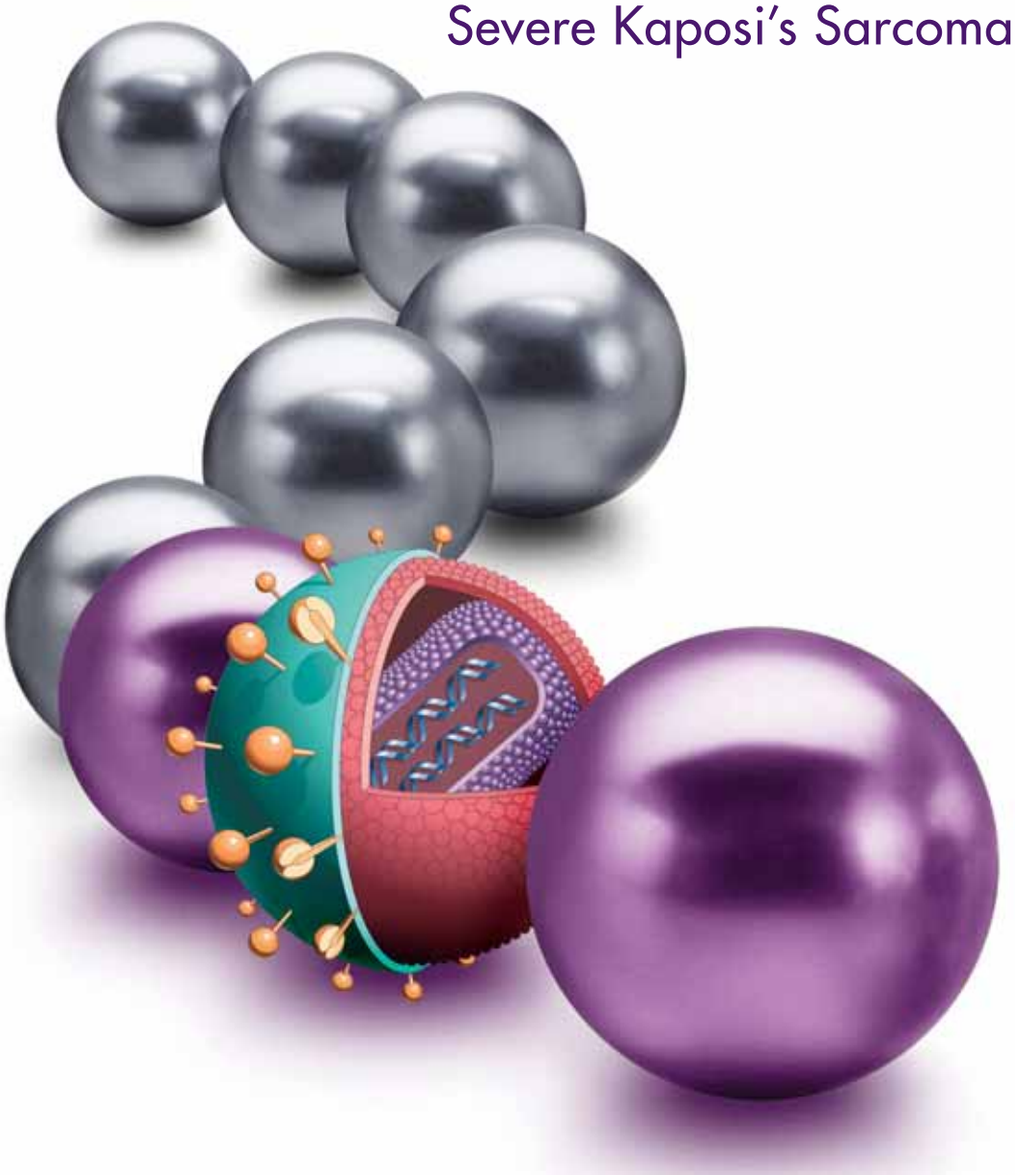

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DES MARTIN – A TRIBUTE

Professor Des Martin was the visionary who in 1998 saw a need and pulled together a group of HIV specialists who became the founder members of the HIV Clinicians Society of South Africa. It has become the largest interest group of the South African Medical Association and now has branches throughout the SADC region. This phenomenal growth is a tribute to Des's extraordinary ability to inspire and challenge others to take up the cudgels and fight the good fight. The mushrooming number of branches in other countries in this region also speaks to Des's passion for Africa and his deep-seated commitment to see capacity grow throughout the continent. He has personally visited most of these branches at their inaugural meetings and then singlehandedly nurtured them to independence. Many branches now provide some of the most critical support and continuing medical education to HIV doctors in their areas.

Des is no stranger to hard work. Born and bred in Johannesburg, educated at Wits, he started his career as a general practitioner first in Johannesburg but then moving to the 'Eastern Transvaal' where he became a household name among the farmers and townspeople of the Nelspruit area. He devoted 20 years to general practice before heeding the call to academia and returning to Wits to specialise in clinical virology. Subsequently Des has held pivotal posts in the National Institute of Virology and national pathology structures. He is currently a consultant virologist at Toga Laboratories, and a senior member of the Departments of Virology at Wits and the University of Pretoria.

Des launched the *Southern African Journal of HIV Medicine* as president of the Society in August 2000. From the first distinctive edition with its bold design and eye-catching colour the journal has gone from strength to strength. Remarkably, Des has involved world-renowned HIV specialists on the editorial board and forged important and strategic partnerships with a wide range of people, institutions, funders and organisations.

Des has a wonderful ability to spot talent, especially in younger members, and has framed the careers of many who now play important roles in South African HIV and virology. Encouraged by Des, Francois Venter took over the reins as president of the Society in 2005, and Linda-Gail Bekker stepped into his shoes as editor just in the last two months. Des is a hard act to follow. He describes himself as a 'fence sitter', but in fact it is his masterful diplomacy and artful chairmanship of meetings, especially in the presence of strong personalities and opinions, that (together with an incorrigible sense of fun and outstanding sense of humour) have made him stand out as a statesman of note.

Des is a devoted family man, father to five grown children and some grandchildren, and loves nothing better than to spend time on the golf course, or at their holiday home in KwaZulu-Natal, with his talented wife Lori. He is a sportaholic who can be relied upon to know the score of most cricket and rugby matches while they are still being played.

Professor Des Martin, the Society and the editorial team salute you for all your years of commitment and service. We wish you well as you take a little more time for relaxation, but greatly appreciate your ongoing wisdom with so much still to be done in combating the HIV epidemic in South Africa.

LINDA-GAIL BEKKER

Editor

THE SOUTH AFRICAN NATIONAL STRATEGIC PLAN: WHAT DOES IT MEAN FOR OUR HEALTH SYSTEM?

W D Francois Venter, *FCP (SA)*
Reproductive Health and HIV Research Unit, Department of Medicine, University of the Witwatersrand

South Africa has a new and highly ambitious guiding document to comprehensively deal with HIV over the next 5 years, the National Strategic Plan (NSP)[1] (Table I). The country has an HIV problem resulting in huge mortality and morbidity, with an associated tuberculosis crisis, a growing orphan population, and a range of well-documented adverse social and economic impacts.[2]

In 2000 the South African government, under siege internationally for its denialist President and combative Health Minister, hurriedly unveiled its 5-year programme for HIV. The plan was vague and committed the government to very little of substance, and its soft wording contrasted with the strong and clearly defined advocacy campaigns around prevention of mother-to-child transmission (PMTCT) and antiretroviral therapy (ART) provision, nutrition and unscientific supplements. In 2003, the release of the ART component of the Operational Plan for Comprehensive HIV and AIDS Care, Management, and Treatment resulted in the provision of antiretroviral treatment throughout the country over the next 4 years.[3]

The original Plan expired in 2005, but it was only when the absence of an updated version was highlighted in the media, that the Department of Health began responding by drawing up a new Plan. An initial very rough draft, released after some consultation with special interest groups in the middle of 2006, rapidly attracted civil society interest and mobilisation, as well as strong media interest.

PROCESS OF WRITING

The subsequent consultative process, ostensibly co-ordinated through the South African National Aids Council (SANAC) but in reality co-ordinated by health officials and key civil society members with some political guidance from SANAC, engaged in a laborious but highly participatory series of sectoral discussions, engaging labour, gender groups, traditional leaders, the disabled, business and academia, as well as many other sectors, including education and prisons. Ready access to e-mail meant a large number of submissions from a range of organisations and individuals were submitted electronically.

Interestingly, the process of writing was made significantly more complex by recognition that in several areas related to HIV – including poverty, housing and TB – there were existing government policy and targets, and the process of harmonising these with the new Plan was not always possible.

The writing of the final 159-page report was a consensus event by a few key individuals, and the final version was released at the time of writing, in June 2007.

STRUCTURE OF THE PLAN

The structure of the document broadly follows the original 2000 version, with four key areas:

- Prevention
- Treatment, care and support
- Research, monitoring, and surveillance
- Human rights and access to justice

TABLE I. PRIMARY AIMS OF THE NSP

The primary aims of the NSP are to:

- Reduce the rate of new HIV infections by 50% by 2011.
- Reduce the impact of HIV and AIDS on individuals, families, communities and society by expanding access to appropriate treatment, care and support to 80% of all HIV positive people and their families by 2011.

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The intention is that 'all government departments and sectors of civil society will use this plan as a basis to develop their own HIV and AIDS strategic and operational plans to achieve a focused, coherent, country-wide approach to fighting HIV and AIDS'.

An introduction and overview sketches the epidemic with all the usual sobering indicators, and has a sanitised description of the various conflicts over the last few years between government and sectors of society. The epidemiology descriptions are a useful summary of the evolution and current status of the epidemic, and the discussion on the drivers of transmission is necessarily cursory but frank. There is a section on the process of development of the Plan, and a description of the formal governmental political process that overviews the AIDS agenda.

The bulk of the document sketches targets in the four key areas, with objectives, interventions, timelines for implementation, and lead agencies. The final section details the significant cost projections, and some key implementation suggestions, including the establishment of district committees.

STRENGTHS OF THE PLAN

Undoubtedly, the strength of the plan relates to the setting of aggressive targets (see Table II). In the old Plan, provinces were left to set their own targets, often with no measure against local prevalence rates or population size. This led to a situation where some provinces, with very high prevalence, had set themselves low targets, which could easily be met. It also allowed for priority setting in the wrong areas, often because managers and policy makers lacked the skills to identify critical concerns. In some instances, politicians used this unfocused approach to follow an unscientific and denialist agenda, channelling resources to interventions that are not evidence based.

TABLE II. SELECTED TARGETS

Target	2007	2011
PEP for sexual assault survivors	30% coverage	90% coverage
% of pregnant women tested for HIV	70%	95%
% of HIV-positive women given PMTCT	60%	95%
Adult population tested annually	7%	25%
New adult initiates on ART	120 000	420 000
% adult initiates started on ART *outside* hospital setting	30%	70%
% adult initiates started by nurses on ART	10%	80%
% HIV exposed children screened by PCR	45%	90%
New child initiates on ART	17 000	40 000
% of TB patients screened for HIV	40%	90%

PEP = post-exposure prophylaxis; PCR = polymerase chain reaction.

South Africa has excellent epidemiological provincial data, and extrapolating these targets set by the new Plan down to a district level will not be difficult. Our unapologetically hard-nosed treasury has held government departments accountable for their budgets against outputs, and it would appear that local health departments will be pushed to achieve targets once they are given adequate funding.

The wide consultative process for the new Plan brings with it unprecedented support from a broad panel of stakeholders. The inclusion of experts from throughout the country has also meant that a variety of ideas were checked against current scientific consensus. The restructuring of the health care system will require creativity and patience from all stakeholders. The consultative process may allow for some of this patience.

There is a strong emphasis on monitoring and evaluation, and adequate and committed resources are suggested for this component. 'Core' indicators are currently being developed, with other measured priorities also reviewed regularly but less often. There is commitment to supporting research, mirrored by a consultative research colloquium at the time of the Plan's launch.

There is significant focus on the specific needs of women and children, as well as special groups such as sex workers. Testing strategies and the specific issues of pregnancy are recognised, with specific indicators measuring the impact of interventions in each group. Continuity of care is also stressed, and regular CD4 measurements for people not needing ART are one of the targets.

The budget for the plan was drawn up under difficult conditions, with many details of the Plan unclear or in the process of being written. However, the Treasury has allocated significant resources to the Health Department, and will no doubt allocate more if the Plan appears to be successful.

WHAT ARE THE CHALLENGES OF THE PLAN?

A more accurate title for the Plan would have been National Strategic Targets, as the Plan gives little guidance on implementation. This may be a necessary tactic to produce a final document, but does leave provinces in a similar position to before, with little guidance on how to implement multiple complex and integrated programmes.

There is no order of priorities within the Plan. This may also be a function of the consensus building process, as well as the fact that in some cases it may truly be difficult to prioritise (how does one weigh poverty reduction against treatment?), but again leaving it up to individual provincial interpretation may lead to key targets not being met. Achieving targets in one area may be seen as permission to underachieve in

another. The implementation process will require clear national leadership and active monitoring.

Multiple government departments are responsible for many of the targets. Achieving buy-in from non-health and social welfare departments has been notoriously difficult. SANAC, tasked with the multi-sectoral response, will have its work cut out to ensure adequate commitment of energy from departments that do not see HIV as their primary focus.

Prevention is a major part of the plan. To an HIV doctor, the ambitious and noble target of reducing infection rates by 50% is, on the face of it, something to be applauded. However, the interventions are disturbingly short on detail, especially considering that current prevention efforts are having little or any impact. Behavioural interventions listed are vague and contain little evidence base. Some of the language within the prevention section borders on rhetoric, and it is unclear why continuing with current approaches would make an impact, especially an impact as great as a halving of incidence. Mechanisms for measuring new infections, which is difficult, are unclear, although the regular HSRC survey, using BED assays, may be one solution.

The XDR outbreak of tuberculosis in Tugela Ferry has triggered a much-needed interrogation of South Africa's TB programme. The NSP attracted strong submissions suggesting that strengthening the TB programme should be integrated within the document. However, there was disagreement, and the position was taken that TB has its own programme that the NSP should support, rather than that the NSP should guide the TB programme. There has been criticism of this approach, especially as the prior separation of TB and HIV has compromised both programmes.

Finally, at the time of the release of the plan, 2007 was half over. The 2007 targets are modest 'stretch targets', and failure to achieve our initial aims would be very demoralising.

SO WHAT DOES THIS ALL MEAN FOR THE SOUTH AFRICAN HEALTH SYSTEM?

Taken individually, HIV testing, PMTCT and ART targets individually would each involve an enormous refocusing of health systems. The targets collectively are phenomenally ambitious, and references to 'stretch targets' peppered all the consultative meetings. However, a radical restructuring in the way that health care is delivered will be required to ensure delivery.

CONCLUSION

The targets throughout the plan are very ambitious. The prevention targets appear to be unrealistic without a more creative and aggressive approach to the issue of behaviour. However, the testing and treatment targets, and the strong commitment to a human rights agenda and societal mitigation and stigma reduction, allows for the planning process to continue on a provincial and local level with firm treatment goals in mind. Government will need all the help it can get, however, and it will be time for civil society, health care workers and policy makers to fully commit to the new Plan.

South Africa has a long history of producing policy papers that look good but fail to facilitate delivery due to lack of implementation. It must not happen with the National Strategic Plan.

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ETHICAL-LEGAL CHALLENGES IN ADOLESCENT HIV VACCINE TRIALS

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South Africa is likely to enrol adolescents into a phase IIb proof of concept HIV vaccine trial in late 2007 or early 2008, which would make it the first country in the world to enrol adolescents into HIV vaccine trials. These healthy adolescents will be at high risk of HIV infection. They will have to undergo a general physical examination, answer questions about their personal HIV risk, be administered an experimental HIV vaccine or placebo via injection, have blood drawn for laboratory safety and immunogenicity testing, and have regular testing for HIV infection.[1] Many ethical/legal complexities exist, in part due to our fluctuating ethical-legal framework, the lack of legal guidance on issues such as adolescent privacy rights in research, and differing approaches towards child antonomy in child care and health legislation that enable children of a certain age to consent independently to medical treatment but not to research.

Against this backdrop, in 2005 a member of the UCT Research Ethics Committee (REC) initiated a process of research into the minimum legal requirements that need to be met to ensure that adolescent HIV vaccine trials are lawful. As a result, a unique collaboration was established between an ethics and law research unit, (the HIV/AIDS Vaccines Ethics Group – HAVEG); members of the UCT REC, and researchers at the Desmond Tutu HIV Centre, Cape Town, and the Perinatal HIV Research Unit, Soweto. This collaboration resulted in the development of a roadmap of issues that ought to be addressed in order to promote the rights and welfare of adolescent participants in HIV vaccine trials, which was published in *Biomedical Central: Medical Ethics* in 2007.[1] From November 2006 onwards, work began to apply these legal principles to a protocol for an adolescent HIV vaccine trial and its accompanying informed consent/assent forms. This article summarises the issues identified by this unique and on-going collaboration, published in an earlier article.[1]

CONSENT CHALLENGES

No provision currently in operation sets out when children may provide their own independent consent to research. In the future, in terms of Section 71 of the National Health Act (NHA),[2] consent for research participation will have to be obtained from a parent or legal guardian until the age of majority is reached. Other caregivers or custodians will not have the authority to provide consent for child research. Until 30 June 2007 minority ended at the age of 21.[3] However, section 71 of the new Children's Act[4] was implemented on 1 July 2007 which lowered the age of majority to 18.

A further complexity is that the NHA provides that adolescents will consent with their parents if they have sufficient understanding. This means that researchers must anticipate how they will assess adolescent understanding to determine when adolescents possess the higher standard of competence required for consent.

Finally, in order for adolescent participation in these trials to be lawful in South Africa, common law requirements must be met, namely, consent to such research must be legally permissible or in line with public policy.[5] A key issue in making this determination is to establish if the research interventions pose acceptable standards of risk. Ethical guidelines in South Africa are approaching agreement on this issue – three out of four South African ethical guidelines[6-8] assert that when the intervention or research *does not* hold out the prospect of direct benefit, the risk must be 'minimal' or 'negligible' (i.e. the risks of daily life or routine medical and psychological tests), although a minor increase over such risk is allowed. However, draft regulations[9] are slightly more restrictive, i.e. they do not appear to permit non-beneficial research or interventions to exceed minimal risk, which is out of step with the majority of our guidelines. RECs will have to make complex assessments about whether vaccine trial interventions meet acceptable risk standards in terms of our national framework. In addition, enrolling over-16-year-olds in an efficacy trial requiring them to be sexually active would not be contrary to public policy, given that sex over the age of 16 is lawful.[10]

PRIVACY CHALLENGES

Adolescents in these trials will not consent independently to trial enrolment, but will be assisted by their parent or legal guardian. Accordingly, a number of complex privacy issues must be managed. These include whether adolescents will enjoy confidentiality regarding their HIV status, sexually transmitted infection (STI) results, pregnancy test results and sexual risk information. Unfortunately neither the current nor the future law deals directly with a child's right to privacy in research. The lack of legal guidance means that the general legal principles relating to privacy must be applied to a research context to fill this vacuum. These principles provide

that the right to privacy only extends to those aspects of a person's life that the person him- or herself, as well as society, recognises should be kept private.[11] This means that adolescents will have the right to privacy for STI results (for example) if it can be shown (*i*) that they would expect these results to be private, and (*ii*) that this is reasonable because they would have this right outside of the research context provided they were over the age of 14 and could consent independently to such tests. Consent forms will need to delineate the boundaries of adolescent privacy rights.

MANDATORY REPORTING CHALLENGES

South African children often live with high levels of violence, poverty and abuse. The law has responded by providing special protections for children who may be facing abuse, ill-treatment or neglect. The Child Care Act requires *medical practitioners*, among others, to report suspected ill-treatment, abuse or neglect of children to the Department of Social Development.[12] Failure to report is a criminal offence. Additionally, the Family Violence Act[13] states that *any person* who examines, treats, attends to, advises, instructs or cares for any child, and suspects that the child has been ill-treated, must report this to a Commissioner of Child Welfare, a social worker or the police. The future Children's Act[4] obliges *any person* to identify children in need of care and protection (e.g. living in a child-headed household, required to perform child labour, being maltreated, abused, or exploited) and to refer these to a social worker.[1] Site staff would have a legal duty to report abuse or ill-treatment disclosed by an adolescent in a trial. This means they would have to recognise when disclosures trigger a mandatory reporting response. Consent procedures will have to inform parents and adolescents about this limit to confidentiality.[1]

APPROVAL CHALLENGES

Approval challenges relate primarily to (*i*) the circumstances in which RECs would regard such trials as ethical, and (*ii*) the data that will be required by the Medicines Control Council (MCC) before approving such research. Regarding RECs, the NHA (Section 73) sets out the current legal obligations of RECs. It provides that RECs must approve research where it meets the ethical standards of the committee. RECs that will review adolescent HIV vaccine trial protocols will have to network with each other to build consensus about adolescent trials. In addition, they will have to debate their role in relation to establishing lawfulness, given that their primary brief is to ensure that protocols are ethical and they may already be burdened. In many cases, RECs that comply with the principles set out in ethical guidelines may be simultaneously abiding by legal values, and researchers who craft their protocols with thoughtful attention to ethical guidelines may meet most, if not all, of the legal requirements. Where the law is unclear, researchers should consult with their REC or get legal advice from a lawyer trained in research ethics and law.[1]

With regard to the MCC, in terms of the regulations on the control and conduct of clinical trials, all trials must be conducted in accordance with Good Clinical Practice guidelines.[14] The MCC has also prepared a set of guidelines for phase I trial applications.[15] However, they have not issued any guidance on adolescents. They should be requested to articulate the data they will require, *firstly* to allow adolescents into trials and *secondly* to license an adolescent vaccine.

Finally, if such trials are classed as 'non-therapeutic', when Section 71 of the NHA is implemented, 'non-therapeutic' research on minors may not be done without first obtaining consent from the Minister of Health. This requirement has a number of ambiguities, including which research falls into its scope, and its place in the sequence of approvals.[16] This detail is also not provided in the draft regulations.[9] South African researchers will have to anticipate the public policy assessment that the Minister will have to undertake by framing their protocols in a way that assists the Minister, or a delegated authority, to make a speedy determination. They can do this by explicitly addressing the four factors the Minister must consider in terms of the Act when deciding whether to authorise such trials.

CONCLUSIONS

This collaboration between researchers and law/ethics advisors has facilitated research into the minimum legal requirements for lawful research with adolescents, and consideration of how to apply these requirements in a way that facilitates research and protects participants' rights. It has identified that South African investigators and RECs will have to deal with: (*i*) consent challenges (e.g. who must consent? what can be consented to?); (*ii*) privacy challenges (determining the boundaries of adolescent privacy rights for STI, HIV and other test results); (*iii*) challenges around obligations to protect children from abuse and maltreatment (e.g. responding to disclosures by adolescents that they have been raped); and (*iv*) procedural challenges (e.g. need for guidance from the MCC and the impending 'Ministerial Consent' requirement). Additional networking, tool development and training processes are needed to make sound adolescent trials a reality.

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Approved Name and quantity: Didanosine capsules 250mg, Didanosine capsules 400mg. **Trade name:** Videx EC™. **Indication:** Videx EC™ should be used as part of or in combination with other antiretroviral agents for the palliative treatment of adults with advanced HIV infection. **Dosage:** Due to the reduced absorption in the presence of food, Videx EC™ should be taken on an empty stomach at least one hour before or two hours after a meal. Adults weight dependent >60kg 400mg once a day <60kg 250mg once a day. **Side effects, precautions, contra-indications:** Safety in pregnancy, lactation and children has not been established. Impaired hepatic function, diarrhoea, peripheral neurologic symptoms/neuropathy, rash/pruritis, abdominal pain, pancreatitis, nausea, vomiting, headache. **Warnings:** Fatal and non-fatal pancreatitis has occurred during therapy with didanosine used alone or in combination regimens in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression, lactic acidosis, liver failure, retinal/optic nerve changes. **Schedule, pharmaceutical classification:** S4 A20.2.8 Antiviral Agents. **Registration Number:** 36/20.2.8/0065/6. **Name and address of applicant:** Bristol-Myers Squibb (Pty) Ltd, 47 Van Buuren Road, Bedfordview, 2008. **Date:** December 2004.

Approved Name and quantity: Didanosine Tablets 25mg, Didanosine Tablets 50mg, Didanosine Tablets 100mg, Didanosine Tablets 150mg, Didanosine Paediatric Powder 2g. **Trade name:** Videx™. **Indication:** Videx™ should be used as part of or in combination with other antiretroviral agents for the palliative treatment of adult and paediatric patients (over 6 months of age) with advanced HIV infection. **Dosage:** *Adults:* weight dependent >60kg 200mg 12 hourly or 400mg once daily, <60kg 125mg 12 hourly or 250mg once daily. *Paediatrics:* according to body surface area 1,1 - 1,4m^2 100mg 12 hourly, 0,8 - 1,0m^2 75mg 12 hourly, 0,5 - 0,7m^2 50mg 12 hourly, ≤0,4m^2 25mg 12 hourly. **Side effects, precautions, contra-indications:** Safety in pregnancy, lactation and children under 6 months of age has not been established. **Warnings:** Fatal and non-fatal pancreatitis has occurred during therapy with Videx™ used alone or in combination regimens in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression. **Single exit price (excl VAT):** Didanosine Tablets 25mg R114.87, Didanosine Tablets 50mg R114.87, Didanosine Tablets 100mg R114.87, Didanosine Tablets 150mg 172.37, Didanosine Paediatric Powder 2g R114.87. **Schedule, pharmaceutical classification** S4 A20.2.8 Antiviral Agents. **Registration Number:** 27/20.2.8/40/41/42/43/45. Bristol-Myers Squibb (Pty) Ltd, 47 Van Buuren Road, Bedfordview, 2008. **Date:** December 2004

Approved Name and quantity: Stavudine 20mg capsule, Stavudine 30mg capsule, Stavudine 40mg capsule, Stavudine 1mg/ml powder for oral solution. **Trade name:** Zerit™. **Indication:** Zerit™ is indicated in combination with other antiretroviral agents, for the treatment of adults and children 6 months and older with HIV infection for whom zidovudine therapy is not or no longer appropriate. **Dosage:** *Adults*: weight dependent >60kg - 40mg every 12 hours, <60kg - 30mg every 12 hours. *Paediatrics:* (older than 6 months) <30kg - 1mg/kg every 12 hours, ≥30kg - <60kg - 30mg every 12 hours, >60kg 40mg every 12 hours. **Side effects, precautions, contra-indications:** Toxicity is dose-related and seen most frequently in subjects receiving >2mg/kg/day. Major clinical toxicity is peripheral neuropathy. **Warning:** Lactic acidosis, hepatic dysfunction, abnormal laboratory tests, diabetes mellitus, lactose intolerance and drug interactions with zidovudine. **Single exit price (excl VAT):** Stavudine 20mg capsule R37.83, Stavudine 30mg capsule R37.83, Stavudine 40mg capsule R37.83, Stavudine 1mg/ml powder for oral solution - R67.57. **Schedule, pharmaceutical classification** S4 A20.2.8 Antiviral Agents. **Registration Number:** 32/20.2.8/265/6/7/8. **Name and address of applicant:** Bristol-Myers Squibb (Pty) Ltd, 47 Van Buuren Road, Bedfordview, 2008. **Date:** December 2004

THE COST-EFFECTIVENESS OF HIV CONTROL: GETTING THE PRIORITIES RIGHT

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A growing body of international and local evidence shows that infectious disease control and HIV prevention and treatment are the most efficient ways for governments to spend their money to improve the lot of their citizens, in both developed and developing countries.

Apart from overwhelming mortality figures, economic arguments exist for keeping up, if not accelerating, the pace of antiretroviral therapy (ART) provision in South Africa and elsewhere. In June 2006, the Copenhagen Consensus re-emphasised the importance of HIV and infectious disease control. The authors called for its prioritisation ahead of a multitude of other worthy causes – based not on the need of people, but on the cost-effectiveness of interventions to remedy this plight.

The Copenhagen Consensus, set up in 2004 by the Danish environmentalist Bjorn Lomborg, works to answer a single question: What are the most cost-effective ways for a government to improve or save its citizens' lives? The novelty of this approach is to draw on experts, findings and methods from a large variety of scientific areas, while forcing a consolidation of results to a single common denominator for better comparison: the quality-adjusted life-year, or QALY.[1] For the first time interventions as diverse as combating climate change and combating malaria could be compared in respect of their outcome in a meaningful way.

The process lists 40 interventions tackling 10 areas of global concern (including communicable diseases, sanitation and water, education, malnutrition and hunger, subsidies and trade barriers, education, corruption, conflicts, and financial instability), which are being ranked in order of priority. In the first round in 2004, a group of academically acclaimed economists reviewed the papers summarising the evidence on each of these interventions and ranked them accordingly. Back then, HIV prevention and treatment was awarded the highest priority among the 40 interventions, being judged to be able to save the most lives at the lowest cost (Fig. 1).

Project rating		Challenge	Opportunity
Very good	1	Diseases	Control of HIV/AIDS
	2	Malnutrition	Providing micronutrients
	3	Subsidies and trade	Trade liberalisation
	4	Diseases	Control of malaria
Good	5	Malnutrition	Development of new agricultural technologies
	6	Sanitation and water	Small-scale water technology for livelihoods
	7	Sanitation and water	Community-managed water supply and sanitation
	8	Sanitation and water	Research on water productivity in food production
	9	Government	Lowering the cost of starting a new business
Fair	10	Migration	Lowering barriers to migration for skilled workers
	11	Malnutrition	Improving infant and child nutrition
	12	Malnutrition	Reducing the prevalence of low birth weight
	13	Diseases	Scaled-up basic health services
Bad	14	Migration	Guest worker programmes for the unskilled
	15	Climate	Optimal carbon tax
	16	Climate	The Kyoto Protocol
	17	Climate	Value-at-risk carbon tax

Fig. 1. Outcome of ranking exercise during the Copenhagen Consensus 2004 (for more information see www.copenhagenconsensus.com).

In June last year, the process was repeated as a ranking exercise among UN diplomats from China, India, Pakistan, Tanzania, Thailand, the USA, Vietnam and Zambia. In a slightly different take on the original task, the ambassadors listened to presentations from experts on each problem and were then confronted with the question: How would you spend

US$50 billion to make the world a better place? This time, scaling up basic health services was awarded top priority, with HIV control coming sixth (Fig. 2).

CHALLENGE	OPPORTUNITY
1 Communicable diseases	Scaled-up basic health services
2 Sanitation and water	Community-managed water supply and sanitation
3 Education	Physical expansion
4 Malnutrition and hunger	Improving infant and child nutrition
5 Malnutrition and hunger	Investment in technology in developing country agriculture
6 Communicable diseases	Control of HIV/AIDS
7 Communicable diseases	Control of malaria
8 Malnutrition and hunger	Reducing micronutrient deficiencies
9 Subsidies and trade barriers	Optimistic Doha: 50% liberalisation
10 Education	Improve quality/systemic reforms

Fig. 2. Outcome of ranking exercise during the Copenhagen Consensus 2006: a United Nations perspective (for more information see www.copenhagenconsensus.com).

The results of the Copenhagen Consensus process mirror the conclusion of the Commission for Macroeconomics and Health, set up by the World Health Organization in 2001, that 'as with the economic well-being of individual households, good population health is a critical input into poverty reduction, economic growth, and long-term economic development at the scale of whole societies'.[2]

As with every other science, many of the results of economic analyses, and the advice to policy-makers based on them, depend on having asked the right question, and pursuing answers with the right tools. The Copenhagen Consensus process, particularly in its second version, depends extensively on the quality of the evidence presented. In 2004 assessment of interventions against HIV and AIDS was based, in the absence of large-scale public sector ART programmes in low-income countries, on the hundredfold higher costs of programmes in industrialised countries at that time. Despite these much higher costs, ART was still highly recommended on the basis of cost-effectiveness alone.

From a large body of research in industrialised countries, and increasingly from non-industrialised ones, we know the reasons for the striking cost-effectiveness of ART: In delaying the onset of opportunistic infections and the costly hospitalisations they necessitate, ART defers resource use and costs for the health system and adds not only length but also quality to a patient's life.[3-5] In a cost-effectiveness analysis that takes all three factors into account (costs, life expectancy and quality of life), these benefits are large enough to offset the additional costs of the drugs, and of the systems that have to be put in place to reliably provide them.

A number of local economic analyses and modelling exercises has shown that this cost-effectiveness can be achieved in South Africa as well. One of these used data on costs and outcomes of ART provision at the MSF-led HIV clinics in Khayelitsha, showing that in this setting providing ART was more cost-effective than HIV care without ART.[6] MSF (Médecins Sans Frontières) is a non-governmental organisation dedicated to improving health care and access to essential medicines in emergency and low-income settings. Providing ART in this setting cost R13.754 per QALY versus R14.189 per QALY for patients who did not receive ART, in 2002 South African rands.

An analysis of ART provision in a standard public-sector clinic would probably yield even more favourable results, as the staffing levels at Khayelitsha are higher than in a public sector clinic, and ARV drug costs were significantly higher at the time of the study. Overall, there is a scarcity of economic analyses of ART provision in low-income settings that use data from real-world settings to analyse cost factors and advise on the efficiency of public sector roll-out programmes.

In South Africa, despite the significant political progress of the last few months and the latest figures for patients initiated on ART showing that South Africa has the largest ART programme in the world in terms of absolute numbers, there remains a need for massive upscaling of ART provision This will continue for quite some time – a time in which the deadly toll from AIDS is set to continue to rise.

It is high time for governments to invest accordingly. Governments in southern Africa need to support the enormous task of providing HIV care financially and politically. The hierarchy of cost-effective interventions noted by the Copenhagen Consensus can guide governments towards effective spending across all sectors, not just health. For South Africa this means maintaining the collaborative spirit shown in setting up the Inter-Ministerial Working Committee on HIV and AIDS and revamping the South African AIDS Council, while continuing to support the efforts of health-care professionals and volunteers who refuse to be intimidated by the enormous scale of the task. After all, a cost-effective medical intervention offers the best of two worlds, saving lives as well as money.

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SECURE THE FUTURE: SEVEN STEPS TO INVOLVE THE COMMUNITY IN HIV/AIDS TREATMENT SUPPORT PROGRAMMES

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In this issue of the *Southern African Journal of HIV Medicine,* Secure the Future is pleased to present in CD form the manual, *Seven Steps to Involve the Community in HIV/AIDS Treatment Support Programmes.* The manual is the product of 4 years of intensive work on the implementation of a programme of community-based treatment support for patients with HIV/AIDS. Its overall purpose is to guide any group in how to integrate medical care with the power of community mobilisation and community services provided to patients in their homes and communities.

In 1999, Bristol-Myers Squibb Company and Bristol-Myers Squibb Foundation launched a programme called *Secure the Future* (*STF*) to support the development and evaluation of cost-effective, sustainable and replicable models for providing care and support for people living with HIV/AIDS (PLWHA) in Africa. The programme was first launched in southern Africa (Botswana, Lesotho, Swaziland, Namibia and South Africa), and by 2004 had expanded to East and West Africa (Burkina Faso, Cote D'Ivoire, Mali, Senegal, Uganda and Malawi).

During the first 3 years of the STF programme, funding was provided to more than 160 projects addressing critical areas of need in community outreach and education and medical research. This phase of broad-based grant making put resources directly into the hands of small, community-based organisations that were the 'first responders' to the HIV/AIDS crisis and created innovative models of care. The programme also supported African researchers who studied the development of low-cost diagnostic and disease monitoring tools and conducted trials on locally relevant topics such as diagnosis of smear-negative tuberculosis (TB) and the efficacy of prevention of mother-to-child transmission (PMTCT) medication given to the newborn infant only, in cases when the mother presented at the hospital after delivery.

By 2002, the international community and many national governments in sub-Saharan Africa began working towards providing free antiretroviral therapy (ART) to the HIV-infected population. At its biannual meeting in April 2002, the Technical Advisory Committee endorsed the recommendation of STF staff that the programme redefine its role and join this effort.

In the following months, STF staff consulted extensively with national governments in southern Africa on challenges and gaps in rolling out ART. A commonly raised issue related to roll-out to remote communities where health care infrastructure, capacity and other resources were limited. Many regarded these communities as too challenged by poverty, lack of healthcare infrastructure and healthcare worker capacity, lack of food security, unemployment, and high levels of stigma to establish and sustain long-term efficacious treatment. There was not only concern about how to guarantee equity in ART roll-out, but also the need for innovative models and comprehensive actions to make sure ART could also be provided in poor communities. Using these consultations and drawing on lessons from the grants made in the first 3 years of the programme, the Community-Based Treatment Support (CBTS) Programme model was developed.

The CBTS model (Fig. 1) emphasises that PLWHA in resource-limited settings need both clinical services and community services to effectively enhance their quality of life and outcomes. The model also places equal emphasis on supporting the needs of PLWHA receiving ART and patients whose disease has not yet progressed to the need for treatment.

The model, therefore, employs supportive services like nutrition support and home-based care to help PLWHA manage their chronic HIV disease outside the clinic and in their homes and communities. The model leverages the strengths of government, private sector and community-based organisations to offer a true continuum of care, or as STF refers to it, '23$^1/_2$ hours' of disease management and psychosocial support that takes place in the patient's home and community following a 'half hour' of medical care in the clinic.

The resulting STF programme was launched at five sites in southern Africa, chosen after consultation with the respective governments. And the effectiveness of the CBTS model has been demonstrated by a 3-year operational research study conducted at the five sites: namely Katima-Mulilo in Namibia, Bobonong in Botswana, Maseru in Lesotho, Mbabane in Swaziland and Ladysmith in South Africa.

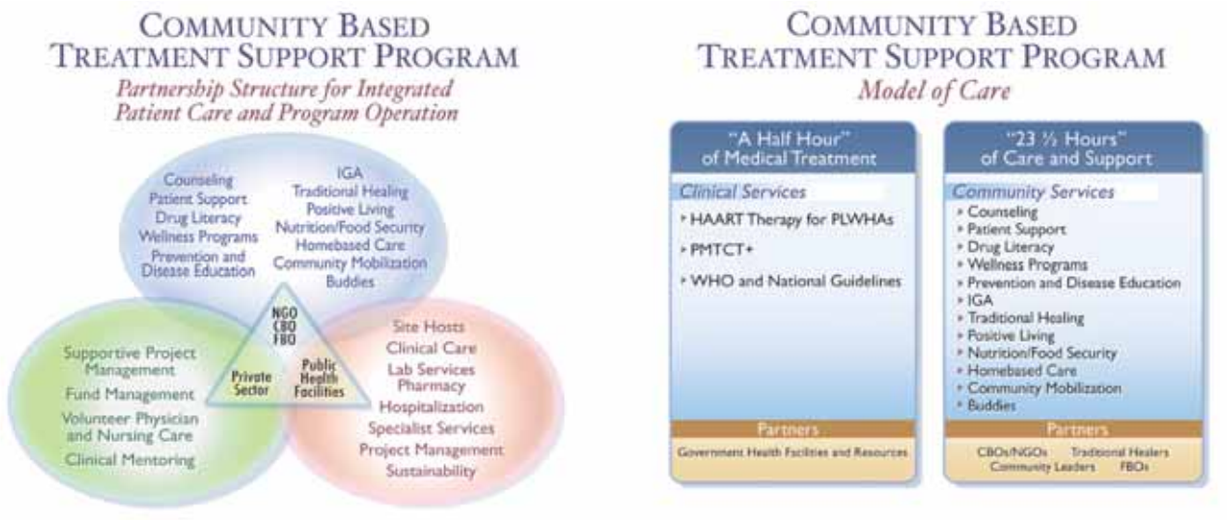

Fig. 1. Community-based treatment support model of care.

Clinical outcomes and the added value of community support were evaluated by rigorous collection of data according to protocols developed by BMS and Family Health International. Full details of the methodology and analysis are to be found in the manual itself, but the following is a summary of key findings.

- Increased voluntary counselling and testing and clinical uptake. Overall, the uptake of VCT increased approximately 10-fold within 2 - 3 months from the start of community mobilisation. Uptake of clinic services mirrored this. By November 2006, more than 16 000 patients had been enrolled
- Excellent adherence. At 12 months, 84.5% of patients were still more than 95% adherent.
- The added value of community support:
  - CD4 counts increased significantly more and to significantly higher levels in patients on ARVs who accessed community support than those who did not: from median values of 129 and 127 to medians of 326 and 268 respectively.
  - Patients satisfied with the level of community support they received also experienced better quality of life and adhered better to their ARV medication than those who were not satisfied.
  - Food security and home-based care were the two services statistically related to better adherence.
  - The lost-to-follow-up rate in STF CBTS programmes was only 5.1%. In Swaziland's PMTCT programme, all 224 women and their babies were accounted for up until 12 months of the child's age, thanks to community workers who intensively tracked defaulters.
  - Community services helped prepare patients for ART and 'levelled the playing field' by dealing with psychosocial problems, inadequate nutrition and logistical issues, such as transport to the clinic and disclosure of status to a significant other.

In summary, with community mobilisation and support, a patient is more likely to present for testing and treatment, will be better prepared to begin and adhere to ART, is less likely to default and is more likely to have a better clinical outcome.

And the impact at a community level was dramatic. For example, approximately 66 000 people live in the Bobirwa sub-district of Botswana. The Bobonong Primary Hospital, where the CBTS model was established, is the only hospital serving this population. By 2006, 2 years after the CBTS model was adapted and implemented in the sub-district, 1 546 patients were on ARVs and the following notable results were achieved:

- Hospital bed occupancy by HIV patients decreased from 93% to 52%
- In-hospital mortality due to HIV/AIDS decreased from 25% to 13%.

The model is now presented in the manual as a partnership involving government, the private sector and community-based organisations, using a seven-step implementation process as illustrated in Fig. 2.

The manual also includes 22 technical tools and resources to assist the provision of quality services to clients, as well as case study profiles of five southern African community-based treatment sites, outlining their adaption and implementation of the programme. These case studies illustrate the flexibility of the model.

The manual is intended for public health officials, project managers, service providers, AIDS service organisations, funders and communities seeking to initiate, enhance or expand comprehensive HIV/AIDS treatment and care programmes in resource-limited settings.

The steps outlined in the manual will allow a logical, optimal and effective path to implementation. The key objectives, expected outcomes and lessons learnt according to STF are detailed below.

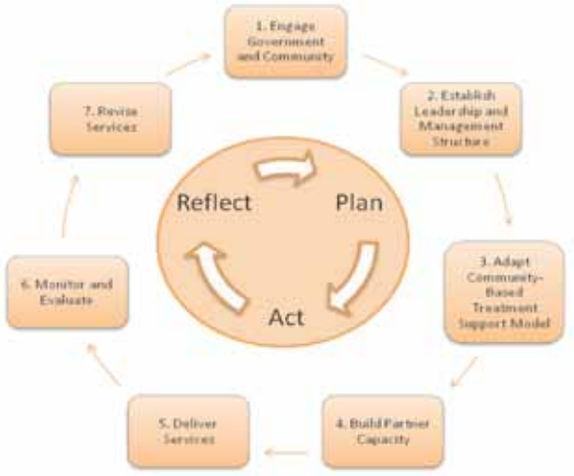

Fig. 2. The seven-step process.

STEP 1: ENGAGE GOVERNMENT AND COMMUNITY

The first step recognises the critical need of obtaining government support for introduction of the CBTS model. It guides the implementer in how to advocate for establishment of an integrated, community-based approach for HIV/AIDS care and treatment, which includes the government, private sector and community in multidisciplinary teams. At the end of this step, a business case for the programme will have been created and government buy-in secured.

STF learnt that governments can be engaged if the CBTS programme and model align with national policies and address critical challenges. Engagement should now be eased because of the positive data included in the manual, attesting to the effectiveness of the community-based approach.

STEP 2: ESTABLISH LEADERSHIP AND MANAGEMENT STRUCTURE

This step leads to the appointment of a skilled and preferably experienced project manager, as strongly recommended by STF, and to the development of a project charter that specifies objectives and deliverables as well as a management structure with clear roles, responsibilities, and reporting relationships through collaborative and transparent workshops.

Another key learning by STF was that for the CBTS programme to succeed, it is important to place equal importance on the role of all partners and give them equal say in planning and implementation.

STEP 3: ADAPT THE COMMUNITY-BASED TREATMENT SUPPORT MODEL

The CBTS model is flexible. Indeed adaptation is essential and is described in this step, which leads to selection of clinical sites and of community services, the elaboration of a patient flow map, the development of a patient documentation system and an implementation plan.

Perhaps the most important learning of this step is that a carefully designed patient flow map is the key to quick and accurate adaptation of the model to any particular programme location.

STEP 4: BUILD PARTNER CAPACITY

This step describes how to train and build capacity of all stakeholders to deliver services and other skills dictated by the shared goals of the project.

Capacity building is not just about training, but can be facilitated by providing appropriate, sometimes innovative upgrades or modifications to workplaces and other physical structures. STF also learnt that training personnel to understand the CBTS concept itself is necessary for effective implementation.

In Namibia, an NGO Village was constructed inexpensively employing indigenous construction techniques.

STEP 5: DELIVER SERVICES

The first objective of this step is mobilisation of the community to support and engage in new and improved services, particularly newly accessible ART and community services integrated with ART. Thereafter attention is paid to how to deliver high quality, accessible and integrated clinical and community services to the targeted numbers of patients, how to prepare patients who need ART for treatment and how to track and retain them in the programme. The manual also

More than 5 000 people attended the public launch of the ACHIVA programme at Ladysmith Provincial Hospital in KwaZulu-Natal, South Africa, in 2004.

A woman in Bobonong, Botswana, proudly tends her door-sized garden.

addresses how to provide community support for patients not yet clinically eligible for ARVs. STF learnt the importance of this, because inattention to these patients can demotivate them and they may then drop out of the programme. STF also learnt that selection of patients for ARV therapy should be based largely on clinical criteria and remain uninfluenced by social discrimination, because social and psychological problems can usually be managed.

'Buddies' trained by the NGO COCEPWA in Gaborone, Botswana, prepare to go to work.

In terms of community services, home-based care was found to be one of the most important for HIV/AIDS patients and has been shown to impact on clinical outcomes. The job description of home-based care workers has been transformed with the advent of ARV therapy from palliative care to supportive care. In addition, adequate nutrition is essential for optimal response to treatment, but it is important to encourage self-sufficiency by teaching patients how to grow their own food.

STEP 6: MONITOR AND EVALUATE AND STEP 7: REVISE SERVICES

Step 6 guides the development of a monitoring and evaluation framework while step 7 explains how to reflect on progress, successes and challenges, making use of monitoring and evaluation data. Corrective action can be taken with input and agreement from relevant partners.

In publishing the manual, it is the hope of STF that the experience gained and lessons learnt can be utilised by others wishing to provide holistic and effective care and support to patients with HIV/AIDS in resource-limited settings.

Food security in action: Workers in their community garden in Lesotho.

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NUTRITION AND HIV/AIDS

Nutritional Guidelines for HIV-infected Adults and Children in Southern Africa: Meeting the Needs

D C Spencer, C Harman, T Naicker, S Gohre, for the Nutrition Focus Group of the SA HIV Clinicians Society
Reviewers: N Rollins, D Labadarios, M Visser

'Despite progress in boosting democracy, ending wars and improved economic growth, Africa is the only region in the world becoming less able to feed itself'.[1]

1. NUTRITION, WEIGHT LOSS AND HIV IN AFRICA

1.1 INTRODUCTION

The HIV epidemic affects large numbers of people living in the southern African region.[2] Despite more than 2 decades of research, a cure remains elusive.[3] The implementation of proven preventive interventions has had limited success; and the uptake of antiretroviral (ARV) drugs has lagged far behind the estimated numbers in need.[4] Furthermore, the production of food in Africa may well be adversely influenced both by the epidemic itself and by global warming.[5] Nutrition, specifically the use of food, special diets, micronutrients and so-called immune boosters and supplements, has been suggested as an affordable and practical means of 'delaying the onset of advanced HIV infection'.[6] Is this true? And if it is, how secure is access to food and good nutrition in Africa? Floods, drought, famine, poverty, war and political instability define much of the everyday life of millions on this continent. Secure and reliable access to food is extremely important in these circumstances. In some instances, sex will be exchanged for food and employment far from home may result in risky sexual behaviour. The science of nutrition is more than the science of food itself.[5] It is about people, their access to food of a suitable quality and quantity, and in addition it is about the production of food and its utilisation. It is also about maintaining access to food over decades so as to ensure that the children and adults of Africa – including those who are HIV-infected – grow and realise their full potential.

Discussion about food and diet in the HIV era also requires that due attention be given to the interactions and toxicities of the ARV group of drugs. These have revolutionised the management of HIV infection. Sooner or later all who are infected will need to take these agents. Some ARVs are best given on an empty stomach, some with food and others with a fatty meal. Many give rise to metabolic alterations, such as insulin resistance and glucose intolerance, fat abnormalities (lipodystrophy, hyperlipidaemia), lactic acidosis, liver enzyme abnormalities, anaemia and osteopenia.[7] Certain herbs and foods interfere with the bioavailability of the ARVs. Various micronutrients have been shown to benefit the HIV-infected. Home-grown diets, herbal concoctions and vitamin supplements have been advanced by some as alternatives to the ARVs and as cures of the disease, but without providing evidence of their benefit.[8] Where denial and stigma and commercial interests have dictated the political and social response to this epidemic, it has been a simple matter to add nutritional nonsense and personal economic gain to the general confusion that has defined public discussion.[9]

The science of nutrition and HIV infection intersect at several strategic levels. Evidenced-based research confirms the following four concepts:

- Weight loss predicts death.[10]
- Energy and nutrient needs are increased in the HIV-infected.[11]
- Adequate food – and not just vitamins and so-called immune boosters – constitutes an appropriate supplement for those in need.[12]
- Nutritional security: Food alone is not enough. Children and adults who are malnourished, whether they are infected, exposed or affected, need comprehensive medical and nutritional care and social support.[13]

These concepts will be discussed in detail in later chapters.

1.2 EPIDEMIOLOGY AND BASIC SCIENCE

The human immunodeficiency virus (HIV) crossed into the human race from its primate host in the early decades of the 20th century.[14] Since that time it has spread throughout the globe and has caused more than 20 million deaths worldwide.[15] Sub-Saharan Africa has borne the greatest burden of the infection. Without access to ARV drugs average

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survival is about 10.3 - 10.8 years.[16] The HIV virus is spread from human to human via direct contact with sexual fluids and blood (blood products) and to infants and children during pregnancy and lactation.[17] Since the mid-1990s, drugs called antiretrovirals (ARVs) have been used to control viral replication, and to prevent neonatal transmission and accidental exposure to the virus. These interfere with the growth cycle of the virus. Some prevent the virus from entering the human cell (viral entry inhibitors), while others inhibit viral enzymes that assist in the reproduction of the virus: the nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs and NtRTIs) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs). The protease inhibitors (PIs) block the assembly of newly formed viral proteins. A further class of ARVs, the integrase inhibitors, impair the integration of viral DNA into the human genome. Interactions with food and other drugs, including herbs and the so-called immune boosters, are well documented. These interactions may impair viral control by a variety of mechanisms.

The virus targets the cells of the immune system, particularly the CD4 lymphocyte (the 'helper-T cells').[18] Despite the increased production of these cells, they are ultimately sacrificed to the virus. Eventually this progressive immune deficiency leads to life-threatening infections and cancers: the acquired immunodeficiency syndrome (AIDS). Once within a cell, HIV-1 reproduces rapidly. From a single infected cell thousands of new viral particles are released into the bloodstream. In the laboratory this is measured as the viral load. Nevertheless, most of the virus remains undetectable within the cells of the body.[19] Together with the medical history and examination, the measurement of the CD4 cell count and the viral load (VL) provide a platform from which to assess the patient. Because of the effect of the infection on nutritional status, this assessment should include the nutritional evaluation of the patient. What does growth failure and loss of weight mean in HIV-infected children and adults?

1.3 WEIGHT LOSS IN HIV-INFECTED CHILDREN AND ADULTS

Weight loss is a strong predictor of death in HIV-infected adults and children.[20]

WEIGHT LOSS PREDICTS DEATH

- Low weight reflects advancing disease
- Weight loss often indicates opportunistic infections or progressive disease
- Weight loss should be a warning to the doctor/nurse to initiate investigations and treatment

During the 1980s and early 1990s, 'Slim Disease' was a term used throughout central Africa to characterise a patient with end-stage HIV infection or AIDS.[21] Indeed, weight loss is used in both the World Health Organization (WHO) and the Centers for Disease Control (CDC) adult staging systems: unintentional weight loss of < 10% = WHO stage II and > 10% = stage III and CDC stage C, i.e. is AIDS defining.[22] In children older than a year, weight loss resulting in a fall of 2 or more percentile lines is AIDS defining if accompanied by chronic diarrhoea or fever. Also AIDS defining is a child in the 25th percentile of weight-for-height (on consecutive measurements separated by more than 30 days).[23] Severe wasting in adults is defined by the CDC as a body mass index (BMI) < 18.5 $(kg/m)^2$ or unintentional weight loss of > 5% of usual body weight within 6 months.[24] Growth faltering and stunting are common in children with HIV infection and occur early in life.[25-27] In children, wasting is particularly associated with the loss of lean body mass and failure to gain height.[27]

Weight = heaviness measured in kilograms

Lean body mass = the total of all body components except storage lipid (fat) and bone

Fat-free mass = the same as lean body mass

In adults both lean mass and fat are lost, though the loss of lean mass predominates.[24] In contrast, starvation leads primarily to fat loss.[24] Both the loss of lean mass and poor linear growth in HIV-infected children are closely associated with poor survival and protecting lean body mass prolongs survival.[24, 27]

Weight loss in the HIV-infected is the sum of a number of causes. Energy requirements are increased even in the asymptomatic state.[28,29] These needs soar under periods of stress and during malnutrition.[29] Cytokines such as tumour necrosis factor-α (TNF-α) and interleukin-1 (IL-1) released during episodes of infection and even during the 'asymptomatic' phase of HIV infection, promote increased metabolism, glucose recycling, muscle catabolism and negative nitrogen balance.[29,30] They may also reduce appetite even when there is no overt opportunistic disease. This results in the characteristic wasting associated with AIDS.[31] Levels of interferon-α (INF-α) are persistently elevated in full-blown AIDS.[29,31] Apart from these underlying metabolic factors, the inability to eat or to swallow food and the increased loss of dietary nutrients from vomiting and diarrhoea will lead to wasting and malnutrition. Wasting also accompanies the opportunistic infections and cancers of advanced HIV-infection.

1.4 WEIGHT LOSS: ITS CAUSES AND INCREASED ENERGY REQUIREMENTS (Table 1.1)

1.4.1 Increased and often unmet energy requirements during all stages of HIV infection

Energy requirements are likely to increase by 10% just to maintain body weight and normal physical activity in asymptomatic HIV-infected adults and to maintain normal growth in asymptomatic, infected children. During symptomatic stages and particularly during AIDS (opportunistic diseases) these energy requirements increase by 20 - 30%. Energy needs may even increase to levels of 50 - 100% above

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TABLE 1.1. INCREASED ENERGY NEEDS OF HIV-INFECTED ADULTS, ADOLESCENTS AND CHILDREN[28,29]

	HIV-positive phase	Energy
Adults and adolescents	Asymptomatic	10%↑
	Symptomatic (mild)	20 - 30%↑
Children	Asymptomatic	10%↑
	Symptomatic (mild)	20 - 30%↑
	Symptomatic (moderate to severe)	50 - 100%↑*

*In the presence of severe malnutrition.

normal in children who are severely malnourished and who are experiencing weight loss.[28,29] When enriched with various fats (peanut butter) or oils (olive, canola), food will provide greater 'energy content'. This 'enriched' food is needed to supplement the daily, baseline dietary requirements if the malnutrition and weight loss are to be corrected.

MANAGING WEIGHT LOSS EFFECTIVELY

- Record weight at each visit, usually 3 - 4 visits annually.
- Identify the reason for the weight loss
- Control the HIV infection where indicated: ARVs may be needed
- Treat malnutrition: Food, supplements, micronutrients where needed
- Diagnose and treat opportunistic disease
- Symptomatic control of: Nausea, anorexia, vomiting, diarrhoea
- Examine the oral cavity: Treat thrush, gingivitis and oral ulcers
- Stop smoking, alcohol abuse and recreational drug use
- Exercise and strength training may have a role in some
- Exclude hypogonadism (rare) and consider use of appetite 'stimulants' such as megesterol acetate, anabolic steroids and dronabinol for nausea where appropriate (benefit controversial)
- Involve social support mechanisms: Social worker, income grants, NGOs including faith-based groups that provide nutritional support, exclude depression and anxiety, consider incorporating a family member or 'concerned other'.

1.4.2. Decreased energy intake and the increased loss of nutrients

Anorexia, nausea, gingivitis, oral sores and dysphagia will impair food intake and promote weight loss. At times the ARVs and the anti-TB drugs are poorly tolerated – nausea, anorexia, and vomiting. Fortunately this situation is generally short-lived and usually restricted to the first weeks after the start of therapy. Depression and anxiety suppress appetite and result in weight loss. Religious and cultural practices that require regular fasting, purging and dietary restrictions may be harmful in the context of advanced HIV infection. Food access and food security can be significantly affected when material resources are lost - income, the inability to work. Chronic diarrhoea and malabsorption may cause wasting: direct viral invasion of gastrointestinal cells (HIV-enteropathy) can be demonstrated in some patients.[32] Both localised gastro-intestinal and overwhelming generalised infections are frequent in Africa. Pulmonary and extra-pulmonary TB, salmonella, *Escherichia coli,* cryptosporidia and isosporiasis may present with fever, anorexia, nausea, vomiting and diarrhoea. Undiagnosed and untreated, these infections will lead to wasting and ultimately death.

The prevention and treatment of weight loss is a priority for patients who are HIV-infected. What can be done for patients who are at risk?

1.5 WEIGHT LOSS. ASSESSMENT AND TREATMENT

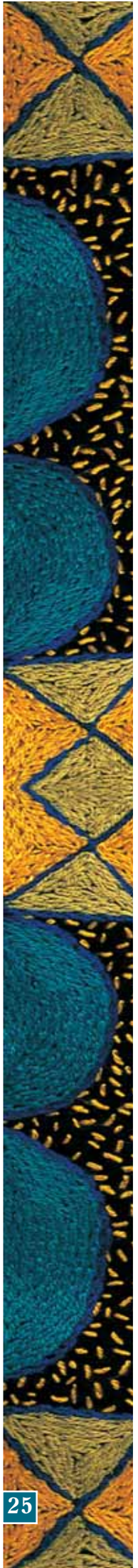
1.5.1 Assessing weight loss

All infected children and adults must be regularly followed up. This includes taking a medical and nutritional history. The patient must be thoroughly examined. It goes without saying that in southern Africa, every effort MUST BE MADE to identify the infected so as to offer them protection from advancing HIV disease and facilitate the control of the epidemic. The following measurements are essential: weight, height/length in children, the mid-upper arm circumference (MUAC) and the CD4 and viral load. MUAC is a useful means of assessing lean body mass. Additional investigations are discussed in a subsequent section.

1.5.2 Managing weight loss

Attention must be given to the causes of weight loss and the diagnosis and control of anorexia. Poverty, food insecurity and related socio-economic issues ought to be recognised and managed in as practical a way as possible. The timeous provision of ARV therapy is a very appropriate means of preventing weight loss and the secondary opportunistic infections associated with it.[33]

Provide food. Provide nutritional counselling. Provide support – but aim to make the patient and their family independent of food parcels and short-term solutions. A team approach (nurse, doctor, dietician and trained nutritional advisor) works best. Diagnose and treat intercurrent disease. Check the CD4 and viral load and any other relevant tests as suggested by the clinical examination. Consider starting ARV therapy where appropriate. 'The best way to achieve protein repletion in clinically severe HIV/AIDS is to establish effective ARV therapy.'[34] Once an adult has achieved his/her normal body weight, discourage further weight gain in those on ARVs. Obesity is to be avoided. Fat redistribution, hyperglycaemia and insulin resistance, the metabolic syndrome, hyper-lipidaemia and cardiovascular disease are recognised complications.[35-37] Wasting and severe malnutrition may require enteral and parenteral feeding. This is usually undertaken in a hospital or clinic. Nutritional supplements such as fortified porridges and food itself ought to be accessed on behalf of the patient. The use of specific micronutrients generally follows recommendations for the population at large. Safety, tolerability and cost are the important drivers in this regard.[24] The role of individual supplements will be discussed later. Exercise – including resistance training – has been found to improve the patient's quality of life, to build up lean body mass, and in those on



ARVs, to improve serum lipid profiles.[38,39] The simplest monitor of nutritional recovery in adults is the measure of sequential weight gain. But weight alone will not discriminate between the return of lean muscle and/or fat, or for that matter indicate the return of good health. Other measurements in addition to that of weight will be needed.

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2. NUTRITION, HIV AND CLINICAL MEASUREMENT

2.1 NUTRITION: TAKING A DIETARY HISTORY

'A simple nutritional assessment is available to all and requires only an interview, a scale and a tape measure.'[1] This assessment begins with history taking: 'What do you eat on a typical day?' 'When last did you have a meal?' 'Tell me everything you've had to eat or drink in the last 24 hours.' The nutritional history needs to give the interviewer a clear sense of the client's diet, its contents, amounts of food taken, regular and reliable access to good food, and in the context of the HIV epidemic, the stage of the infection and use by the client of prescribed medication, herbs and traditional or so-called complementary treatments.

It may be helpful to use actual plates, cups and spoons to estimate the size of food portions. A diary card may be helpful: 'Record everything you eat and drink for the next week. Add in the amounts that you consume ...'[2] If the patient is an infant, enquire as to what feeds are being given. Formula? Breast? Exclusive or mixed breastfeeds? How is the food prepared? What understanding does the client have of hygiene and food? ARV drugs may cause physical changes: ask about weight loss and breast enlargement and the loss of fat on the face, arms and legs. What is the stage of HIV infection? Have opportunistic diseases such as TB been experienced? Co-morbid conditions such as diabetes, liver and cardiovascular disease will require dietary advice and the outlining of potential ARV drug and food interactions.[3,4] 'Do you or the family ever go without food?' Enquire about the patient's access to an income and food. In busy public clinics trained caregivers from the community can assist with history taking, and the weighing and measuring of patients. The goal of the dietary analysis is to prevent weight loss and optimise nutrition: the counselling that takes place will foster the patient-doctor/nurse relationship and improve communication.[5,6] However, providing specific advice is difficult. Diets vary between and within populations. Familiarity with local foods, food preparation and the culture and traditions of a

community will root any advice offered within the context of the patient's life. Dietary advice needs to be culture sensitive and feasible. See also Appendices 1 and 2 for action to be taken in response to nutritional risk.

DIET HISTORY

A diet history is a detailed dietary record that may include a 24-hour recall, a food frequency questionnaire and other information such as weight, history, previous dietary changes, the use of supplements and known food intolerance.

NUTRITIONAL QUESTIONNAIRE

Question 1. Baseline assessment. What is your usual weight and height (adult)? Is the child being regularly weighed and having his/her height/length measured at the clinic? May I see the child's clinic card, please?

Question 2. Weight loss: Have you recently lost weight? Do your clothes still fit? Have you noticed weight gain and body changes on the antiretrovirals (ARVs)?

Question 3. Appetite: Has your appetite changed?

Question 4. Digestion: Do you have any of the following:

- Difficulty with swallowing?
- Discomfort or pain in the mouth?
- Nausea and vomiting?
- Diarrhoea?

Question 5. Food access and food security: In the past week have you missed any meals? Do you or your children ever go hungry? Are you able to eat meat or fish regularly? How often?

Question 6. Non-prescription medication. Do you take any immune boosters, vitamin supplements or traditional medicines? How much alcohol and/or recreational drugs do you take each day or each week?

Question 7. Prescription medication. Do you know which of your ARVs need to be taken with or without food/a meal? What medicines other than ARVs are you taking?

Question 8. Stage of HIV infection: Have you been admitted to hospital or been diagnosed with tuberculosis in the last 3 to 5 years? Do you know your most recent CD4 level?

2.2 NUTRITION: MEASUREMENT

Medical science is built upon practices that have measurable and reproducible outcomes. The measurement of human nutrition is based upon anthropometric, biochemical, clinical and dietary parameters – the so-called 'ABCD' of nutritional assessment.[7,8] Included in the anthropometric measurement are body weight, length or height, the body mass index (BMI) and the mid-upper arm circumference (MUAC). If performed reliably, these form a baseline from which to judge growth failure or abnormality. Often the measurements can be carried out by a trained non-medical clinic or community member. Results must be tabulated in the clinic file at each visit, preferably before the patient is seen by the nurse or doctor. A reduction in lean body mass in children is detectable before a deceleration in linear growth (length/height) and is important to document and act upon.[9] Waist circumference is a measure of cardiovascular risk, type 2 diabetes, hypertension and increased cholesterol risk in non-HIV infected adults. This may also be a helpful measurement in patients on ARVs at risk for the metabolic complications of therapy.[10]

Paediatric growth charts record both height and weight: height-for-age, weight-for-age, and weight-for-height. All three measurements must be plotted at each visit.[8] In young children, body length will replace height. MUAC and subscapular and triceps skin-fold thickness reflect lean body mass and fat stores in adults and children older than 1 year. About 50% of body fat is subcutaneous.[11,12] MUAC is generally the preferred measurement. MUAC is an essential component of malnutrition assessment and is routinely used in World Health Organization (WHO) and UNICEF-sponsored relief programmes.[6] Intercurrent illness will alter these measurements: repeated measurement reveals the emergence of trends and the early onset of new disease.

MUAC IN ADULTS AND CHILDREN

By convention the tape is placed around the left upper arm midway between the tip of the acromion process (shoulder) and the olecranon (elbow). Values in adult men of < 23 cm and women of < 22 cm represent malnutrition. Paediatric measurements vary with age and will be detailed in the (later) paediatric chapter.

WEIGHING THE PATIENT

Subjects are weighed in light underclothing without shoes. Heavy items of jewellery, wallet, keys, etc. should be removed and the patient advised that a large meal just prior to the measurement and a full bladder at the time of measurement will increase the reading. Where available a beam or lever balance is more reliable. Bathroom scales are generally unreliable. The scale must be regularly serviced and checked, preferably monthly. Babies are weighed naked and without their nappies.

In adults the body mass index, BMI = weight (kg)/height $(m)^2$ (Table 2.1), is a sensitive measure of both under and over nutrition. (The BMI can be read directly from a nomogram – usually present in most practices, or worked out from the above equation.)

TABLE 2.1. THE BODY MASS INDEX (BMI) – A MEASURE OF THE RISK OF UNDERNUTRITION AND OBESITY

Classification	BMI (kg/m^2)
Severe undernutrition	< 16
Underweight	< 18.5
Normal	18.5 - 24.9
Overweight	25.0 - 29.9
Obesity, class I	30.0 - 34.9
Obesity, class II	35.0 - 39.9
Extreme obesity, class III	> 40

Source: National Heart, Lung and Blood Institute, National Institutes of Health, USA. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. NIH Publication No. 98-4083.

2.3 NUTRITION: THE LABORATORY

Laboratory tests in HIV patients are restricted to those with clinical value. The CD4 cell count and viral load are essential and provide a direct measure of the patient's immune system and the virus. Often included in the routine workup are tests that indicate whether vital organs are functioning normally: blood, the full blood count (FBC); liver – the alanine aminotransaminase (ALT) level; and kidneys – urea or creatinine and urine dipstix. From time to time sophisticated diagnostic tests are indicated (blood cultures, malaria smears, sputum analysis for TB and urine microscopy), but tests that directly measure the micronutrient status of the patient are seldom required. In general, the clinical evaluation and anthropometric measurements discussed above will guide the clinician in deciding what additional investigations are necessary.

2.3.1 Anaemia

Anaemia is an independent predictor of mortality in HIV patients. It is therefore important to document and to follow and act upon.[13] The common nutritional deficiencies associated with anaemia are iron, folate and vitamin B_{12}. However the most common cause of anaemia in HIV-infected patients is 'the anaemia of chronic disorders', an anaemia seen in many chronic inflammatory or infective conditions and not related to any nutritional deficiency.[14] The haemoglobin, red cell mass and haematocrit are decreased. The laboratory will provide a comment on the peripheral blood smear and record the mean corpuscular volume (MCV), a measure of the size of the red cell. The MCV is usually normal in the anaemia of chronic disorders (normocytic anaemia), while in iron deficiency the red cells are small and the MCV is less than normal (microcytic anaemia). In folate and B_{12} deficiencies, the MCV will usually be elevated (macrocytic anaemia). Other causes of anaemia are occasionally present: red cell haemolysis, drug-induced toxicity (the ARVs: zidovudine, combivir), bone marrow infiltrate (e.g. tumour or infection such as TB) or infection with HIV itself. Not every HIV-infected person requires iron supplementation. Indeed most have an excess of storage iron (ferritin), and added iron may be harmful.[15,16] Nevertheless during pregnancy and lactation supplementation with iron, folate and multivitamins is given to both HIV-infected and non-infected women. In other circumstances, iron supplementation should only be provided if iron deficiency has been confirmed on laboratory testing. In many parts of Africa malaria and hookworm infestation are common. These must be excluded in any investigation of anaemia in patients from rural or endemic areas.[17]

2.3.2 Serum micronutrients in the HIV-infected patient

The persistent presence of the virus in the human host ensures that the immune system is chronically stimulated. Hence the frequently elevated total proteins in HIV-positive patients – resulting from the chronic overproduction of gamma globulins, including antibodies. Intercurrent illnesses cause additional inflammatory stress. An 'acute-phase response' follows. For the clinician, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level help to define such periods.[18,19] Local and systemic cytokine levels rise and fall. Micronutrient concentrations mirror these changes. Some increase, others decrease.[20,21] Some micronutrients such as vitamins A, C and E, and zinc may behave as antioxidants. Low serum levels may therefore indicate utilisation rather than an underlying deficiency.[22,23] Blood levels are an incomplete measurement of the body's micronutrient status. Without the clinical context of the patient and knowledge of the micronutrient status of the community, the meaning of an individual result is of limited value.[24] Studies from the Cape and KwaZulu-Natal confirm generally low levels of micronutrients among HIV-infected South African children and adults.[25-27] Furthermore, micronutrient supplementation with vitamin A reduces morbidity, growth failure and death, while zinc supplementation reduces the duration of diarrhoea and associated fluid losses in young HIV-positive children.[27,28] Selenium and zinc also behave as acute-phase reactants: their levels fluctuate during infection. The value of observational and cross-sectional micronutrient studies and studies that ignore the acute-phase phenomenon remain difficult to interpret.[29-31] Any measurement of individual micronutrients must place the result within its clinical context. Where these issues are ignored, clinical studies fail to provide convincing data.[29] The routine measurement of micronutrients is expensive, difficult to interpret and generally not warranted in the southern African situation. But it goes without saying that well-planned clinical studies in this area are urgently needed to supplement the sparse data currently available.

2.3.3 Liver function tests: albumin and serum ALT

A low serum albumin level may indicate poor nutrition, and indeed low serum albumin predicts both death and length of stay in hospitalised HIV-positive patients.[5] But malnutrition is just one of several causes of low albumin: liver disease with decreased protein synthesis, renal disease with protein loss (albuminuria), enteric infections with chronic diarrhoea and malabsorption are also associated with low albumin levels. In addition, as an acute-phase reactant, a low albumin level may simply behave as a marker of an active inflammatory state.

Liver-related disease has become a significant cause of death of patients on long-term ARV therapy.[32] Prolonged survival on ARVs has increased exposure to the following:

- Persistent liver damage resulting from uncontrolled hepatitis B or C virus infection.[33]
- Non-alcoholic steatohepatitis (NASH) may result from HIV infection itself and from exposure to the metabolic side-effects of the ARVs.[34,35]
- Direct drug toxicity. All drugs are potential hepatotoxins but certain ARVs are more frequently associated with liver toxicity, e.g. nevirapine in women with CD4 counts > 250 cells/µl and men with CD4 counts > 400/µl, the combination of stavudine and didanosine, and the protease inhibitor ritonavir.[32,35,36]

Elevated transaminases, e.g. ALT, may accompany liver damage and must be checked two or three times a year while on the

NUTRITIONAL ASSESSMENT OF THE HIV-INFECTED PATIENT[7]

History	Examination	Laboratory tests (baseline assessment and as indicated clinically thereafter)
Weight loss	Weight	Full blood count and haemoglobin (anaemia)
Dietary history	Height or length	Serum iron studies only if significantly anaemic, Hb < 8 - 10 g/dl otherwise clinically indicated
Access to food and food security	Body mass index (BMI) (normal value: 18.5 - 24.9 kg/m^2)	
Stage of HIV infection	Mid-upper arm circumference (MUAC) (normal values: adult males > 23 cm; adult females > 22 cm; pregnant females > 23 cm)	Viral hepatitis serologies (HBV, HCV) and additional liver tests as clinically indicated
Use of medication including the antiretrovirals		Plasma fasting cholesterol and triglyceride
Pregnancy, lactation and the 'child under 5'		Plasma fasting blood glucose
Micronutrient and vitamin use	Waist circumference, 'at risk values' (adult males ≥ 102 cm, adult females ≥ 88 cm)	The albumin level, and specific micronutrient levels are not routinely assessed
Family and/or community support		Serum amylase not routinely assessed
	Clinical examination of the patient: signs of wasting, evidence of stunting in children, signs of advanced HIV infection, signs of specific nutritional deficiency syndromes, signs of treatment-related fat redistribution	
What to do?		
History:	*Examination*	*Laboratory tests*
Identify food insecurity	Weight loss is significant and is associated with mortality in the HIV infected. Check measurements to exclude significant weight loss and malnutrition (weight, BMI)	Anaemia, low serum albumin levels indicate an increased risk of death in the HIV infected.
Assist families/patients with accessing government support and welfare grants		All abnormal investigations must be explained and acted upon
Identify lack of nutritional knowledge	Lower than normal MUAC levels: loss of lean body mass	Anaemia: check the MCV and find the likely cause and correct this
Refer to counsellor to assist with practical support of the mother/ child/patient	Correct underlying malnutrition and ensure virus is brought under control	Serum iron, % saturation, transferrin and ferritin levels may be helpful if iron deficiency is suspected
Identify a responsible home or community member who can assist	Assess food access, intake and utilisation	Elevated ALT: check the AST, alkaline phosphatase, GGT and HBV, HCV antibody tests. Decide whether this is a medication-related toxicity or an opportunistic process. If necessary follow up with a hepatic ultrasound to exclude a space-occupying lesion, fatty liver or NASH, enlarged abdominal lymph nodes
Identify opportunities to prevent HIV transmission	Examine patient to exclude active opportunistic disease and uncontrolled HIV infection	
Assist the pregnant patient with making informed choices including exclusive breastfeeding	Increased abdominal circumference: check which ARVs are being used and confirm metabolic abnormalities with appropriate investigations	
Where weight loss is confirmed, examine and investigate to exclude opportunistic disease, e.g. tuberculosis, advanced HIV	Give dietary advice and refer where available to dietician	
	Weight reduction and exercise programme may be indicated	

ARVs. Elevated transaminases ought to direct the physician to excluding alcohol (GGT>>AST >>ALT) and the activity of the hepatitis viruses (HBV and HCV) as possible causes.[37,38] Elevated alkaline phosphatise and gamma-gluteryl transferase (GGT) may suggest an infiltrative process including the presence of hepatic granulomas, e.g. TB or cotrimoxazole-induced hepatitis.[39]

2.3.4 Miscellaneous tests

Amylase levels are checked in symptomatic patients with suspected pancreatitis: abdominal pain, nausea, vomiting while taking didanosine or the combination of didanosine and stavudine, and rarely, lamivudine in children. Concomitant use of alcohol, pentamidine, hydroxyurea and steroids including anabolic steroids, will increase the risk.[40] Serum amylase is not tested routinely.

Fasting plasma cholesterol and triglycerides, glucose (or urine dipstix) are suggested at baseline assessment and annually in patients with known risk factors for cardiovascular disease, diabetes, etc. Patients on ARVs associated with lipodystrophy are at an increased risk of cardiovascular disease and insulin resistance. These will also need annual or bi-annual fasting lipids and sugars.[4]

2.4 NUTRITION: THE CLINICAL ASSESSMENT

See also Appendices 1 and 2.

The assessment of the nutritional status of HIV-infected patients begins with the initial interview. A clinical examination follows. This is combined with measurements that are repeated during subsequent follow-up visits: weight, height/length to enable a BMI measurement to be made, MUAC, and in patients on lipid-altering ARVs, waist

circumference can be considered. Baseline and follow-up blood and urine tests complete the assessment and permit clinical staging of the patient. At this time the patient will want to know whether ARV drugs are needed and what if any, is the role of diet, micronutrient supplements and vitamins. These topics will be addressed in the next chapter.

The following chapters of this Guideline will appear in subsequent issues of the *Journal*.

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APPENDIX 1

ENTRY AND EXIT CRITERIA: ADULTS > 14 YEARS

NUTRITION RISK SCORE

If the total score exceeds 6 points, the patient can be seen as nutritionally at risk and requires food and to be provided with long-term nutritional support and access to government or NGO assistance or welfare grants. Where practical, the patient should be referred to a dietician for appropriate nutritional intervention.

	DATE AND SCORE						
1. Weight loss in 3 months							
• None	0						
• 3 kg (< 1clothes size)	1						
• 3 - 6 kg (1 - 2 clothes size)	2						
• > 6 kg (> 2 clothes size)	3						
2. BMI							
• ≥ 18.5	0						
• 17.0 - 18.4	1						
• 16.0 - 16.9	2						
• ≤ 16	3						
3. Appetite							
• Good (most of plate)	0						
• Poor (half of plate eaten)	1						
• Unable to eat (no food in 2 days)	2						
4. Ability to eat							
• No problems	0						
• Mild vomiting/diarrhoea	1						
• Difficult swallowing/chewing	2						
• Severe vomiting/diarrhoea	2						
• Need help feeding	3						
5. Stage of infection (WHO stage classification)							
• Stage I	0						
• Stage II	1						
• Stage III	2						
• Stage IV	3						
6. Other problems							
• None	0						
• TB	2						
• Pregnant/lactation	2						
• Social problems	2						
TOTAL SCORE							

Source: Harman C. Nutritional Assessment Chart. Nutrition Unit, Department of Paediatrics, Chris Hani Baragwanath Hospital, Soweto, 2007.

APPENDIX 2

ENTRY AND EXIT CRITERIA: CHILDREN < 14 YEARS

NUTRITION RISK SCORE

If the total score exceeds 6 points, the child is nutritionally at risk and needs to be given food and provided with long-term nutritional support and access to government or NGO assistance or grants. Where practical, the patient should be referred to a dietician for an appropriate nutritional intervention. Where acute malnutrition is diagnosed, this child MUST BE ADMITTED to hospital and provided with appropriate formula feeding as per WHO guidelines. RTHC = Road to Health Chart.

	DATE AND SCORE					
Is this child malnourished?						
1. Present weight:						
0 - 3 years (RTHC)						
• Following a curve on the RTHC	0					
• Inadequate weight gain, growth faltering	2					
• ≤ 3rd percentile RTHC	4					
• ≤ 60% of expected weight on the RTHC	6					
2 - 14 years BMI						
• ≥ 50th percentile	0					
• < 50th percentile	2					
• ≤ 25th percentile	4					
• < 3rd percentile	6					
3. Appetite						
• Good (5 meals a day)	0					
• Poor (less than 3 meals daily)	2					
• Unable to eat (no food in 2 days)	4					
4. Ability to eat						
• No problems	0					
• Mild vomiting/diarrhoea	1					
• Difficult swallowing/chewing	2					
• Severe vomiting/diarrhoea	4					
5. Stage of infection						
• Stage I	0					
• Stage II	1					
• Stage III	2					
• Stage IV	3					
6. Other problems						
• None	0					
• TB	2					
• Pregnant/lactation	2					
• Social problems	2					
TOTAL SCORE						

Source: Harman C. Nutritional Assessment Chart. Nutrition Unit, Department of Paediatrics, Chris Hani Baragwanath Hospital, Soweto, 2007.

Lancet Laboratories launches HIV Care and Counseling Centre

Lancet Laboratories, South Africa's foremost independent pathology laboratory recently opened an HIV and AIDS Care and Counseling Centre based close to the Milpark Hospital in Northern Johannesburg. The centre offers a comprehensive HIV service programme covering testing and diagnosis, disease management and ongoing counseling services to industry and the general public.

The Care Centre has access to the latest HIV research and development findings through BARC SA, an international clinical trials unit operating in South Africa since 1996, as well as LANCET LABORATORIES internationally accredited diagnostic and pathology service. The centre provides a walk-in service for HIV and AIDS information, Voluntary Counseling and Testing (VCT), support as well as treatment and care.

The Centre forms part of LANCET LABORATORIES efforts to take action against the HIV and AIDS pandemic sweeping through South Africa. The centre manager Martie Redelinghuys says "we can no longer afford to sit back and watch the devastating impact the disease has on society, that is being felt across our country and economy, now is the time for positive and urgent action."

The centre with its trained disease management and counseling staff see their role as one of leadership in the fight against the dread disease. The counseling programmes as provided by the centre are designed to change behaviour through education that encourages and supports HIV negative people to stay negative, and those living with HIV and AIDS to lead healthy, productive functional lives.




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ABSTRACTS

CROI 2007

The Conference on Retroviruses and Opportunistic Infections is held annually in the USA. This meeting, organised by the Foundation on Retroviruses and the Centers for Disease Control, has a mission to provide a forum for basic scientists and clinicians to present, discuss, and critique their investigations into the biology and epidemiology of human retroviruses and the diseases they produce with the ultimate goal of translating laboratory and clinical research into progress against the AIDS epidemic. The 14th conference was held in Los Angeles from 25 to 28 February 2007. This conference is relatively small with steep competition to get abstracts accepted for posters and presentations, yet South Africa has a growing representation at this prestigious and excellent meeting. The *Journal* invited a selection of South African authors whose abstracts were accepted and published to describe the background and relevance of their work and contextualise their findings for us in South Africa.

SEVERE HYPERLACTATAEMIA COMPLICATING ANTIRETROVIRAL THERAPY WITH STAVUDINE FIRST-LINE THERAPY IN SOUTH AFRICA: INCIDENCE, RISK FACTORS AND OUTCOMES

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Symptomatic hyperlactataemia (SHL) and lactic acidosis (LA)result from mitochondrial toxicity caused by nucleoside reverse transcriptase inhibitors (NRTIs) (especially stavudine (d4T) and didanosine (ddI)). High rates of these conditions are being reported in the SA public sector ART programme. We undertook this study to document the incidence, risk factors and outcomes of severe SHL (defined as serum lactate ≥ 5 mmol/l) at one referral facility in Cape Town, G F Jooste Hospital. We also assessed the safety of re-challenge with AZT (an NRTI that carries a lower risk for mitochondrial toxicity than d4T) in a select group of patients with less severe presentations. G F Jooste Hospital is a public sector hospital which serves a population of approximately 1.5 million people. There are 6 primary care ART clinics which refer to G F Jooste. There were two parts to the study. The first was a retrospective observational study on patients referred to G F Jooste Hospital with severe SHL. All patients with a lactate ≥ 5 mmol/l attributed to NRTIs during the period 1 August 2003 to 30 November 2005 were included. We calculated cumulative exposure to ART among patients attending the 6 ART clinics to derive an estimated rate of referral. Secondly, a matched case-control study which used incidence density sampling and was based on the cases sampled in the observational study outlined above was conducted. For practical reasons, controls were randomly selected from the same cohort (the same month commencing ART and at the same clinic – i.e. matched on facility and duration on ART) as each case.

MAJOR FINDINGS

OBSERVATIONAL STUDY

Seventy-three patients were diagnosed with severe SHL during the study period. During this period there was a cumulative exposure to ART of 7 080 patient years at all 6 ART clinics in the referral area, resulting in an estimated rate of referral for severe SHL of 10/1 000 years of treatment.

Sixty-nine patients (95%) were female. All 73 patients were on d4T-containing regimens, or had been switched off d4T in the preceding few weeks. The median duration on ART was 10 months (IQR = 8 - 11.3). The median serum lactate was 7.6 mmol/l. Thirteen patients (18%) had standard bicarbonate (SBC) ≥ 20 mmol/l, 49 patients (67%) < 20 mmol/l (i.e. lactic acidosis), and in 11 (15%) SBC was not measured.

Eleven patients died acutely (15%), and 1 patient died 4 months later. SBC below 15 mmol/l was the only risk factor consistently associated with acute mortality in univariate and multivariate modelling (OR = 35, p = 0.004, adjusted for age).

MANAGEMENT AND OUTCOME

All patients were managed acutely according to a management guideline which included general supportive therapy, vitamin supplementation and treatment of complications. ART was immediately interrupted in 66 patients. In the other 7 patients d4T was switched to AZT and ART was not immediately interrupted. However, in 5 of these 7 patients there was continued clinical or biochemical deterioration necessitating ART interruption. Thus 71 patients in total interrupted ART.

Of the 62 initial survivors, 3 were lost to follow-up and 59 patients were re-established on safer ART regimens. These included the 2 successful switches, plus 57 patients rechallenged with safer ART regimens once lactate levels had normalised after a mean 87-day treatment interruption.

The outcomes of those re-established on ART were: 29 patients with less severe presentations (all these patients had lactates < 10.4 mmol/l and SBCs > 14 mmol/l and none had pancreatitis) were restarted on an ART regimen which contained AZT and 3TC, with lactate monitoring. One of these patients was lost to follow-up. The remaining 28 patients were still in care on the same regimen at the time of data censure, with no recurrence of hyperlactataemia. A cumulative follow-up of 1 137 weeks (mean = 39 weeks) was available on these patients without recurrence of SHL. The other 30 more severe cases were re-initiated on a tenofovir-containing regimen or an NRTI-

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sparing regimen (i.e. Kaletra + NNRTI). There were no recurrences among these patients.

MATCHED CASE-CONTROL STUDY

DEMOGRAPHIC AND CLINICAL FEATURES AT BASELINE ASSOCIATED WITH SUBSEQUENT SHL

In multivariate analysis, compared with people with a baseline weight below 60 kg, those between 60 and 74 kg were 5 times more likely to experience severe SHL (95% CI 1.6 - 15.4) while those over 75 kg had an increased 19-fold risk (95% CI 4.8 - 77.1). The odds ratio for females was 44.2, with a wide confidence interval due to the paucity of men in the study (95% CI 6.4 - 303.8).

CLINICAL VARIABLES ASSOCIATED WITH SHL DURING FOLLOW-UP

In a regression model, patients having at least one of the listed major symptoms (abdominal pain, diarrhoea, nausea, and vomiting) within 80 days prior to case presentation were 18 times (95% CI 3.5 - 97.6) more likely to present with severe SHL. Weight gain of ≥ 6 kg in the first 3 months on ART was a further clinical association with severe SHL, with an odds ratio of 11 (95% CI 1.9 - 67.5). Patients with weight loss of ≥ 3 kg during the last 3 months prior to diagnosis were 12 times (95% CI 2.2 - 62.1) more likely to present with severe SHL. Concurrent peripheral neuropathy was also found to be independently associated with developing severe SHL (OR 8.4, 95% CI 1.4 - 51.8).

WHAT ARE THE IMPLICATIONS FOR CLINICAL PRACTICE?

The rate of severe SHL (referral rate of 10/1 000 patient treatment years) was higher than that reported from many developed-world settings. This is likely due to uniform use of d4T in first-line therapy, but may also be related to the risk factor profile of patients starting ART in SA. In order to minimise the morbidity and mortality related to this condition it is important to develop strategies to address prevention, earlier diagnosis and appropriate management.

Preventive measures may include:

- Changes in drug regimens on a programme level: an example would be substituting d4T with tenofovir, a drug which has not by itself been associated with lactic acidosis.
- Dose reduction of d4T: the WHO now recommends d4T be dosed at 30 mg bd in all patients regardless of weight. This is anticipated to reduce mitochondrial toxicity rates.
- Strategies focusing on high-risk patients: our study identified female gender, higher weight and rapid weight gain after starting ART as risk factors for severe SHL. One strategy that has been advocated and is supported by these data is to start overweight women on AZT (or tenofovir) rather than d4T and to switch those who become overweight on ART from d4T to AZT (or tenofovir).

To facilitate early diagnosis it is essential that a high index of suspicion for SHL is maintained. Clearly those at highest risk (overweight women) should be monitored most closely. Our study shows that symptoms such as abdominal pain, diarrhoea, nausea, and vomiting, weight loss ≥ 3kg as well as symptoms of neuropathy are important heralds of the condition. Also, most patients (85%) in this study presented with severe SHL after having been on ART for between 6 and 14 months. This period is thus the critical time to monitor for symptoms of SHL and weight loss.

Management of patients with severe SHL involved stopping drugs and a range of supportive measures.[1] It is worth noting that in 7 patients d4T was switched to AZT and ART was not immediately stopped. This strategy however failed with 5 of these patients deteriorating and requiring that ART be stopped. It is thus advisable that in all patients presenting with SHL and lactate > 5 mmol/l ART be immediately stopped.

Once ART was stopped it took a mean of 3 months for the lactate to normalise so that ART could be re-initiated. We were encouraged to find that our practice of re-challenging with an AZT-containing regimen in a group of 29 patients with less severe presentations (all had lactate < 10.4 mmol/l and SBC >14 mmol/l and none had pancreatitis) was well tolerated with no recurrences of SHL. Lactate levels and symptoms were closely monitored in these patients on rechallenge. This provides a Kaletra-sparing alternative, while we wait for tenofovir to be available in the public sector, for carefully selected patients who can be monitored on rechallenge.

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ASSESSING THE RISK OF CONTAMINATION BETWEEN SAMPLES DURING THEIR EXCISION FROM DRIED BLOOD SPOTS FOR HIV-1 DNA PCR TESTING

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It is now well established that early infant diagnosis is critical for implementation of early antiretroviral (ARV) treatment, stratification of health care services, monitoring the success of prevention of mother-to-child transmission (PMTCT) programmes, and reducing maternal anxiety. The diagnosis of HIV below 15 - 18 months of age requires the use of virological nucleic acid testing strategies. Qualitative DNA-based assays such as the Roche DNA polymerase chain reaction (PCR) assay have stood the test of time in South Africa, being conducted at 6 weeks of age with sensitivities and specificities of 98.8% and 99.4%, respectively.[1] Local work has also revealed that the collection method of choice for clinical sites is the dried blood spot (DBS), which facilitates easy collection by relatively unskilled staff and reduces transport difficulties. The performance of the Roche PCR assay using DBS has been evaluated and demonstrates comparable results to those obtained on liquid blood samples.[2] DBS prepared from capillary (e.g. heel prick) versus venous blood in 206 children also yields highly accurate HIV DNA PCR results with a sensitivity of 98.3% and specificity of 98.7%.[3]

Concerns have been raised over the following aspects of large-scale implementation of this technology in South Africa: (*i*)

the need for automation of this methodology; and (*ii*) concerns of contamination when spots are punched out either manually or via an automated punch. The issue of automation has been addressed at several levels within the laboratory: (*i*) automation of the punching step, using the BSD1000 GenePunch; (*ii*) at the extraction step, by conducting DNA extraction from both liquid blood samples and DBS using automated extraction systems such as the Roche MagNapure instrument; and (*iii*) investigation of more automated amplification and detection systems, such as the Roche Taqman DNA qualitative assay, which are ongoing studies.

We investigated the second concern expressed by laboratory scientists, that of contamination. In this study, the risk of contamination between samples was assessed during the excision of DBS for HIV-1 DNA PCR testing using a manual punch and an automated punching system.

For both the manual and the automated punch, a spot from a known HIV-negative patient was excised after a spot from a known HIV-infected patient. For the hand-held punch, 3 to 4 × 6 mm discs (± 50 µl) from a total of 372 samples using three different cleaning methods applied between each sample was evaluated. Cleaning methods included: (*i*) punch swabbed with Virkon/ethanol; (*ii*) punching a clean card; and (*iii*) no cleaning ($N = 124$ for each method). For the automated punch investigation, 7 × 3.2 mm discs were excised per spot (± 75 µl) from 202 samples and a clean card punched between each sample. This was followed by genomic DNA extraction from the discs followed by amplification and detection using the Roche Amplicor HIV-1 DNA assay version 1.5.

The manual punching method produced no false-positive HIV DNA PCR results. We obtained 1 and 3 equivocal results on HIV-negative samples with cleaning interventions (*i*) and (*ii*), respectively. This may represent a degree of contamination that was insufficient to affect the assay's specificity. The automated punch yielded 2 equivocal and 2 false-positive results (specificity 98%). Of the latter, 1 sample of DNA extracted from the same disc produced a negative HIV DNA PCR result, confirming that contamination had arisen downstream from the excision step. The other sample for which a false-positive result was obtained could not be retested (specificity 99%).

We concluded that available punching methodologies for DBS excision present very low risks of contamination. The automated punch option, although working well, is complicated by cost and significant space requirement. This work, together with publications cited above, suggest there can no longer be any reason for not scaling up early infant diagnosis in South Africa.

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EARLY MORTALITY AMONG PATIENTS WITH HIV-ASSOCIATED TUBERCULOSIS IN AFRICA: IMPLICATIONS FOR THE TIME TO INITIATION OF ANTIRETROVIRAL TREATMENT

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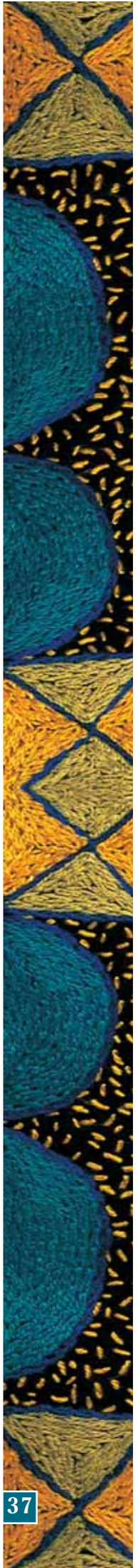
The HIV epidemic has been associated with major increases in tuberculosis (TB) notification rates in South African townships over the past 10 years, principally among young adults.[1] Not surprisingly, as antiretroviral treatment (ART) clinics have been established in these communities, TB has emerged as a key challenge. The burden of TB within ART clinics is very high. We have previously reported from an ART service in Gugulethu, Cape Town, that among patients enrolling in the clinic, 52% have previously been treated for one or more episodes of TB, 26% have an active diagnosis of TB and a further 10% develop TB during the first year of ART.[2] Overall, during the first year from enrolment, approximately one-third of patients receive concurrent antituberculosis treatment and ART.

The impact of this huge burden of TB within ART services in sub-Saharan Africa has not been fully characterised, but it might be expected to contribute to the high early mortality in programmes in the region.[3] Indeed, we have previously reported from the clinic in Gugulethu that patients who have TB at entry to the programme have a 2-fold greater mortality risk in the first year of ART compared with those who remain TB-free.[2] While not altogether surprising, this observation nevertheless warrants careful examination to gain a better understanding of the factors contributing to this high early mortality as some deaths may be preventable.

Firstly, it might be expected that among patients receiving concurrent TB treatment and ART, pharmacokinetic drug interactions and impaired treatment adherence (due to high pill burden, reduced regimen tolerability and overlapping toxicity profiles) would undermine responses to ART and thereby increase mortality risk. However, we and others have found this not to be the case, with good immunological and virological responses being observed among patients receiving rifampicin-containing TB treatment and efavirenz-based ART in standard dosages.[2,4,5] Secondly, concurrent use of rifampicin with nevirapine, another non-nucleoside reverse transcriptase inhibitor (NNRTI), has been associated with reports of severe hepatotoxicity.[6] However, in Gugulethu where efavirenz is the NNRTI routinely used and where monitoring of serum hepatic transaminases is available, no deaths attributable to efavirenz/rifampicin co-toxicity have occurred.[7] Thirdly, initiation of ART among patients receiving treatment for TB is commonly associated with immune reconstitution disease (frequently referred to by clinicians as immune reconstitution



inflammatory syndrome or 'TB IRIS'). However, although we have found that IRIS is common among patients with advanced immunodeficiency starting ART early in the course of TB treatment in the Gugulethu clinic, it is most commonly self-limiting and is an infrequent cause of death.[8] Indeed, IRIS associated with cryptococcal disease is a far more important cause of mortality than TB IRIS in this setting.[9,10]

None of the above factors therefore account for the high early mortality among TB patients accessing ART. A further critical question, though, is whether the timing of initiation of ART affects mortality risk among TB patients. This is potentially a very important variable, as it is one over which the clinician has direct control. We have previously shown that the mortality rate of patients entering the Gugulethu ART service is extremely high and even short delays in ART initiation may potentially be associated with appreciable mortality risk.[7,11] We therefore decided to study in more detail the early mortality among TB patients accessing ART with a focus on the timing of treatment initiation and presented these data at CROI.[12]

WHY WAS THIS STUDY DONE?

The aim of this study was to determine the mortality risk associated with TB among patients enrolling in the ART service in Gugulethu and to assess the association between mortality and the timing of ART initiation during TB treatment. These analyses were done to provide insights into the appropriate timing of ART in patients with HIV-associated TB.

WHAT DID THE RESEARCHERS DO AND FIND?

Mortality occurring in the two intervals between programme enrolment, initiation of ART and the first 16 weeks of treatment was prospectively studied among patients with (*N* = 213) and without (*N* = 675) TB accessing the ART service in Gugulethu, Cape Town. The mortality rate among those with TB was 1.8-fold (95% confidence interval (CI) = 1.62 - 2.80) greater than that of patients who were TB-free (40 versus 21 deaths/100 person-years; $p = 0.003$). When the TB patients were subdivided into those with active TB (*N* = 73) or inactive TB (*N* = 140), the mortality rate was significantly greater in both groups (44 and 37 deaths/100 person-years, respectively) compared with those who were TB-free (21 deaths/100 person-years) ($p < 0.01$ for each comparison).

Patients with TB, however, had lower CD4 cell counts than those who were TB-free, and this was potentially an explanation for the higher mortality rates observed. We therefore did multivariate analysis to assess risk factors for mortality in the whole cohort. In this analysis, TB (either active or inactive) was no longer significantly associated with mortality risk. Instead, mortality risk was only independently associated with baseline CD4 cell count < 100 cells/µl (adjusted hazards ratio (AHR) = 2.85, 95% CI = 1.52 - 5.34) and WHO clinical stage 4 disease (AHR = 2.94, 95% CI = 1.80 - 4.82). This analysis therefore showed that the high excess mortality risk among patients with TB was largely explained by advanced immunodeficiency and not with TB disease activity or even with diagnoses of TB *per se*. This is consistent with findings in cohorts in Zambia and Malawi.[13,14] Since mortality risk is predominantly associated with immunodeficiency, delays in the initiation of ART should be minimised.

We next examined the association between the timing of ART initiation in TB patients and mortality risk. Of patients with TB diagnosed within the programme prior to ART initiation (*N* = 73), 48 had received ART by data censorship after a median of 42 days from TB diagnosis. A total of 14 patients died. Just 4 deaths occurred after initiation of ART of which 2 were due to immune reconstitution disease. However, 10 deaths (71%) occurred in patients waiting to commence ART, most (*N* = 8) within the first 6 weeks of antituberculosis treatment. All those who died waiting to commence ART had either a CD4 cell count < 100 cells/µl or WHO stage 4 disease.

These data are observational (non-randomised) and therefore potentially subject to bias. However, baseline patient and disease characteristics did not differ when comparing those who died with those who survived or when comparing those who did or did not receive ART. Mortality risk was only associated with ART status. However, if ART were commenced earlier, it is not known what proportion of deaths might be prevented and also to what extent TB IRIS would become a greater problem.

WHAT DOES THIS MEAN?

These data are important with regard to the optimal timing of commencement of ART in patients with TB. There is no consensus between various national and international guidelines in respect of this timing. Moreover, it will be several years before the results of randomised controlled trials will become available to address this issue definitively. In the interim, these observational data therefore provide important insights for patients being treated in South Africa and elsewhere in sub-Saharan Africa.

Collectively these data indicate that patients with TB have high mortality risk due to advanced immunodeficiency and that with the current median delay of 42 days in this programme between TB diagnosis and starting ART, many patients die waiting to start ART. Clearly, the mortality risk associated with delays in ART in this service greatly exceeded any mortality risk associated with early initiation of ART (e.g. due to TB IRIS). Those at greatest risk of death were those with CD4 cell counts < 100 cells/µl and those with WHO stage 4 disease. Such patients should be prioritised in respect of early initiation of ART.

The optimal time for ART initiation cannot be determined from these non-randomised data. However, the current WHO guidelines for resource-limited settings recommend that TB patients with CD4 cell counts < 200 cells/µl should commence ART between 2 and 8 weeks of ART.[15] Data from this study strongly suggest that those with CD4 cell counts < 100 cells/µl and WHO stage 4 disease should commence ART as early as possible within this time-frame (i.e. after 2 weeks of TB treatment).

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ADOLESCENTS AND HIV VACCINE TRIALS

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The incidence and prevalence of HIV infection among adolescents and young adults in South Africa is extremely high, particularly among girls. Data from national seroprevalence surveys estimate the prevalence of HIV to be 9.4% among 15 - 19-year-old girls and 23.9% in women aged 20 - 24.[1] Four young women between the ages of 15 and 24 are infected for every man in the same age group. Despite current efforts, including HIV prevention programmes targeted to youth, HIV infection rates have shown no sign of decreasing. The lack of a substantial decline in HIV incidence among young women in South Africa may be attributed to the marked changes in society seen since the transition from apartheid with concomitant rapid rates of urbanisation, disintegration of family structures, and a general lack of understanding of adolescent sexuality, current youth attitudes and practices. Currently HIV prevention programmes within South Africa have not been context-specific, which may have contributed to the lack of appreciable behaviour changes seen, despite high levels of HIV/AIDS awareness. As South Africa will be the first country to enrol adolescents aged 16 - 18 years into a phase IIb efficacy HIV vaccine trial (the HVTN 503 study), it is imperative to understand some of the challenges to adolescent enrolment in HIV vaccine trials.

Studies performed to date in Soweto include a cross-sectional survey of knowledge and attitudes to HIV/AIDS and HIV vaccines and willingness among adolescents and their stakeholders to participate in a hypothetical study, as well as a small longitudinal cohort study that assessed sexual risk behaviour and knowledge and attitudes to HIV among Soweto youth aged 12 - 21.

ADOLESCENT INVOLVEMENT IN VACCINE TRIALS

A two-stage sampling procedure was used. The first-stage sampling units were all 72 public high schools in Soweto. Ten schools were randomly selected and the first four were approached regarding participation. All pupils in the selected schools from whom parental consent and child assent could be obtained were eligible for participation. A self-administered, facilitated questionnaire was completed by participants. Two hundred and seventy-seven school-going youth (mean age 16.2 years, range 10 - 25, 53.1% female) participated in this survey. Of 240 responses to the willingness item, 84 (35%) indicated they were probably and 126 (52.5%) definitely willing to join a study of a vaccine to prevent HIV. There were no significant differences in willingness by gender, age, school grade, or institution. Factors rated as 'very important' in determining willingness included receiving current information about HIV research (*N* = 209, 88.2%), getting free counselling and testing every 6 months (*N* = 168, 70%), indicating that participants would be doing something to honour people who have HIV/AIDS or have died of AIDS (*N* = 168, 70%), and that participants may receive some protection against HIV infection from the vaccine (*N* = 167, 70.5%). Some misconceptions regarding vaccine research were common, particularly regarding placebo and potential eligibility criteria for vaccine trials. Soweto school-going youth report high degrees of willingness to participate in HIV vaccine trials. Whether hypothetical willingness translates into participation will await data from adolescent HIV vaccine trials.

ADULTS' PERCEPTIONS REGARDING ADOLESCENT PARTICIPATION IN VACCINE TRIALS

This study was conducted in Soweto between August 2005 and March 2006. The participants for this study were recruited using convenience and snowballing techniques as well as through community outreach. A self-administered questionnaire in English was completed by participants, with facilitation by study staff. The sample size was 64 (mean age, 41.3 years), 57% of participants were women, 55 were parents and 9 were teachers. Regarding adolescent sexual risk, of the 64 adults who participated in this research, 31 (55%) believed that the sexual debut of Soweto children may be as early as age 9 and 39 (70%) believed that these children were vulnerable to HIV infection. Sixty per cent (*N* = 33) of participants believed that adults spoke to their 9 - 10-year-olds about HIV. Most adults indicated that they would want to know if their child is sexually active (91%) and that should their child participate in an HIV vaccine trial, they would want to know their HIV test results.

A great concern to researchers involved in HIV vaccine research is the issue of 'social harm' that trial participation may cause. Potential social harms that may impact on trial participation include the perception of being at high risk of HIV acquisition, or being thought to have AIDS. In this study, more than half the adults sampled did not believe that the perceived stigma of HIV vaccine trial participation would impact on their decision to allow their adolescents to

participate in a HIV vaccine trial (Table I). The relationship between trial participation and stigma in this research did not distinguish between participation in phase I, II or IIb/III trials and the potential distinction made in the trial eligibility criteria with regard to the sexual risk profile of participants. Moreover, the figures presented here reflect attitudes of an uninitiated population. It is not beyond reason that attitudes towards HIV vaccine trial participation may change with better understanding of the clinical trial process.

Willingness to participate in a hypothetical HIV vaccine trial may not reflect participation in an actual trial. This notwithstanding, 44 (80%) indicated willingness ('Probably would' (27%) or 'Definitely would' (53%)) to allow adolescent participation and 51 (91%) indicated that they would also want to be involved in the research. Of the respondents 48 (86%) indicated that they have confidence in medical research; however, 9 (16%) thought that HIV vaccine research was unsafe and 18 (32%) were unsure whether vaccine research is unsafe. Factors cited as important for deciding on trial participation included potential benefits of participation, such as access to information and counselling; potential impact on risk behaviour; and potential protection against HIV from the vaccine. Participation was also seen as altruistic and socially beneficial. Access to counselling and testing, current information, and potential impacts on improving motivation to reduce risk behaviour were very important for determining willingness to participate.

The Soweto community, located within Gauteng province where an estimated 14.5% of its population is estimated to be HIV infected,[1] is heavily affected by HIV. It is therefore not surprising to see the high level of HIV discourse occurring and the low levels of reported stigma. Most (49/50) of the adults we sampled had spoken to others about HIV, 43/48 had spoken to family members, 30/50 had ever been tested for HIV, and only 9/50 felt afraid of people with HIV while 12/50 felt uncomfortable around people with HIV.

ADOLESCENT HIV PREVENTION AND VACCINE PREPAREDNESS STUDY

This study was conducted to demonstrate that adolescents could be retained in a longitudinal cohort study. This study also assessed over time: risk behaviour; willingness to participate in vaccine trials; knowledge and attitudes towards HIV/AIDS; and documented for the first time in an African setting, family and social networks of participants, enabling a more dynamic delineation of risk. From July 2005 to November 2005, 52 'index' adolescents (adolescent initially contacted and enrolled) and 19 'alter' adolescents (adolescents referred by the index from their family or social network) were enrolled into the study (Table II). Overall, 69 participants were eligible for follow-up. More than 50% of participants were female. Most (56) participants were in school, with the median year of schooling being approximately 10 years. Only 5 participants had previously had access to HIV testing and counselling. Most participants (56/65) were willing to undergo HIV testing and counselling. Twenty-six (37.7%) participants reported that they had had penetrative sex. However, only 9 (35%) reported consistent condom use, with 3 (11.5%) reporting that they had never used a condom, and 5 (19%) reporting use of condoms for more or less half the time.

Birth control was not widely used, with only 10 (26%) participants using condoms as a birth control method, 1 participant using withdrawal as a contraceptive method, and 1 participant using hormonal contraception. One participant reported ever having been pregnant. Preliminary data available from the 2-week post-prevention intervention session designed to deal with HIV vaccine research demonstrated that adolescents need more information and education to understand some of the fundamentals of HIV vaccine research. The concept of placebo was not fully understood; some adolescents (15%) believed that an HIV vaccine could give one HIV. The issue of vaccine-induced seropositivity appeared to be understood by most participants. Approximately two-thirds of adolescents were willing to participate in HIV vaccine trials and almost 70% were comfortable about referring other adolescents or family members for participation in such trials. Interestingly, most adolescents were willing to participate in future vaccine research. There appeared to be few barriers cited for vaccine trial participation. Motivators for being involved in vaccine trials were mostly related to altruism or a desire to learn more about HIV/research. Almost a quarter of participants indicated that receiving reimbursement for trial participation would be a reason to be involved in research. Thirty per cent of adolescents indicated they would be wary of trial participation because of potential side-effects, 20% indicated that they needed more information before they could make up their minds regarding trial participation, and 60% agreed that they were at risk of HIV acquisition and therefore would consider trial participation.

TABLE I. STIGMA AND HIV VACCINE TRIAL PARTICIPATION

	How important to decision? (*N* (%))			
Factor	Very	Somewhat	Slightly	Not at all
My child may be discriminated against at school	12 (22)	4 (7)	9 (16)	30 (55)
People may avoid my child	12 (22)	6 (11)	7 (13)	30 (55)
People may think my child has HIV or AIDS	5 (9)	8 (15)	4 (7)	38 (69)
People may think my child is at high risk of HIV or AIDS	5 (9)	9 (16)	10 (18)	32 (57)
People may not want to have sex with my child	15 (27)	5 (9)	9 (16)	27 (58)

TABLE II. DEMOGRAPHICS OF ADOLESCENTS PARTICIPATING IN THE HIV PREVENTION AND HIV VACCINE PREPAREDNESS STUDY

	Index (*N* = 50)	Alter (*N* = 19)
Gender	25 female	11 female
Median (yrs)	16.68	17.05
Soweto residents	45	17
Ethnicity	Black = 50	Black = 18*
Scholars	37	19
Median years of education (IQR)	9.78	10.44
Sexually active	18	8
Drug use	6	1
Alcohol use	32	14

*Missing = 1.

CONCLUSION

Taken together, these preliminary studies indicate a high degree of willingness to participate in HIV vaccine trials among Soweto youth and adults. The need for regular risk reduction counselling was highlighted as an important benefit by both youth and adults, indicating the perceived need for developmentally and culturally tailored tools, as well as for services for youth. The adolescent vaccine preparedness study has been critical to developing site expertise in studies with adolescent participation. This programme also highlighted several key developmental issues that would require adaptation of existing risk reduction counselling formats and content to fully address the needs of Soweto youth.

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EMERGING HIV-1 DRUG RESISTANCE PATTERNS FROM TWO JOHANNESBURG CLINICS ON THE SOUTH AFRICAN ARV ROLL-OUT PROGRAMME

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The South African government began the antiretroviral (ARV) roll-out programme in April 2004, and over 250 000 AIDS patients have been enrolled to date. The programme uses two standardised regimens for all patients accessing care, with the first-line regimen consisting of lamivudine (3TC), stavudine (d4T), efavirenz (EFV)/nevirapine (NVP) and the second line consisting of didanosine (ddI), zidovudine (AZT) and Kaletra. There are already reports of treatment failures in South African HIV-1 subtype C-infected patients accessing ARV drugs, attributed to the emergence of drug-resistant viruses. However, there are currently no published data available on the development of ARV drug resistance (DR) in South African HIV-1 infected individuals on the chosen public sector regimens. Routine resistance testing is currently not available in South Africa owing to prohibitive costs of current sequencing-based assays.

There is no consensus yet in the literature about the possible effects of the genetic diversity of HIV-1 on the development of DR, although several publications describe subtype-specific DR mutations/polymorphisms. ARV DR studies conducted in subtype C-infected individuals failing therapy from Zimbabwe,[1] Brazil,[2] Ethiopia,[3] and Botswana[4,5] revealed that HIV-1 subtype C developed similar ARV mutation profiles to HIV-1 subtype B. However, comparisons of subtype C reverse transcriptase (RT) and protease (PR) sequences to subtype B sequences, and corresponding clinical data have revealed subtype C-specific polymorphisms that impact on treatment outcome. For example, V106M has previously been shown to be a subtype C-specific mutation in patients failing EFV,[6,7] and is a result of a natural polymorphism that occurs at this codon. The K65R mutation may emerge at a higher frequency in HIV-1 subtype C-infected patients on certain nucleoside reverse transcriptase inhibitor (NRTI)-containing regimens,[5] and its rapid emergence has been shown to confer resistance to tenofovir in cell culture.[7] The K103N mutation occurred at a greater frequency and higher levels in women infected with subtypes C and D as opposed to subtype A.[8] In addition, the pathways leading to non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI) resistance may be subtype-specific. For example, Grossman *et al*.,[9] and Douella-Bell *et al*.,[5] showed that HIV-1 subtype C-infected patients on nelfinavir-containing regimens developed resistance to this PI through distinct mutational pathways from subtype B. A number of other studies have confirmed the presence of baseline polymorphisms in subtype C in the protease regions.[10,11] These data confirm the need for continued evaluation of drug resistance patterns in HIV subtype C.

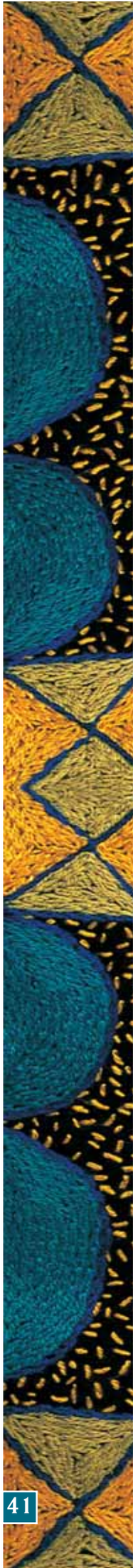
In an effort to begin to understand the evolution of HIV-1 subtype C drug resistance (HIVDR) in South Africa, a pilot study was performed in patients demonstrating treatment failure in two Johannesburg clinics. This study looked at HIVDR patterns emerging in patients failing either the first- or second-line regimens or a combination thereof.

One hundred and fifteen patient samples from the two Johannesburg clinics were sent for HIVDR testing. Clinics 1 and 2 defined virological failure differently. Clinic 1 defined it as HIV RNA levels greater than 1 000 copies/ml on two consecutive visits, whereas at clinic 2 it was classified by a repeated viral load greater than 5 000 copies/ml. The average viral load from patients failing therapy at clinic 2 was found to be 0.8 log higher than clinic 1. The RT mutation patterns seen in our two cohorts have been documented previously in subtype B, with a few exceptions. The mutations that occurred at the highest frequencies (>10%) at both clinics were M184V, K103N, V106M, G190A, D67N and can be directly attributed to the ARV drug pressure exerted from the prescribed regimens in South Africa. However, the ARV DR mutation profiles in patients failing therapy were different in the two clinics, with clinic 2 appearing to have significantly more complex resistance profiles for the RT-associated mutations. These complex mutation patterns may be a result of leaving patients on a failing regimen for an extended period of time.

The higher frequency of the K65R mutation, 7.87% and 11.54% at clinics 1 and 2, respectively, is unusual as it is not commonly associated with the prescribed regimens. Two factors may potentially be contributing to this increase in K65R. Firstly, studies have shown that patients left on failing regimens accumulate several mutations, one of which is K65R, which may be the case in clinic 2. Secondly, the bases at this codon are different from those in HIV-1 subtype B and may have resulted in a faster switch to the K65R mutation.

There was also an increase of thymidine analogue mutations (TAMs) at clinic 2, which accumulate over time and confer cross-resistance to most NRTIs, making salvage therapy difficult. Previous studies have suggested that a delayed switching causes complex resistance patterns to arise (as seen in clinic 2), resulting in reduced susceptibility to most if not all NRTIs and the PIs being the only effective drug in the second-line regimen.

As in other studies, both clinic 1 and 2 showed a high prevalence of secondary mutations and several naturally occurring polymorphisms in the PR region. The presence of these polymorphisms in HIV-1 subtype C PR region may have



an impact on the efficacy of the PI drugs that will be included in future drug regimens.

CONCLUSION

ARV drug treatment failure in HIV-1 subtype C-infected patients is associated with the development of DR, and these mutation patterns are similar to subtype B. The data suggest that the longer the treatment is continued in the presence of drug-resistant viruses, the more DR mutations accumulate. Viral load monitoring of HIV treatment may therefore be important even in resource-poor countries. High-level DR mutations that lead to broad-class DR for NRTIs were demonstrated, providing concern for the use of tenofovir in second-line treatment, and strategies of recycling NRTIs in second-line treatment. Finally, these preliminary findings need to be further investigated and confirmed on a larger sample size in a controlled study.

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OUTCOMES OF CHILDREN ON NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR VERSUS PROTEASE INHIBITOR HAART REGIMENS IN RESOURCE-LIMITED SETTINGS

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Few data exist as to the most effective highly active antiretroviral therapy (HAART) regimens for children with vertically acquired HIV infection. Most countries in southern Africa have limited regimens based on nucleoside analog reverse transcriptase inhibitor (NRTI) backbones combined with either a non-NRTI (nNRTI) or a protease inhibitor (PI). The World Health Organization (WHO) recommends nNRTI-containing regimens as the first line for children despite the fact that nevirapine (NVP) is often used for vertical transmission prevention (PMTCT) in these settings. In addition, recent evidence suggests that recommended dosing for NVP and efavirenz (EFV) in children may be too low.

WHY WAS THIS STUDY DONE?

1. To evaluate the outcomes of children on HAART in a resource-limited setting.
2. To compare laboratory and clinical outcomes of children on PI versus nNRTI-containing regimens.
3. To determine the correlates of virological suppression (VS).

WHAT DID THE RESEARCHERS DO AND FIND?

This study describes the outcomes of a cohort of 389 children on HAART treated in a public sector hospital-based antiretroviral programme. Children were started on HAART that included two NRTIs, and either an nNRTI (NVP or EFV) or a PI (lopinavir/ritonavir or ritonavir). Approximately 50% of the children received a PI (N = 199) v. nNRTI (N = 188). Few children in this group were exposed to NVP for PMTCT.

The median age at baseline was 26.3 (intraquartile range (IQR) 12.4 - 53.8) months, the median baseline CD4 percentage 13% (IQR 8.0 - 17.0%) and median viral load 5.5 $\log_{10}$ (IQR 4.8 - 6.0 $\log_{10}$). The median baseline weight-for-age Z-score (WAZ) was –2.5. There was no significant difference in baseline characteristics of patients on the different regimens with viral load, CD4 percentage or WAZ; however infants initiating treatment with an nNRTI were older (34.3 v. 21.8 months, $p < 0.01$).

There were obvious improvements in the infants in all parameters after the initiation of HAART. The overall increase in CD4% from baseline to 24 months on treatment was 13% (double that at baseline), and increase in WAZ of 1.8. An overall viral load log drop of 2.6 $\log^{10}$ occurred at 24 months of treatment. However, when comparing PI versus nNRTI regimens, a significantly better virological response was seen among those children receiving a PI at all times through 48 months, although there were no differences in CD4%, WAZ or in survival.

In a multivariate analysis predicting VS, PI-based regimens were independently associated with VS, as was CD4 percentage, WAZ, and age. This association was evident even when adjusting for year of starting HAART.

WHAT DO THESE FINDINGS MEAN?

HAART greatly improves the health of children in resource-limited settings. However, despite profound improvements in outcomes, this study found nNRTI-based regimens inferior to PI regimens in achieving and maintaining virological suppression. This difference did not seem to have clinical implications during the study period, since there was no difference on growth, immunological outcomes, or survival. Nevertheless, the implications of detectable viraemia in

children are that resistance may develop and switches to second-line regimens may therefore occur sooner. In developing country settings where regimens are limited, the goal of HAART should be to reach and maintain undetectable viral loads for as long as possible. The effectiveness of regimens containing nNRTIs may be decreased in this setting because of less than optimal dosing, drug-drug interactions (such as tuberculosis therapy), or PMTCT programmes. There is an urgent need to further explore optimal regimens, dosing, and pharmacokinetic interaction studies for children on HAART in these settings.

This work was supported in part by the Kidzpositive Family Fund and the One to One Children's Fund.

RECRUITMENT AND SEXUAL RISK ASSESSMENT OF HIV-NEGATIVE ADOLESCENTS AGED 14 - 17 YEARS IN PREPARATION FOR HIV VACCINE TRIALS

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The majority of new HIV infections in sub-Saharan Africa occur between ages 15 and 24 years, so adolescents are important targets for HIV preventive vaccination and must be included in HIV vaccine trials. To date no HIV vaccine trials have included adolescents, in part because of the challenges associated with HIV prevention research in young people, including issues of recruitment, informed consent, confidentiality, stigma, and potential for behavioural disinhibition. Adolescents are likely to be 'hard to reach', and may be difficult to recruit into long-term studies. Phase I to III vaccine trials require participants of specific sexual risk, but adolescents may not freely admit their sexual behaviour. More information is needed to assess the feasibility of recruiting adolescents of varying sexual risk into HIV prevention research.

WHY WAS THIS STUDY DONE?

- To assess the feasibility of recruiting HIV-negative 14 - 17-year-olds, with parental consent, from a community in which HIV vaccine trials are planned.
- To compare different methods of recruiting adolescents into HIV prevention research.
- To assess self-reported HIV risk-related perceptions, knowledge and behaviours in this group.

WHAT DID THE RESEARCHERS DO AND FIND?

Adolescents aged 14 - 17 were recruited from a peri-urban Xhosa-speaking community. Consent was obtained from all adolescents and a parent or legal guardian. HIV and syphilis testing was performed, and pregnancy testing where applicable. Participants completed interviewer-assisted paper questionnaires on demographics, sexual risk behaviour, HIV knowledge, and perceived risk for HIV.

There were 107 adolescents screened; 3 failed screening due to HIV infection and 3 due to pregnancy, and 1 was underage. The study was fully enrolled in 4 months. Challenges arose in obtaining consent from parents, and required after-hours home visits. Of the 100 adolescents enrolled, 98 were recruited through outreach activities.

The mean age of the cohort was 15 years, and 70% were female. All participants were attending school with a median level of education of 8th grade. In general, HIV knowledge was high, except that only 78% knew that an infected person could test negative on routine HIV testing, and only 93% thought a person with HIV could look healthy.

Risky sexual behaviour was reported by the participants, with 43% reporting sexual activity, and 30% of these reporting more than one partner in the past year. Only 19% knew the HIV status of their partner, yet 21% had never used a condom in the past 6 months. The adolescents perceived themselves to be at low risk of infection with HIV despite this behaviour, with only 3% reporting that they were at risk, and 63% believing that their bodies could fight off HIV. However, one-third felt that getting HIV would be bad for their futures and their family relationships. Among the sexually active adolescents, condom use was not associated with perceived risk ($p = 0.32$). Perceived risk was not associated with HIV knowledge ($p = 0.30$). Females were more likely to perceive themselves as at high risk for HIV ($p = 0.06$); however, this association did not persist when adjusting for sexual activity. In a multivariate analysis predicting sexual activity, adjusting for HIV knowledge, perceived personal impact of HIV, and gender, only perceived risk for HIV was positively associated with sexual activity.

WHAT DO THESE FINDINGS MEAN?

Recruitment for this study was relatively rapid, but required flexibility in clinic hours. Recruitment via outreach activities seems to be far more effective than through voluntary counselling and testing (VCT), a method often used for recruitment of adults. This may be due to the poor VCT attendance of adolescents in this community. The high level of sexual risk-taking in this population suggests that young people are at substantial risk of HIV infection, yet these adolescents do not perceive themselves to be at high risk for HIV. This is not due to poor HIV knowledge, as the level of HIV knowledge among these adolescents was high. HIV prevention intervention studies will therefore need strong age-appropriate risk-reduction counselling. As shown in prior studies, young females are more often sexually active, and therefore at higher risk for HIV, than young males. Yet these young women are also more aware of their HIV risk. There is an ethical imperative to facilitate inclusion of adolescents in HIV vaccine trials in order to ensure rapid licensure of a successful vaccine for this high-risk group.

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CHALLENGES OF TB DIAGNOSIS AND TREATMENT IN SOUTH AFRICA

Roche Symposium, 3rd South African AIDS Conference, Durban, 5 - 8 June 2007

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It is estimated that 2 billion of the world's population are latently infected with *Mycobacterium tuberculosis* (Mtb) with a resultant 8 - 9 million cases of active tuberculosis (TB) and 1.6 million deaths annually.[1] The tools used for diagnosis of TB have remained largely unchanged since the 1880s when sputum microscopy, Mtb culture on solid media, tuberculin skin testing and chest radiology were initially developed. In 1991 the World Health Assembly set targets to be reached in 2005 for 70% case finding of smear-positive TB, which represents 6 million cases to be identified per annum.[2] A second target was that 80% (5 million) of those identified cases should complete anti-TB treatment.[2] Subsequently the millennium development goals of 2000 set a target of halving the prevalence of TB disease from 300/100 000 to 150/100 000 and deaths from 30/100 000 to 15/100 000 by 2015.[3] While progress toward these targets was being made in countries with established market economies there was a quadrupling of TB incidence between 1990 and 2005 in most African countries. In 2005 the World Health Organization Regional Committee for Africa declared TB an emergency for the African region.[4]

In South Africa in 2005 the WHO estimated that of 284 592 TB cases 270 360 were notified to the national TB control programme, representing a somewhat ambitious reported case finding proportion of 95%.[5] The proportion treated under the directly observed treatment (DOTS) programme is 94%, and HIV prevalence among notified cases was 58% (97.5% confidence interval (CI) 49 - 65%). South Africa is a middle-income country and is relatively well provided with 143 laboratories performing sputum smears, and 18 culture laboratories also capable of performing drug sensitivity testing.[5] Multidrug resistance (MDR) in new TB cases varies between provinces from 0.9% to 3.6%, while MDR is higher among retreatment cases, with prevalence rates varying between 1.8% to 13.7% in different provincial surveys.

THE CHALLENGE OF HIV IN TB CONTROL

The HIV epidemic in South Africa has been associated with a similar increase in TB case load as reported in other sub-Saharan countries. The incidence of TB has increased markedly among HIV-infected individuals, with a proportional increase in smear-negative pulmonary disease, extrapulmonary involvement, frequent atypical clinical presentations, an increased mortality and a strong association with multidrug and extreme drug-resistant TB. The impact of HIV on a TB clinic is illustrated by the changes in TB notification data from a Cape Town peri-urban township over the last 10 years as HIV adult seroprevalence has increased from 8% in 1996 to 23% in 2005.[6] During this period TB incidence rates have increased 4.75-fold from 400/100 000 in 1996 to 190 000/100 000 in 2005, with the highest increase occurring in 20 - 40-year-olds.[6] In 2005 the overall TB notification rate was 5.4-fold higher among HIV-positive individuals (5 140/100 000) than HIV-negative individuals (953/100 000) (Table I). Smear-negative disease notification was 8-fold higher among HIV-positive individuals (1 891/100 000) than HIV-negative individuals (238/100 000). Despite a plateauing of HIV seroprevalence, TB notifications have continued to increase.[6]

THE CHALLENGE OF TB IN AN ART PROGRAMME

The diagnosis of TB is particularly challenging in patients accessing antiretroviral therapy (ART) when their HIV infection is advanced. The Hannan Crusaid clinic was the first dedicated public sector ART facility in South Africa and

TABLE I. ADULT PULMONARY TB NOTIFICATION RATES PER 100 000 IN A CAPE TOWN PERI-URBAN TOWNSHIP 2005

TB type	Total adult population	HIV-positive adults	HIV-negative adults	HIV+ve/HIV -ve ratio
(PTB)	1 931	5 140	953	5.4
Smear-positive PTB	1 307	3 248	715	4.5
Smear-negative PTB	624	1 891	238	7.9

PTB = pulmonary tuberculosis.

currently provides treatment to 3 000 patients. Eighty-nine per cent of those accessing ART have symptomatic HIV disease (WHO clinical stage 3 and 4) with a median CD4 cell count of 95 cells/µl. More than 50% have a history of prior completed TB treatment, 15% are on current TB treatment, 11% are diagnosed with previously undiagnosed TB, and a further 10% develop new incident TB after initiation of ART.[7] Multivariate analysis identified risk factors for development of incident TB to be WHO stage 3 and 4 disease (relative risk (RR) 5.9, 95% CI 3.2 - 10.9 and 8.9 95% CI 4.6 - 17.3 respectively), baseline CD4 cell count (RR 1.41, 95% CI 1.2 - 3.1 for each 50 CD4 cell count decline) and baseline viral load (RR 1.4, 95% CI 1.1 - 1.8). A history of completed TB treatment within the previous 2 years was associated with significant protection against incident TB (RR 0.21, 95% CI 0.2 - 0.7).

THE CHALLENGE OF HIV/TB IN A COMMUNITY

The high case finding proportion (close to 100%)[2] reported for the South African TB control programme is based on an estimate of the TB burden. The programme is based on passive case finding together with directly observed therapy of those cases identified. Active case finding enables a direct assessment of TB burden and can identify differing case finding proportions for either HIV-negative or HIV-positive individuals. Active TB case finding and HIV testing of a randomly selected sample of 762 individuals living in Masiphumelele, a peri-urban township outside Cape Town, was performed in 2005 and identified 23% of adults to be seropositive for HIV, 11 individuals with prevalent treated TB and a further 12 individuals with previously unrecognised smear-positive ($N = 6$) and culture-positive ($N = 6$) pulmonary TB.[8] Both HIV infection and a history of recent incarceration were strongly associated with TB. The TB prevalence among HIV-infected individuals was 7.6%, of which 4.4% was smear-positive disease. The case finding proportion for HIV-negative individuals (ratio of prevalence of treated to prevalence of treated and untreated with smear-positive disease) was 67% (95% CI 41 - 100), while that for HIV-positive individuals with smear-positive disease was 37% (95% CI 25 - 53) (Table II). In this community, with a single TB clinic providing care to the whole community, the TB control programme appeared to perform less well for those with HIV infection than for those who were HIV negative.

THE CHALLENGE OF MULTI- AND EXTREMELY DRUG-RESISTANT TB

In 2005 an outbreak of extremely drug-resistant TB (XDR) was recognised in Tugela Ferry, situated in a rural area of northern KwaZulu-Natal. A report of the first 53 cases was published in 2006.[9] The epidemic was recognised in predominantly HIV-positive individuals and was characterised by an extremely high early mortality rate. Over 50% of cases of XDR died within 30 days of presentation. Eighty per cent of the identified cases had positive sputum smears and 25% had evidence of extrapulmonary involvement. Analysis of risk factors for XDR identified that 55% had no history of prior treatment for TB, indicating that these cases had primary rather than acquired resistance. Only 15% had a history of treatment default or failure. The one factor which was of concern was that 67% gave a history of admission to the local health facility, raising the concern that nosocomial transmission may have played a significant role in the epidemic. XDR cases have continued to be recognised, and 266 cases have been confirmed of which 264 were HIV-positive. This epidemic illustrates the potential problems associated with integration of HIV and TB programmes and the increasing need for rapid diagnosis of initial TB infection in both HIV-positive and negative individuals and recognition of early treatment failure and development of resistance within a treatment programme.

TABLE II. PREVALENCE OF TREATED AND UNTREATED SMEAR-POSITIVE PULMONARY TB WITH ACTIVE CASE FINDING AMONG HIV-SEROPOSITIVE AND HIV-SERONEGATIVE INDIVIDUALS

	HIV-positive adults	HIV-negative adults
Prevalence of treated smear-positive PTB	1 563 (1 108 - 2 138)	352 (233 - 507)
Prevalence of treated and untreated smear-positive PTB	4 400 (3 619 - 5 299)	527 (280 - 711)
Case finding proportion	0.37 (0.25 - 0.53)	0.67 (0.41 - 1.0)

PTB = pulmonary tuberculosis.

CURRENT TB DIAGNOSTICS

Current TB diagnostics, TB skin testing (TST), sputum smear and culture and radiology have remained the mainstay of TB diagnostics since 1882. TST has been used to support the diagnosis of TB in populations where TB infection is low. In South Africa a positive TST can be used to support the diagnosis in paediatric TB but is of limited use in adult diagnosis. TST is however still a useful tool for epidemiological studies of the annual risk of infection in children but by adulthood the majority of South Africans have been exposed to TB. In industrialised countries the TST identifies a minority of individuals who are at increased risk of disease progression, to whom diagnostic and preventive resources can be targeted. In contrast, in South Africa the majority of adults have already been exposed to TB and in those with advanced HIV infection, who are at highest risk of disease progression, the test has low sensitivity with up to 50% false negatives.

Sputum smear microscopy has high specificity in high TB prevalence settings. Sputum microscopy has been the mainstay of TB control programmes as it is able to identify the most infectious cases. The test is relatively inexpensive and widely available. Despite its wide availability in the field it is dependent on highly motivated technicians. The overall sensitivity for identifying TB infection is 35 - 70%, but the sensitivity in HIV-infected cases can be as low as 20%.

Diagnosis of TB with a chest X-ray is fast, convenient and has high sensitivity in HIV-negative individuals. In HIV infection the radiological findings of active TB disease decrease with the level of immune suppression, resulting in low sensitivity in advanced disease.[10] The occurrence of opportunistic diseases that can also mimic the radiological changes of TB results in lowered specificity in AIDS cases. The combination of relative expense, restricted availability and low sensitivity and specificity in HIV infection limits the role of radiology for TB control in the high HIV prevalence setting.

Mtb culture is sensitive and specific for pulmonary TB in both HIV-positive and HIV-negative individuals. Solid media culture, however, is limited by the prolonged time required for positive and negative results, which can be delayed for 6 - 8 weeks. Culture of sputum has low sensitivity for extrapulmonary TB, which occurs more commonly in HIV-infection. TB culture also requires a high level of laboratory bio-safety, which consequently restricts its availability to sophisticated centralised reference laboratories.

NEW TECHNOLOGIES

Serological diagnosis of TB is a relatively simple and inexpensive technology which could be a potentially attractive strategy for paediatric and adult extrapulmonary TB diagnosis. A large number of commercially marketed antibody detection tests are available. In 2005 the WHO performed an evaluation of available TB rapid diagnostic antibody tests. Nineteen of 27 invited manufacturers agreed to submit their products for evaluation against a panel of known specimens. The evaluation study found that the performance of antibody tests varied widely with high 'lot to lot' and 'reader to reader' variability. The specificity was less than 80% in the majority of products. Those tests with higher sensitivity lacked specificity and detected fewer than 40% of TB cases. The conclusion of the study was that none of the antibody assays performed well enough to replace microscopy.[11]

Liporabinomannan (LAM) is a component of Mtb cell walls, which is excreted unchanged in urine. A quantitative enzyme-linked immunoassay (ELISA) has been used to demonstrate a correlation between urinary LAM concentrations and the level of Mtb organism load in the sputum of pulmonary TB cases.[12] Urinary LAM concentrations may therefore be a reflection of infecting Mtb organism load, able to diagnose TB in both HIV-positive and HIV-negative individuals. The quantitative thresholds of urinary LAM for diagnosis and sensitivity, and specificity for identifying pulmonary and extra-pulmonary TB, are still to be defined. The LAM ELISA format is suited for peripheral laboratory use; however, a simpler 'tube format' test has also been shown to be robust and does not require a cold chain. A dipstick format of the test is under development, which could possibly prove be the first TB diagnostic suitable for use in 'point of care' clinics.

Cytokine detection assays are based on the observation that lymphocytes with immunological memory produce interferon-gamma (INF-γ) when re-exposed to a specific antigenic challenge. Two commercially available assays have been developed; the QuantiFERON®-TB GOLD, which uses whole blood as its substrate, and the T-SPOT TB assay, which uses isolated peripheral blood mononuclear cells. Both assays use Mtb specific antigens and therefore should not be subject to cross-reactions due to exposure to other environmental mycobacteria or exposure to the *M. bovis* strain used for BCG vaccination. The performance criteria of these tests for identifying latently infected individuals in published studies is in the range of 0.75 - 0.95 for sensitivity and 0.9 - 1.0 for specificity; however, the sensitivity in HIV-infected individuals may be reduced.[13] The advantage of INF-γ assays over TST, of a single visit with a result not subject to observer error, is offset by the requirement of venepuncture, the cost and the need for laboratory infrastructure. Although cytokine assays appear to be more sophisticated and sensitive versions of the TST, these tests may be measuring differing aspects of the immune responses to Mtb infection. INF-γ secretion by cells incubated with mycobacterial antigens over a week may reflect long-term immunological memory, while the shorter 3-day incubation may reflect more recent immunological memory. We have shown that the 3-day INF-γ secretion from PBMCs co-incubated with Mtb antigens is similar in both HIV-negative and HIV-positive controls, but the secretion from cells of those with a history of recent TB treatment was significantly lower than controls (S D Lawn – personal communication).

CULTURE TECHNIQUES

Culture of Mtb remains the gold standard for both diagnosis and drug sensitivity testing. The characteristics of culture and media and growth detection are shown in Fig. 1. Culture in liquid media is faster, with results available as soon as 7 days compared with 42 - 56 days' required growth on solid media. A variety of growth detection methodologies have been utilised. Early detection of growth may be based on mycobacterial metabolism, identification of microscopic

Culture

- More sensitive than direct sputum smear, requires between 5 and 100 organisms/ml v. 5 000 - 10 000 for positive smear
- Allows species identification and concomitant drug sensitivity testing (DST)

Media

- Solid media requires 6 - 8 weeks for confirmed diagnosis and further 4 - 6 weeks for DST
- Liquid culture is faster with results of diagnosis and DST as soon as 7 days

Growth detection methods

- Radioactivity – BACTEC 460-TB®
- Fluorescence – BACTEC MGIT 960®
- Phage-based tests – FASTPlaque TB-RIF™
- Inverted microscopy – MODS

Fig. 1. Characteristics of Mycobacterium tuberculosis *culture.*

colonies or macroscopic plaques on secondary organisms. The BACTEC 460-TB® commercial assay incorporates a radioactive marker in the liquid media which is detected when growth occurs. A more recent development, the BACTEC MGIT 960® assay, utilises a plastic tube containing a broth with a fluorescence quenching-based oxygen sensor. Consumption of oxygen by growth of Mtb produces fluorescence when illuminated by a UV lamp. The non-commercial microscopic optical detection system (MODS) uses an inverted microscope to detect characteristic tangles of developing Mtb colonies in 96 well pates. The FAST-plaque™ assay identifies viable organisms which have been infected with bacteriophages by the development of macroscopically visible plaques on a lawn of fast-growing *M. smegmatis*.[14]

Drug sensitivity testing (DST) conventionally takes 4 - 6 weeks after confirmation of primary detection on solid media, a process which takes 6 - 8 weeks. Liquid culture media can incorporate antibiotics at the time of initial inoculation, with the inference that surviving organisms are phenotypically resistant to the specifically incorporated antibiotic. DST results can therefore be available within the same time frame as mycobacterial diagnosis.

NUCLEIC ACID AMPLIFICATION TESTS

Nucleic acid amplification (NAA) is a rapidly evolving improvement in the detection and identification of Mtb which requires strong laboratory capacity and good quality control procedures and is relatively expensive. Bacterial or ribosomal RNA transcribed into DNA is amplified, followed by an appropriate reading system using a signal generating probe. The inclusion of internal positive controls reduces the incidence of false negatives, and use of a single tube format can reduce potential for contamination. NAA tests can be used for TB diagnosis but cannot be used for evaluation of patients receiving therapy as the technology cannot distinguish between live and dead organisms. The outstanding feature of NAA tests is that a positive result together with a high degree of specificity can be achieved within hours.

NAA tests usually have high specificity but variable sensitivity, so a positive test is good evidence of infection but a negative test is less informative. It is considered that current NAA tests cannot replace microscopy or culture, are unsuitable for smear-negative disease, and should be used only in conjunction with these tests and clinical data.[15,16] Drug resistance can be identified by identifying sequences in the rpoB and katG genes which encode for rifampicin and isoniazid resistance or by hybridisation of this region with specific DNA probes. Recent advances in NAA technology include the ability to amplify directly from clinical samples, isothermal amplification of DNA and improved amplification product detection.

The AMPLICOR® MTB test can give a result within 6 - 7 hours and is a US Federal Drug Administration (FDA) approved test for confirming smear-positive pulmonary TB. LAMP (loop mediated isothermal amplification) is able to amplify TB DNA directly from clinical samples and does not require a thermocycling device, and a positive result, confirmed by a colour reaction visible with the naked eye, can be achieved within 2 hours. With further development a version of the LAMP test may be suitable for use in peripheral laboratories. A commercial assay (Hain Lifesciences) allows a specific Mtb diagnosis together with detection of rifampicin and isoniazid resistance achieved by PCR amplification of the 16S-23S ribosomal DNA spacer region followed by hybridisation of the amplified DNA product with specific oligonucleotide probes. The probes are immobilised as parallel lines on membrane strip; however the test format is suited to reference laboratories rather than lower resourced peripheral laboratories.

DIAGNOSTIC PIPELINE

There is now more interest and financial investment in the development of new TB diagnostics than has occurred over the prior decades (Fig. 2). The development pipeline is active; however, most of the immediate advances in diagnosis and drug sensitivity testing will be applicable only to the reference laboratory.[17] Advances in peripheral laboratory capacity are 2 - 5 years away and are characterised by improved microscopy techniques and development of simplified nucleic acid amplification methodologies. There is little immediate hope of improved 'point of care' TB diagnostics, where the need is greatest. The time frame for new tests in the peripheral clinic is 3 - 7 years and is dependent on formulating simplified antigen and antibody testing such as dipstick tests. The role of newer diagnostics with potential to address the spectrum of clinical scenarios posed by TB and HIV infection are shown in Table III.

TABLE III. TESTS WITH POTENTIAL TO ADDRESS DIFFERENT CLINICAL SCENARIOS

Clinical scenario	Potentially useful tests
TB infection	
HIV negative	TST, INF-γ whole blood assays
HIV positive	TST, INF-γ isolated PBMC assays
TB disease	
Smear-positive	Direct smear, rapid Mtb culture, phage, NAT
Smear-negative	Rapid Mtb culture, urinary LAM
TB treatment failure	Rapid Mtb culture with DST
Drug sensitivity testing	Rapid Mtb culture, phage assay, NAAT, hybridisation assays

CONCLUSIONS

The HIV epidemic has reversed the advances made in global TB control. The increase in smear-negative disease has exposed the inadequacies of existing diagnostics which have remained essentially unchanged since the 1890s. HIV infection has been associated with decreased sensitivity of all present diagnostic modalities of TST, sputum microscopy, TB culture and radiology. Active community case finding indicates that the present diagnostic algorithm used in the national TB

Target timetable	2007	2008	2009	2010	2011	2012
Reference Laboratory  "Faster than culture"	MGIT-960 diagnosis & DST Phage tests for rifampin resistance	Manual molecular DST	Manual NAAT resistance screen	Automated NAAT Real time PCR		
Peripheral Laboratory  "More sensitive than sputum smear"		Fluorescent microsopy	First generation LAMP	Urinary NAAT		
Clinic Based  "As simple as a dipstick"			Urinary antigen dipstick		Dipstick antibody test test	Second generation LAMP

*FIND = Foundation for Innovative New Diagnostics, NAAT = nucleic acid amplification test; DST = drug sensitivity test; LAMP = loop-mediated isothermal amplification.

Fig. 2. FIND timetable for availability of new Mtb diagnostics.*[17]

control programme fails to identify a large proportion of HIV-associated TB. There is therefore an urgent need for point of care tests with increased sensitivity for screening of HIV-positive individuals.

The association of HIV-infection with MDR and XDR has also driven the need for tests which can be used to recognise early treatment failure and rapid identification of drug resistance. The rapid progression of TB in HIV-infected individuals together with increased mortality has also emphasised a need for much faster identification of infection and failure of therapy. The development of rapid liquid culture assays and NAA assays offer significant advances over conventional solid media culture and drug sensitivity testing.

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You left South Africa to begin a new life elsewhere. I thought it was for good but here you are, home again. So much has changed since then. But in all that time I have had the support of a companion whom I have come to trust over the years. Adcock Ingram.

While you were starting on your new life, I was also starting one of my own.

Living with HIV.

Adcock Ingram's range of generic HIV treatments has seen me through this time. Their treatments are affordable[1] and because they are from ADCO, I know I can trust their quality and efficacy.

Now I look forward to spending more time with you, in this place we both call home.

Your patients trust you. ADCO HIV treatments are bio-equivalent to the originator products[2] and ADCO is a name you have known and trusted for many years. So, when your HIV-positive patient turns to you, make a positive choice - turn to ADCO - Adding Value to Life.

*Adco-**Nevirapine**® tablets*
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S4 Adco-Nevirapine® tablets. A20.2.8. Each tablet contains 200 mg nevirapine. Reg. No. 41/20.2.8/0235.
S4 Adco-Zidovudine® tablets. A20.2.8. Each tablet contains 300 mg zidovudine. Reg. No. 41/20.2.8/0237.
S4 Adco-Lamivudine® tablets. A20.2.8. Each tablet contains 150 mg lamivudine. Reg. No. 41/20.2.8/0236.

References: 1. Blue Book February 2007. 2. Adcock Ingram data on file. Further information available on request. 01/2007.

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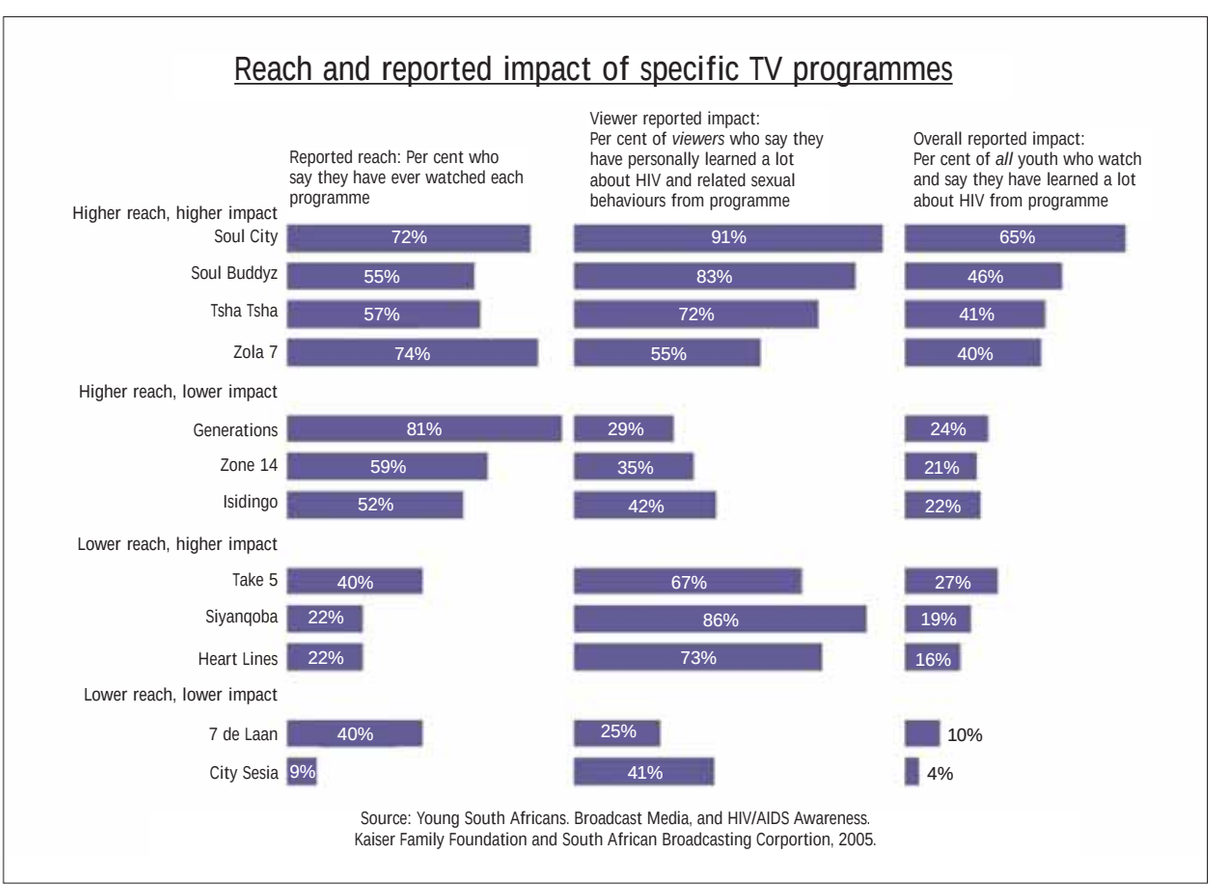
TELLING STORIES TO CHANGE THE COUNTRY – A COMBINED EFFORT BY THE HIV CLINICIANS SOCIETY AND SOUL CITY

The HIV Clinicians Society has joined forces with the popular Multimedia NGO Soul City to help prevent HIV infection in South Africa. The *Soul City* TV series has consistently been in the top five most-watched TV programmes in South Africa, with about 60% of the country watching each episode since 1994. *Soul City* is an entertaining TV series that uses researched edutainment techniques to deliver health information and cause changes in health and social behaviour. Independent research has shown it to have a powerful impact on South African society.

The HIV Clinicians Society and Soul City have worked together on the next series to turn fiction into reality. During the TV series characters phone the AIDS Helpline to find out where they can get tested and treated for HIV. Behind the scenes the Society, Lifeline and Soul City are working together to create the first geographical database of HIV testing and treatment sites in South Africa. You will soon be able to call one number (or search one website) and get directions from where you are standing to your nearest HIV services.

The TV series also focuses on ways to prevent HIV infection, the damaging effects of alcohol in society and how to have a healthy pregnancy. *Soul City* imparts information and impacts on social norms, attitudes and practice. Its impact is aimed at the level of the individual, the community and the socio-political environment. While the TV show is on air, radio talk shows will be broadcast in all nine African languages, and three million booklets on HIV, alcohol and maternal health will be released and distributed nationally, mainly through newspapers. We aim to create an enabling environment empowering audiences to make healthy choices, both as individuals and as communities.

The TV series will be supported by a robust marketing campaign which includes advertising and publicity, to draw maximum audiences, create excitement and keep bums on seats throughout the 13-week broadcast period. The new *Soul City* series will be broadcast on SABC 1 from 4 September to 27 November 2007.



Source: Young South Africans. Broadcast Media, and HIV/AIDS Awareness. Kaiser Family Foundation and South African Broadcasting Corportion, 2005.

Bonnie Henna, who plays one of the main roles as the nurse Zanele, is holding a poster for the Mothers 2 Mothers project. The project aims to support women through the process of PMTCT (prevention of mother to child transmission of HIV).

Skosana, the mother of a child with fetal alcohol syndrome. She is now pregnant and drinking again! Watch the series to see how, with help from friends and nurses, she learns to cope with her problems in a healthier way.

Zuko and his friend Mandla play with condoms in preparation for 'the real thing'. In this series Mandla and his girlfriend Naledi decide that they would like to start sleeping together, but they want to be 100% safe and 100% sure. Watch to see how they do it.

Simphiwe, the baby, is HIV-positive and has been adopted by his Uncle Odwa and Aunt Maria. His teenage mother, Portia, died just after childbirth due to complications arising from hypertension during pregnancy. In this scene you find out how Portia, who was only 15, became infected with HIV.

Schoolchildren campaign against the abuse of alcohol and alcohol advertising near their school.

USER FEES, TRANSPORT COSTS, AND THE ETHICS OF EXEMPTION: HOW FREE IS FREE ART?

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Marlise Richter, *BA Hons, MA, LLM*
School of Public Health, University of the Witswatersrand, Johannesburg

The Southern African HIV Clinicians Society initiated an online discussion forum on 'HIV Ethics and Policy' in 2007. The case study below concerns the 'hidden' costs associated with access to antiretroviral therapy (ART), and discusses a number of proposed solutions to the problems faced by indigent patients with HIV/AIDS (to read the entire debate, see http://groups.google.com/group/policy-ethics/topics?start=10&sa=N).

CASE STUDY

Tertiary hospital

At a large tertiary level hospital in South Africa, patients were in the past expected to contribute to the costs of their care by paying means-tested fees, per visit to an outpatient clinic, or per day in case of a hospitalisation. Fees started at R160 per outpatient visit for the lowest income tier. Patients were exempted from the payment if they could prove that they did not have a regular income.

In practice, patients in the lowest income tier were accepted into the clinic for their first 3 visits, but had to bring proof of no income at their 4th visit at the latest. During the first year of the ART clinic's operation, this proof of income (or the absence of it) could have been a handwritten affidavit stamped at their local police station. During the second year, however, this policy was changed and patients had to supply a print-out from the employment registry at the Department of Labour. Hospital staff observed an increase of patients defaulting from treatment after their third visit. Patients were complaining that the new procedure meant that they had to travel to the city centre and queue for a day at the Department, or sometimes for several consecutive days, in order to obtain the necessary documentation. In October 2006 hospital fees were abolished for patients accessing the ART clinic, but patients were still expected to settle their outstanding fees for the period before this general exemption took hold.

An analysis of patients' transport costs at this clinic shows a mean cost of almost R26 per visit, with 61% of patients using minibus taxis as their means of transport. The analysis found that this amounts to a significant proportion of patients' income, especially as a monthly expense over a long period of time.

Secondary hospital

At another ART clinic in a semi-rural secondary health care hospital, the same analysis showed that while mean transport costs are somewhat lower, patients who do not have the cash for a taxi (about 10% of the clinic population) walk several hours on foot to get to the clinic. The clinic staff are concerned that these patients are going to default from treatment if they get sick or demotivated.

Primary health care hospital

At a third ART clinic, in a rural primary health care hospital, patients from the catchment areas of nearby hospitals that have not yet been accredited for ART are collected by bus once a week and driven to the ART clinic in a scheme financed by the provincial Department of Health. The clinic operates in an area that has no working system of minibus taxi routes. Patients comment on the significant stigmatisation they perceive as being associated with having to wait for the 'AIDS buses' in a central part of their township.

Questions for discussion

1. Is it ethically sound to exempt the patients at the ART clinic from the tertiary hospital's fee policy?
   (a) Should the exemption apply to all ART patients, or only to those without income or employment?
   (b) In the latter case, how should patients be expected to prove that they qualify?

2. Should the exemption policy be applied to other patients in chronic care?
   (a) What about inpatients?
3. What are possible solutions to the problem of transport costs?
   (a) Would voucher schemes or the bus scheme mentioned above be viable alternatives to patient self-funding of transport?
   (b) What should the criteria be for patients to qualify for vouchers?

CASE STUDY RESPONSES

A - SUBMITTED BY JOHN GOSLING

Responses to questions 1 and 2

Patients attending ART clinics should be exempt from all hospital fees – irrespective of their income. Because of the extent of the pandemic and the backlog in providing adequate treatment to the approximate 850 000 people who qualify for ART, all outpatient and inpatient treatment for HIV/AIDS should be provided free of cost. This will encourage better compliance and also pave the way for patients to access treatment more readily, whether they have financial constraints or not.

This tertiary hospital is to be lauded for completely abolishing hospital fees for those patients attending ART clinics. However, it would seem unreasonable to expect patients to settle outstanding fees that were owed before the implementation of this policy. This is especially churlish in view of the fact that the Department of Health regularly fails to spend its allocated budget. Surely some of the unspent finances could be used to settle this outstanding debt, which is probably not very large anyway?

The HIV/AIDS pandemic is of such major proportions, and is claiming the lives of so many whose lives could be extended if they were able to access ART in a timely fashion (it is currently estimated that between 800 and 1 000 deaths due to AIDS-related causes occur every day in South Africa), that there ought to be no question of having to prove whether or not any given patient 'qualifies' for free treatment.

In Brazil, ART has been free since 1996. The programme (including aggressive and frank prevention programmes) has improved the health, and extended the survival, of tens of thousands of Brazilians. It has saved the country an estimated $2.2 billion in hospital costs between 1996 and 2004. Access to free AIDS treatment has made Brazilians more willing to be tested for HIV and has made it easier to address the types of behaviour associated with transmission.[1] If the government of Brazil has been able to provide funding for this treatment programme, which has been so highly effective, it ought to be possible for the South African government to do the same.

The answer to the question whether this policy of free treatment ought to be applied to all chronic medical conditions, including inpatient treatment, should be a resounding yes. Unfortunately, this goal is unrealistic in the immediate foreseeable future because of a very poorly administrated Department of Health as well as crumbling medical infrastructure. However, this goal ought to be one of the main issues to be revisited by the government and should be implemented in the very near future.

Response to question 3

The suggestion of travel vouchers is an excellent one. These ought to be supplied on request to all persons attending ART clinics. Given that most patients attending public clinics are indigent, there is little possibility of abuse of such a system. Travel vouchers would ensure that patients keep their appointments more regularly and therefore become more compliant with their ART regimens. Furthermore, it is the express intent of the state, as enshrined in the Bill of Rights, that 'everyone has the right to have access to health care services'. (section 27(1)(a)). One could argue that this right would include free transport for those who cannot afford the taxi fare and who may live at considerable distances from the clinics.

B – SUBMITTED BY KARIN VAN DEN BERG

It is important to consider that every person in South Africa who is formally employed pays taxes that are used to fund the public health care system in this country. The implication is that those who have the means have already contributed to the public health care system and therefore should not have to pay again. Those who are unemployed clearly do not have the means to contribute, and they should indeed be exempt from payment. Such a system removes the need for a 'means test' or any expensive debt collection system – a system that is not working efficiently. The above policy should be applicable to all persons seeking help at a public health facility, irrespective of the condition for which the help is sought.

With regards to the 'AIDS bus', it would seem unethical to provide certain chronically ill people with a 'better' or more comprehensive service than people who have 'only' diabetes or asthma. It implies that one patient is more important than another. If the same service were provided to all patients requiring monthly chronic medication, there would be no stigma associated with using the service.

CONCLUSION – GESINE MEYER-RATH

1. USER FEES AT HOSPITAL OR CLINIC LEVEL

Background

In 1989 the World Bank, as part of its structural reform approach, issued a document entitled *Financing Health Services on Developing Countries: An Agenda for Reform*.[2] It promoted a number of interventions aimed at improving

health sector financing in low-income countries, including the concept of cost recovery at the level of the health care provider in form of user fees. Subsequently a number of countries introduced user fees in both the health and education systems with varying results, but almost invariably leading to lower-than-necessary access of health care by the poorest sectors of society, and to delayed diagnosis and treatment for a number of diseases, thus ultimately resulting in higher cost. A case in point is provided by Kenya, where user fees for public sector outpatient services were introduced in 1989 and withdrawn after only 9 months in 1990.

A study reviewing access to services for sexually transmitted infections found significant reductions in utilisation during the period of user fees, with a 60% reduction for men and 35% for women, with one exception. For gonorrhoea, women's utilisation increased significantly and progressively during the user fee period. This, the authors hypothesised, could have been due to growing rates of infection secondary to falling rates of treatment.[3]

The impact of user fees on adherence and mortality in patients on ART

For ART roll-out programmes, the literature is unequivocal in describing a detrimental effect of user fees or other cost contributions by patients on adherence and remaining in care, and the relative superiority of free provision over provision in which patients have to bear some or all costs. Table I summarises the findings of the relevant studies published to date.

Interestingly, the first two large reviews of the results of ART programmes in resource-limited settings in terms of mortality and immunological and virological outcomes over the first 12 months of treatment both compared free-of-charge and fee-for-service programmes. They found respectively:

- that 'provision of treatment free of charge in low-income settings was associated with lower mortality',[5] and
- that 'the provision of medications free of charge to the patient was associated with a 29 - 31% higher probability of having an undetectable viral load at months 6 and 12'.[7]

A further study looked at the 'social cost' of a scheme of user fees with exemption in treatment centres in Ouagadougou, Burkina Faso.[9] The researchers describe these costs to include, among others, 'patients' perception[s] of arbitrariness about application of exemptions, to difficulties to adjust [the] payment scheme to changing economic conditions, and to necessary negotiations within the relationship between patients and health workers who decide the rate of payment', and, at the level of the health care worker, the 'means and time necessary for socioeconomic enquiries for exemptions and to the symbolic cost of choosing between patients'.[9]

User fees for hospital services in South Africa

In South Africa, user fees are set at the discretion of the Minister of Health, and in some instances the relevant provincial member of the Executive Council (MEC) responsible for health,[10] and are mostly applied at tertiary (university hospital) level. The argument is that these institutions provide specialised care and have much higher overhead costs than institutions at secondary and primary levels of care. As mentioned in the case study, the tertiary hospital in question has since abolished user fees for patients at the ART clinic. This correctly led to many Discussion Forum contributors demanding the same exemption to apply to all patients who have to access the hospital regularly for chronic care. Generally, the question remains whether the amount that can be recouped by charging patients is higher than, and therefore justifies, the administrative costs of collecting these charges.

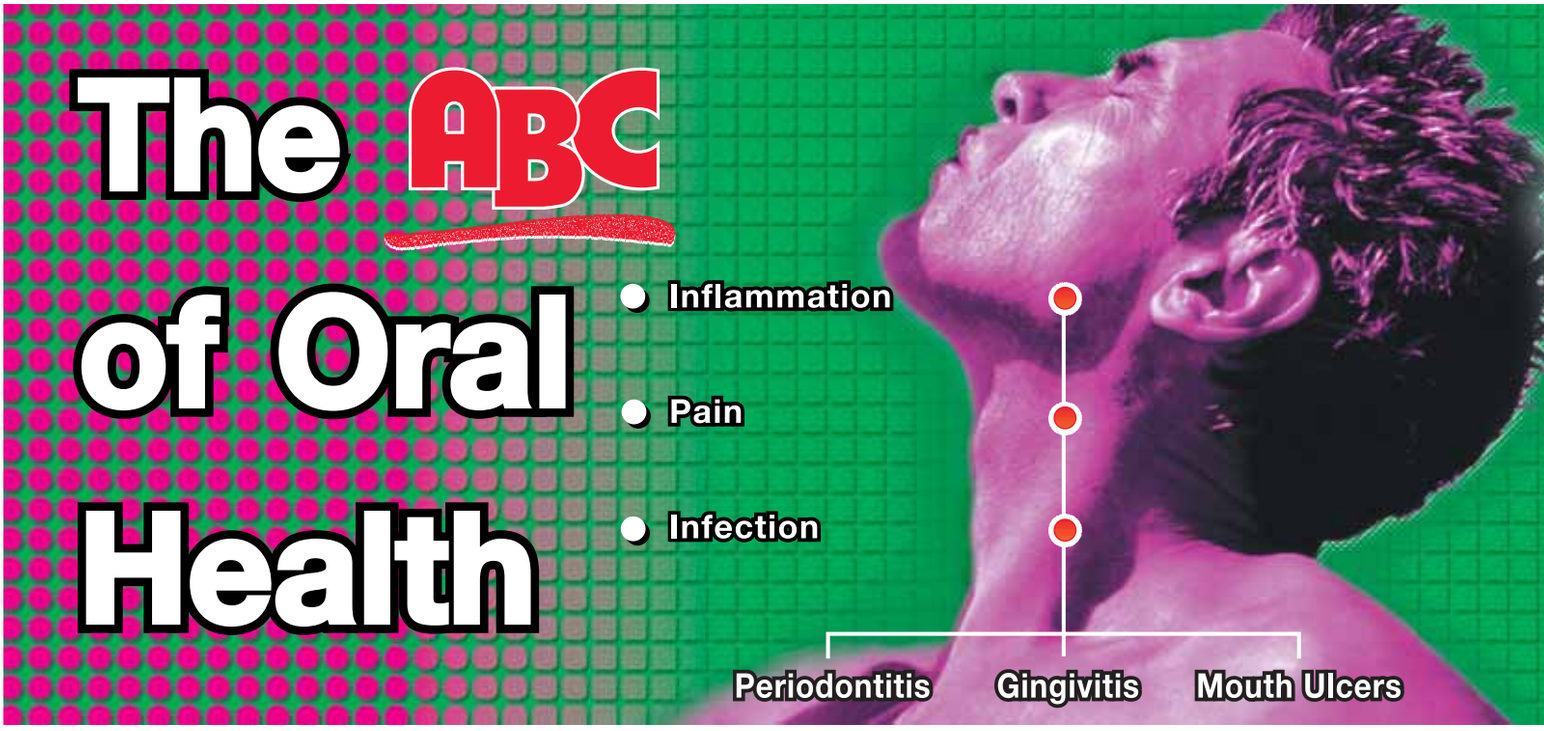
A second argument for introducing user fees, that they help to minimise the 'moral hazard' of unnecessary demand (i.e. demand for health care that is deemed superfluous or is demanded at a higher level of care than necessary) does not hold in the case of ART, and much other chronic care. This is because the cost of delaying health care is much higher than the cost of accessing care as and when the patient deems it necessary. Comments of contributors to the Discussion Forum were motivated by concerns about the long-term sequelae of financially motivated treatment interruption or cessation, especially the development of drug-resistant virus. Indeed, the preliminary results of a file review at the tertiary hospital show that especially during the first months of its operation in 2004, many of the newly joining patients had previously accessed some form of ART in the private sector, often sub-optimal dual therapy, and had had to interrupt 'buying the drugs' when they ran out of money. Whether this translates into higher rates of resistance development for these patients compared with the clinic population that was treatment-naïve on entry into to the clinic is still subject to analysis.

2. BUT USER FEES AREN'T THE PROBLEM – WHAT ABOUT TRANSPORT COST?

Questions 2 and 3 approached the problem of the additional burden that accessing an ART clinic on a monthly basis poses to often already overburdened people. The problem of access costs for chronic health care to the poor has been well researched, and a large number of remedies have been designed and tried out in different settings over time. Two of these remedies were included for discussion, travel vouchers and designated bus transfers, with the latter potentially re-introducing the problem of stigma.

The obstacle of transport cost has been quantified for ART patients in a few studies. One study involving 789 patients in public sector and NGO clinics in South Africa showed that patients paid a median R20, R10 and R27 in accessing a public urban hospital, a peri-urban and a rural non-governmental clinic, respectively,[11] with the top decile paying R60, R23, and R71, respectively. This compares well with the mean cost of R26 and R19 for patients accessing the urban tertiary care clinic and the semi-urban secondary care clinic that were mentioned in the case study. Compared to patients' income these costs are high, and it is not clear why they should be borne by the patient.

Andolex™-C



Andolex-C

The No.1 oral rinse for treating painful conditions of the mouth and throat[1]

Andolex-C Oral Gel

Topical anti-inflammatory and anti-septic oral gel

New addition

Reference: 1. IMS Total Private Market November 2005.

3M Pharmaceuticals

Scheduling status: S1 **Proprietary name (and dosage form): ANDOLEX-C Oral Rinse. Composition:** Each 15 mL contains: Benzydamine hydrochloride 22.5 mg, Chlorhexidine gluconate 18 mg, Alcohol 9% v/v. **Pharmacological classification:** A. 16.4 Nasopharyngeal and bucco-pharyngeal antiseptics. **Indications:** For the relief of minor infections and painful inflammatory conditions of the mouth and throat. Chlorhexidine in Andolex-C Oral Rinse helps to reduce the development of plaque. **Contra-indications:** Patients with known hypersensitivity to benzydamine, chlorhexidine or to any of the components of the vehicle. Andolex-C Oral Rinse is not recommended in children under 6 years of age. The safety in pregnancy and lactation has not been established. **Dosage and directions for use:** When used as a gargle, the usual dose is 15 mL (approximately one tablespoon) which should be gargled for at least 30 seconds at 1½ to 3 hourly intervals, as needed. When used as a rinse for oral lesions, the usual dose is again 15 mL (approximately one tablespoon) which should be held in the mouth and swirled around for at least 30 seconds, with repeat use every 1½ to 3 hours throughout the day, as needed. Andolex-C Oral Rinse should generally be used undiluted, but if stinging occurs, the rinse may be diluted with water. Children (6 to 12 years): 5 to 15 mL as a gargle if able to do so, or as an oral rinse, every 3 hours. **Side effects and special precautions:** The most commonly reported reaction is oral numbness. Burning or stinging sensation has been reported. Other local adverse effects include dryness or thirst, gastro-intestinal disturbances, tingling, warm feeling in the mouth and altered sense of taste. Reversible discolouration of the teeth or tongue may occur with prolonged use. Uninterrupted treatment should not exceed 7 days except under medical supervision. **Registration number:** 31/16.4/0143. **Scheduling status:** S1 **Proprietary name (and dosage form): ANDOLEX-C ORAL GEL. Composition:** Benzydamine Hydrochloride 10 mg/g, Cetylpyridinium Chloride 1 mg/g. **Pharmacological classification:** A 16.4 Naso-pharyngeal and bucco-pharyngeal antiseptics. **Indications:** Temporarily relieves painful inflamed conditions of the mouth, including mouth and denture ulcers and sore gums. **Contra-indications:** Patients with known hypersensitivity to Benzydamine or Cetylpyridinium Chloride. The safety of Benzydamine Hydrochloride has not been established in pregnancy and lactation. Andolex-C Oral Gel is not recommended in children under 6 years of age. **Warning:** If a sore mouth is caused or complicated by a bacterial infection, appropriate antibacterial therapy should be considered. **Dosage and directions for use:** 1. Apply approximately 1 cm of gel with finger. 2. Gently massage into sore area. 3. Do not eat or drink for 15 minutes. 4. Apply every 2 to 3 hours up to a maximum of 12 times/day. If symptoms persist, see your doctor or dentist. **Side effects and special precautions:** The most commonly reported reaction is oral numbness. Burning or stinging sensation has been reported. Other local adverse effects include dryness or thirst, tingling, warm feeling in mouth and altered sense of taste. **Registration number:** 33/16.4/0285. **Name and business address of applicant:** 3M Pharmaceuticals South Africa (Pty) Limited, Co. Reg. No. 1952/001640/07, 146a Kelvin Drive, Woodmead, 2191. Tel. No. (011) 806 2000. Please read the package insert for further information. 3M089/05

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TABLE I. CHARACTERISTICS AND FINDINGS OF STUDIES ON THE IMPACT OF PATIENT CHARGES ON ART OUTCOMES

Country	Years	Setting (number of patients in study)	Outcomes	Comments
Uganda[4]	1998 - 2002	St Francis Hospital, Kampala (*N* = 321)	21% of patients interrupted treatment for > 1 year because of financial constraints	Price drops in 2000 led to many patients returning to clinic; regimens often sub-standard and determined by patients' ability to pay
18 countries in Africa, Asia and South America[5]	N/A (before 2006)	Review of mortality data from treatment cohorts in ART-LINC collaboration, 12 of which provide ART free of charge (*N* = 4810)	Provision of treatment free of charge in low-income settings associated with lower mortality (adjusted HR 0.23; 95% CI 0.08 - 0.61)	
India[6]	N/A (before 2005)	Y R Gaitonde Center for AIDS Research and Care in Chennai (*N* = 304)	Cost was most common reason for non-adherence (32%)	'Patients seem to be taking "drug holidays" to save money'
11 countries in Africa, Asia and South America[7]	1997 - 2003	Meta-analysis of effectiveness data from clinical trials and observational studies of ART programmes (*N* = 2464)	Provision of medications free of charge associated with a 29 - 31% higher probability of having an undetectable viral load at months 6 and 12	
Uganda[8]	1997 - 2004	3 treatment centres in Kampala (*N* = 304)	Monthly income < 50 US$ was associated with non-adherence (OR = 2.77, 95% CI 1.64 - 4.67)	Non-adherence defined as > 95% of doses missed in last 3 days

3. THE WAY FORWARD

There is a great need for policy makers to consult more with health care practitioners 'on the ground' whose work provides them with unique insights into the obstacles their patients are struggling with. A number of important initiatives are currently under way to remedy the situation in South Africa, ranging from increased lobbying for the economic rights of people living with HIV/AIDS, to reviewing and improving the current CD4 count-based disability grant criteria, to potentially introducing a chronic illness grant. It seems that after years of political struggle to provide antiretrovirals in the public sector, and with increasing numbers of patients on treatment who expand the collective knowledge and experience of treatment challenges, a second wave of detailed operational thinking and activism has been initiated. Creative research is needed to identify feasible and scaleable interventions that support patients who have expressed their readiness to take lifelong treatment in putting their conviction into action. Three years into the public sector roll-out of ART, the discussion about how to avoid hidden costs and how to increase support strategies for patients on ART has just begun.

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