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FROM THE EDITOR

Of late we have witnessed a number of important initiatives that aim to promote expanded screening for HIV infection. There have been calls by public health authorities, including the World Health Organization, for a move away from the traditional voluntary counselling and testing (VCT) model. One initiative currently underway in many countries, including Botswana, is the 'opt out' model where patients would be subjected to routine HIV testing unless they expressly state that they do not wish to be tested. The Centers for Disease Control has developed a document entitled 'Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health care settings'. This document recommends that HIV testing become a routine part of medical care for all teenagers and adults in the USA. This will have the effect of enhancing HIV case finding and represents a major shift to HIV testing in clinical practice in the USA.

The rationale for this expanded screening meets many of the criteria for an effective preventive practice intervention, in that HIV serological tests are reliable and inexpensive, untreated infection has serious health consequences, and highly effective treatment is now becoming increasingly accessible. Recent cost-effectiveness analyses have demonstrated that HIV screening is as cost-effective as screening interventions for other chronic diseases.

Two articles in this issue of the *Journal* look at various aspects related to testing, VCT and the stigmatisation around HIV. We have published an article by a person living with HIV who describes his personal experiences at the time of testing: how he faced the stigmatisation, how it changed his life, and how he used this life-changing event to become an advocate of promoting VCT in order to know your status. As he says, 'Take action now and know your status'. In common with other scientific journals we have included a personal essay to emphasise the issues at stake.

DES MARTIN

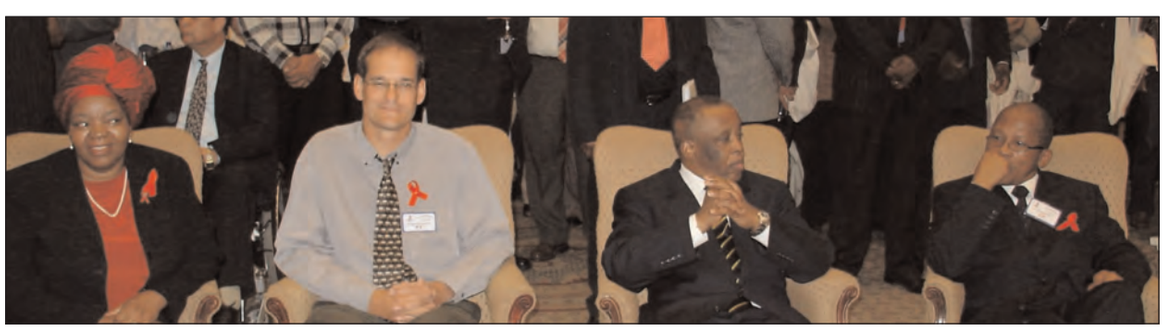
Editor, Southern African Journal of HIV Medicine

MESSAGE FROM THE EXECUTIVE

This issue of the *Journal* is being put to bed as the first Botswana HIV Conference closes. The Conference, put together by a committed group of local members of the Botswana HIV Clinicians Society, has been an overwhelming success – an audience of over 700, international and local experts giving excellent talks, within a professionally run operation. Feedback on proceedings has been very positive, and I would like to congratulate the conference committee and the Botswana branch on an inspired and brave programme. I sincerely hope you repeat it in the future – the flavour was distinctly African, the debate robust and honest, and the clinical exposure impressive. There are rumours of the conference being repeated, and word of mouth on the quality of this one will ensure that the next is even bigger. Congratulations again to Botswana, who seem to know how to lead from the front in all areas of HIV.

FRANCOIS VENTER

President



Professor Sheila Tlou, Botswana Minister of Health, Dr Francois Venter, Southern African HIV Clinicians Society, His Excellency Festus Mogae, President of the Republic of Botswana, and Dr Kgosi Mompati, President of the Botswana branch of the SAHIVCS and chairman of the conference committee.

CONFERENCE REPORT

MICROBICIDES 2006 CONFERENCE

Gita Ramjee, *PhD, Co-Chair, Microbicides 2006 Conference*
HIV/AIDS Lead Programme, HIV Prevention Unit, Medical Research Council,Durban

Sub-Saharan Africa is the region worst affected by the HIV pandemic, hosting over 64% of global infections.[1] Women are disproportionately affected, with reports of almost 60% of infections among women between the ages of 15 and 49 years in sub-Saharan Africa. In South Africa, 1 in 4 women are infected by the age of 25 years. Biological, socio-economic and cultural factors contribute to the vulnerability of women to HIV. The only effective method of HIV prevention, the male condom, is not in the control of women. It has therefore become increasingly clear that female-initiated methods or technologies need to be developed to allow women to have control over their sexual health, and HIV prevention in particular.

Microbicides are one of the female-initiated technologies for prevention of HIV among women. The products could be formulated as gels, creams or suppositories. The concept is based on application of the product in the vagina prior to sexual intercourse to prevent HIV infection. There are several products in the pipeline, their development ranging from early stages to large-scale efficacy trials.

The field of microbicides research is increasingly gaining momentum in South Africa and elsewhere. South Africa is host to five phase III clinical trials; four microbicide trials and one trial of vaginal diaphragms for HIV prevention. The majority of microbicides being tested are compounds called fusion inhibitors which act by preventing the binding of HIV to target cells in the vagina.

South Africa hosted the Microbicides 2006 Conference in Cape Town in late April, with 1 300 registered delegates, the largest ever attendance at a microbicide conference. The conference chairs were Dr Kim Dickson, Professors Helen Rees and Gita Ramjee, from the World Health Organization, the Reproductive Health and HIV Research Unit and the South African Medical Research Council respectively. The conference was supported by a high-level delegation of individuals who expressed their support for microbicide research and echoed the urgent need for HIV prevention options for women. These included Dr Manto Tshabalala-Msimang, Mrs Graça Machel, Archbishop Desmond Tutu, Judge Edwin Cameron, and the Ministers of State and Gender from Rwanda and Uganda respectively.

There were daily plenary sessions over the three days of the meeting. The opening plenary by Professor Sharon Hillier gave a broad overview of the state of microbicide research and development. The optimal microbicide needs to be a physical barrier, to provide lubrication, and to be non-toxic. There is a need for both contraceptive and non-contraceptive products, providing women with the option to have children without the risk of infection. A desirable product will maintain the normal vaginal flora and have an impact on the prevention of other sexually transmitted infections (STIs). While it is acknowledged that the current microbicide products are not going to be 100% efficacious, it is hoped that the new generation of antiretroviral-containing microbicides currently in phase I and II trials will be more specific to HIV and will show greater efficacy. Overall several non-nucleotide reverse transcriptase inhibitors (NNRTIs) are moving forward in early clinical trials, with some incorporated in a sustained-release technology. This is one of the richest pipelines of products ready to move into effectiveness trials.

Dr Zvavahera Mike Chirenje addressed issues of microbicide safety. The main objective is to identify compounds that may induce epithelial toxicity and inflammation of the genital tract. The maintenance of an intact micro-ecological system in the vagina is crucial. The vagina's natural defence against infections includes an acidic environment of pH < 4.5.

Within clinical trials, important safety signals are monitored during exposure to the product. The clinical component of safety testing includes a comprehensive medical history to elicit symptoms such as genital itching and discharge, clinical examination of signs (clinical manifestations) and collection of biological specimens for laboratory validation. Further requirements include colposcopic assessment of cervico-vaginal compartments in phase I studies. Dr Chirenje concluded that safety monitoring remains pivotal to microbicide development and testing. Ongoing research to assess reliable safety markers/surrogates that are reproducible and clinically relevant will add to our knowledge of microbicide safety.

Dr Julie Overbaugh's plenary lecture demonstrated a significant bottleneck in the diversity of virus transmitted from an infectious partner. This bottleneck is reduced in women on hormonal contraception or with other sexually transmitted

diseases, increasing women's susceptibility to a wider diversity of viruses. Mucosal transmission of virus was associated with significant changes in glycosylation (sugar residues) on the HIV viral envelope gp120. These changes may affect the activity of potential microbicides, and may be compounded by differences between viral strains (clades) spread across geographical regions. These observations reinforce the need to evaluate microbicides for activity against primary mucosal isolates.

Benoit Masse discussed the future of microbicide trials once an effective product is identified. Will we still be able to continue with placebo-controlled trials? Trials will need to be designed so that the new product to be tested is not inferior to the active control product and both the products are superior to the placebo. Information regarding the placebo will come from the current wave of trials. Furthermore, past and new trials will need to be very similar. The new wave trials may need three arms (placebo/active/new) with a resultant requirement of larger sample sizes than currently used to demonstrate efficacy.

Professor Ames Dhai provided an overview of ethical challenges that are likely to arise in prevention trials. These include issues regarding cost of care for research-related injuries, legal constraints of International Review Board decisions, ensuring the participants' understanding of the informed consent, and the research process and recruitment incentives. Many of these challenges were addressed in various sessions dedicated to ethical issues and in the standard of care symposium.

Morenike Ukpong discussed the role of communities and advocates in defining the microbicide agenda. The definition of the community should not be restricted to study participants, but should also include civil society, donors, activists and policy makers. She emphasised that civil society engagement and advocacy is needed to prioritise research and development, ensure sufficient resources, speed up recruitment and ensure retention. This involvement will also ensure that the trial conduct is not compromised, that licensure and procurement are not delayed and that people will have access to new technologies.

In addition to the daily plenary, there were four scientific tracks: Basic Science, Clinical, Social and Behavioural Science, and Community, which included advocacy. The highlights of each of the scientific tracks are outlined below.

TRACK A

Chaired by Professor Robin Shattock, Dr Patricia Reichelfelder and Dr Robin Maguire

Work presented in Track A demonstrated significant progress in identifying potential biomarkers of safety in preclinical cellular, tissue and animal models. The track also covered the issue of microbicide formulation leading to the development of microbicide products appropriate to wide-scale use. Professor David Woolfson (Queens University, Belfast) presented the current state of the art for microbicide formulations and drug delivery. Appropriate formulation was seen to be essential to make a usable product in terms of efficacy and acceptability. The Basic Science track demonstrated that there are a wide range of microbicide candidates at different stages of development, providing a broad width of strategies to prevent mucosal HIV transmission. The future development of the field is likely to focus on development of agents with increasing potency and the use of sustained-delivery technology to provide prolonged protection.

TRACK B

Chaired by Anne Coletti, Lut Van Damme and Sinead Delany-Moretlwe

The focus of this track was to cover the clinical aspects of microbicides and barrier method research.

An update of the five phase III ongoing trials was given by respective sponsors (Table I). The Population Council Carraguard trial is currently being conducted at three sites in South Africa. The active ingredient is carrageenan, a seaweed extract. This is the most advanced of the current trials with a population accrual target of 6 639. The accrual rate at the time of the conference was 6 000. The HPTN 035 trial funded by the National Institutes of Health in the USA is testing two products, viz. BufferGel and 0.5% PRO 200/5 Gel. There are five sites, two of which are in South Africa. This is a phase II/IIB safety and effectiveness trial.

The CONRAD sponsored phase III trial of 6% cellulose sulphate is being conducted at four sites, one of which is in Durban. Family Health International (FHI) is conducting additional trials of cellulose sulphate at two sites in West Africa among high-risk women. Another study sponsored by FHI includes a trial of C31G, a surfactant, at two sites. The site in Ghana had to be closed down owing to low HIV incidence and the Nigeria trial is ongoing. The microbicide development programme (MDP) is funding one of the largest trials, with a sample size of 9 673, at five sites in Africa. Three of these are in South Africa.

The key challenges highlighted in each of the presentations were lower than expected incidence rates of HIV. In order to ascertain efficacy of a product, the HIV incidence needs to be high enough in the targeted population. Most of the trials estimated a higher incidence rate, which resulted in development of a study design requiring a smaller sample of women. However, as the trials progressed it has become increasingly clear that the incidence is lower than initially estimated. This has resulted in two trials closing down. Another issue common to all trials is high pregnancy rates. As women become pregnant they are taken off the product, resulting in a dramatic reduction in the power of the study to ascertain product efficacy.

TABLE I. SUMMARY OF STATUS OF CURRENT PHASE IIb/III CLINICAL TRIALS

Network	Products	Design	Population	Endpoints	Progress to date
Population Council	Carraguard Placebo	Phase III RCT	3 sites 6 639 16 - 40 years	HIV	6 000 accrued
HIV Prevention Trials Network (HPTN) 035	BufferGel PRO 2000 0.5% Placebo Condom only	Phase II/IIb safety and effectiveness RCT	5 sites 800 (phase II)	Safety; HIV	827 accrued
CONRAD	CS 6% Placebo	Phase III RCT	4 sites 2 574 HR women	HIV CT, GC	738 accrued
Microbicide Development Programme (MDP)	PRO 2000 0.5% PRO 2000 2% Placebo	Phase III RCT	5 sites 9 673	HIV HSV, GC	640 accrued
Family Health International (CS)	Cellulose sulphate 6% Placebo	Phase III RCT	2 sites 2 160 HR women	HIV CT, GC	1 102 accrued
Methods for Improving Reproductive Health in Africa (MIRA)	All flex diaphragm with Replens Condom only	Open-label RCT	5 000	HIV HSV2 CT, GC, TV Acceptability	Completed accrual
Family Health International (FHI) (C31G)	C31G 1% HEC placebo	Phase III RCT	4 284 HR women	HIV	Ghana closed Feb. 06 2 100 accrued Nigeria

RCT = randomised controlled trial; HR = high-risk women; CT = *Chlamydia trachomatis*; GC = *Neisseria gonorrhoeae*; TV = *Trichomonas vaginalis* – HSV-2 = herpes simplex virus-2.

A pre-phase I study to characterise rectal mucosal safety parameters showed that it is feasible to conduct studies involving regular sigmoidoscopy and biopsy; that cytokine and T-cell measurements are useful markers of safety because they are stable across a number of sites and in a range of men; and that these measures were not influenced by type of sexual practices.

Two studies examining the safety of lime juice as a potential microbicide concluded that lime juice did not appear to be safe in the concentrations of ≥ 50% required to inactivate HIV in semen.

There are several ongoing trials of the vaginal diaphragm for prevention of HIV. New evidence has emerged that a physical barrier covering the cervix may offer safe and effective protection from HIV. A 14-day randomised, controlled trial examining the safety of a silicone diaphragm when used in combination with BufferGel, Acidform or KY Jelly (as placebo) in 81 low-risk women showed no serious adverse events.

Another randomised controlled trial evaluated the safety of the Ortho All flex diaphragm when used with 6% cellulose sulfate (CS) or with KY Jelly (placebo gel) compared with CS gel use alone over 6 months in South African women. This combination was found to be safe with no serious adverse events or adverse events related to diaphragm use reported.

A randomised, controlled non-inferiority trial showed BufferGel, a microbicide, in combination with a diaphragm, to be as effective a contraceptive as a spermicide used in combination with a diaphragm. The combination of BufferGel and diaphragm was acceptable to participants, with 66% reporting that they would use this method in the future.

TRACK C

Chaired by Neetha Morar, Susan Newcomer and Charlotte Watts

This track covered a wide range of social science and ethics of research. There has been a dearth of information regarding acceptability of microbicides. These studies have been conducted with actual use as well as hypothetical acceptability. Acceptability and use is the key to the success of any interventions. A large number of abstracts were on acceptability of microbicides, identifying measurement and challenges of acceptability.

The key issues relating to ethics of research were highlighted by Professor Ames Dhai in her plenary and presented by various speakers during the oral presentations. These included the challenges of informed consent, standard of care for research participants, recruitment incentives, etc. There were

abstracts reporting use of a comprehensive check list in informed consent to ensure understanding prior to enrolment. These documents are translated into the local language for easy comprehension. The standard of care debate regarding access to care for participants who are screened out of microbicide trials and those who seroconvert during the course of the trial has evolved considerably. Presentations in the standard of care sessions covered innovative strategies being put in place, in partnership with local health providers, to ensure ongoing care for participants in clinical trials with the responsibilities to facilitate care coming from the sponsors and researchers.

TRACK D

Chaired by Megan Gottemoeller, Kelly Blanchard, Elizabeth Bukusi and Miriam Katende

This track's inclusion in the conference shows recognition of the important role played by the community and civil society in microbicide research, not just as a participating community but as important stakeholders, who can move research beyond implementation. This track highlighted a clearer definition of community which involved a range of stakeholders. Round-table discussion sessions highlighted the long-term safety of microbicides in HIV-positive women, especially in the light of new-generation products that may contain antiretrovirals. Discussion centred on effective communications of research findings to ensure consumer protection while acknowledging that long-term safety is a moving target.

There are several established and emerging microbicide advocacy groups in various regions of Africa, the USA and Asia. It was apparent from the discussions that it would be important to set an in-country national agenda that aligns itself to global efforts, but ensures that each country's own priorities and resources are identified.

The issue of access to microbicides will depend on donor involvement and commitment. A donor panel in this track discussed the need not only to provide access to microbicides once an effective product is found, but also to ensure smooth and expedited regulatory and licensure procedures for approval. In addition, this panel discussed the need for increased funding, not only for research but for the complementary processes of strengthening health care systems and ensuring sustainability of care.

In conclusion, the resounding success of the Microbicides 2006 Conference can be attributed to the excellent attendance by scientists, donors, ethicists, activists, community representatives and policy makers. The conference highlighted advances in basic science research for appropriate targeting of HIV prevention, as well as considerable advances in our knowledge of microbicide formulations and delivery systems. The clinical track provided an excellent overview of the current status of clinical trials, highlighting some of the challenges and lessons learned. These challenges apply not only to microbicide trials but to all prevention trials.

From the social and behavioural science track we have learnt a great deal about microbicide acceptability and community involvement in ensuring adequate recruitment and retention of trial participants. The standard of care has evolved, with clinical trial sites facilitating access to care for those who become HIV-positive during the course of the trial.

Finally, the importance of involving civil society, research communities, advocates, activists and policy makers was highlighted in the community track, with an emphasis on partnerships for successful trial implementation and outcome, ensuring treatment and care, and access to products when available.

REFERENCE

1. UNAIDS. AIDS Epidemic Update, December 2005.

The following people contributed towards the content:

Track A summary: Robin Shattock, St George's Hospital Medical School, London

Track B summary: Sinead Delany-Moretlwe, Reproductive Health and HIV Research Unit, University of the Witwatersrand, Johannesburg

Track C summary: Neetha Morar, HIV Prevention Research Unit, Medical Research Council, Durban

Track D summary: Megan Gottemoeller, Global Campaign for Microbicides

STRUCTURED TREATMENT INTERRUPTIONS: IS THERE AN ALTERNATIVE TO LIFELONG HAART?

Insights from the 13th Conference on Retroviruses and Opportunistic Infections

Graeme Meintjes, *MBChB, MRCP (UK), FCP (SA), Dip HIV Man (SA)*
G F Jooste Hospital, Cape Town

The 13th Conference on Retroviruses and Opportunistic Infections (CROI) was held in Denver, Colorado, on 5 - 8 February 2006. Several papers were presented on the topic of structured treatment interruptions (STIs) of antiretroviral therapy in adults, and this was probably the most controversial antiretroviral treatment issue discussed at the conference. This article summarises these papers.

Antiretroviral therapy is lifelong and with time carries the risk of cumulative metabolic and cardiovascular toxicities, the accumulation of viral resistance mutations, and treatment fatigue with adherence lapses. The medication is also expensive. For many patients interruptions are inevitable. This had led to an interest in the concept of STIs – providing breaks in therapy in a structured fashion to minimise the long-term complications of highly active antiretroviral therapy (HAART) while not compromising the long-term benefits of therapy or putting patients at risk of immunosuppression-related events during these breaks. The most popular strategy involves a CD4-guided strategy to trigger the recommencement of HAART. STIs are of particular interest for patients who started HAART with high CD4 counts under previous guidelines, the question being whether they can safely interrupt their HAART and allow immunological progression before recommencing.

Major concerns regarding STIs are risk of disease progression during interruptions resulting in new infections and death, promotion of viral resistance, and the acute retroviral syndrome. The latter is a febrile illness similar to seroconversion illness associated with viral rebound after stopping HAART.

Six adult STI studies were reported at CROI from different settings around the world. The study designs, patient baseline characteristics and findings differed. The findings of these studies are summarised in Table I.

THE SMART STUDY[1]

The Strategies for the Management of Antiretroviral Therapy (SMART) study was conducted at 318 sites in 33 countries and was a prospective randomised trial comparing a virological suppression (VS) arm (patients stayed on continuous HAART) to a drug-conservation (DC) arm (in which patients interrupted or deferred HAART with a CD4 count > 350 cells/µl and restarted when CD4 dropped below 250 cells/µl). A total of 5 472 patients had been enrolled in the study by the time it was terminated by the Data Safety Monitoring Board in January 2006 because of an increased risk of disease progression and death in the DC arm. The background of the whole cohort was:

- median age: 46
- median CD4 at entry: 598 cells/µl
- 70% had a viral load (VL) < 400 copies/ml at study entry
- median CD4 nadir was 253 cells/µl (25% of patients had a nadir CD4 less than 154 cells/µl)
- 5% were ART naïve
- median of 6 years on ART
- 24% had previously had an AIDS-defining illness.

The primary endpoint was a combined outcome of death and disease progression. The rate of this was 3.7/100 person-years in the DC arm and 1.5/100 person-years in VS arm giving a relative risk (RR) of 2.5 (95% confidence interval (CI) 1.8 - 3.6). This difference remained significant when the data were stratified according to nadir CD4 (even those with a nadir CD4 > 400 cells/µl showed an increased risk of this primary endpoint in the DC arm). Death was also significantly more common in the DC arm (RR 1.9). The CD4-guided strategy to maintain CD4 > 250 cells/µl and allow STIs was therefore associated with a greater than 2-fold higher short-term risk of disease progression and death, despite the fact that patients in the DC only spent 3% of study follow-up time with a CD4 less than 200 and 32% of the time with a CD4 less than 350.

TABLE I. ADULT STRUCTURED TREATMENT INTERRUPTION STUDIES REFERRED TO AT CROI 2006

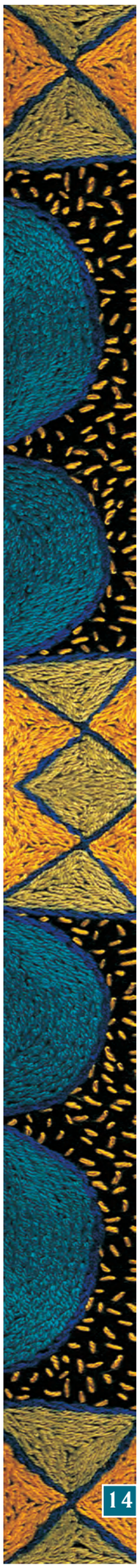
	STUDY					
	SMART	**ANRS 1269 TRIVICAN**	**ACTG 5170**	**STACCATO**	**ISS PART**	**WINDOW-ANRS 106**
N	5 472	326	167	430	273	403
Setting	33 countries	Cote d'Ivoire	USA	Australia, Thailand, Switzerland	Italy	France
Study design	RCT	RCT	Single arm observational prospective cohort	RCT	RCT	RCT
STI strategy	**CD4-guided**: Interrupt CD4 > 350 Restart < 250	**CD4- guided:** Interrupt CD4 > 350 Restart < 250	**CD4-guided:** Interrupt CD4 > 350 Encouraged to restart with CD4 < 250	**CD4-guided:** Interrupt CD4 > 350 Restart < 350	CT v. 5 STIs (defined time periods of 1 - 3 months)	CT v. 8-week-on/ 8-week-off HAART
CD4 nadir in STI group (median)	252	272	436	267	418 (mean)	274
Follow-up period	Median 10 months	Median 19 months	96 weeks	Median 22 months	24 months	96 weeks
AIDS or death/100 PY						
STI	3.7	17.6	2.9	0.2	NR	2 deaths, 0 AIDS
CT	1.5	6.7	–	0.4	NR	0 deaths, 0 AIDS
Main clinical outcomes	Increased HIV progression and death in STI arm	Increased serious morbidity in STI arm	Safe, 5 died (none AIDS related) and 5 CDC B/C events	Clinically safe	14 serious adverse events in each arm	Clinically and immunologically safe
VL outcome	NR	NR	20% virological failure among the 46 who recommenced HAART	92% (CT) v. 90% (STI) suppressed	Similar rates of VL failure: 24% (CT) v. 26% (STI)	More patients in the STI arm had VL > 400 at 96 weeks (19 v.10%, $p = 0.02$)
Resistance	NR	11% in STI arm v. 5% in CT arm (NS)	NR	No difference between 2 arms (2% in each arm)	32% in STI arm demonstrated mutation(s) during STIs	No difference in mutations between 2 arms
SE	More common in STI arm	No significant differences between 2 arms	NR	Diarrhoea, neuropathy and lipodystrophy more common in CT arm	No serious adverse events related to drug toxicity	No difference between 2 arms
Time off HAART	67% in STI arm v. 7% in CT arm	NR	Median 96 weeks	62%	38%	48.5%

RCT = randomised controlled trial; PY = person-years; NR = not reported; CT = continuous treatment; STI = structured treatment interruption; NS = non-significant difference.

What was surprising, given that STIs would be thought to reduce drug side-effects by reducing drug exposure, was that major cardiovascular, hepatic and renal complications were actually significantly more common in the DC arm (RR 1.4).

ACTG 5170[2]

This study assessed the safety of a single treatment interruption in a cohort of patients who started HAART with relatively high CD4 counts under old US guidelines. The hypothesis was that these patients could safely interrupt HAART without significant disease progression over 2 years. There was no control group. In addition the study aimed to define the parameters that would identify patients in whom STIs were low risk. Patients in the cohort were on HAART for at least 6 months with a current and nadir CD4 count > 350 cells/µl and VL < 55 000 copies/ml. HAART was stopped then recommenced at the discretion of the patient and provider,



although recommencement was strongly encouraged when CD4 dropped below 250 cells/µl. Primary endpoints were time to Centers for Disease Control (CDC) B or C event or death or CD4 < 250 cells/µl or resumption of HAART. One hundred and sixty-seven patients were enrolled, and the median nadir CD4 count was 436 cells/µl and entry CD4 count 833 cells/µl. The strategy was assessed as being 'generally safe' and patients spent a median of 96 weeks off HAART. Three CDC B and 2 CDC C events occurred, all in patients with CD4 counts > 350 cells/µl. There were 5 deaths, none HIV-related; 3 of the deaths were cardiovascular-related. Of the patients 28% needed to restart HAART during the study period, and only nadir CD4 count was predictive of the need to re-initiate in a multivariate analysis. The predictors of disease progression, death and CD4 decline in this cohort were a lower CD4 nadir and VL > 50 copies/ml at study entry.

STACCATO[3]

This study was conducted in Thailand, Switzerland and Australia. Of the patients 80% were on ritonavir-boosted saquinavir regimens. In this study the strategy was for patients to stop HAART when the CD4 count was above 350 cells/µl, but to restart when it dropped below 350 cells/µl (higher than the threshold in other studies); 430 patients were randomised to either continuous therapy (CT) or these STIs. Patients had to have a VL < 50 copies/ml on entry. A third arm to the study (one week on and one week off HAART) was prematurely terminated because of a high virological failure rate.

Patients were able to spend a median of 63% of study time off HAART and there was no excess in drug resistance mutations in the STI group. In contrast to SMART there were fewer drug side-effects in the STI group: diarrhoea, neuropathy and self-reported lipodystrophy were all less common in the STI arm. Minor manifestations of HIV infection such as oral and vaginal thrush and thrombocytopenia were more frequent in the STI arm. There were no AIDS-defining illnesses in either arm and there were 2 non-AIDS-related deaths, one in each arm.

At the end of the study continuous HAART was recommenced for 12 - 24 weeks, and 92% (CT) v. 90% (STI) suppressed to a VL < 50 copies/ml. There was little evidence that the STIs predisposed to resistance (resistance mutations were detected in around 2% of patients in both arms).

TRIVICAN[4]

This study was undertaken in Cote d'Ivoire. Patients on HAART with CD4 counts > 350 cells/µl, VL < 300 copies/ml and CD4 nadir > 150 cells/µl were enrolled. The study compared continuous therapy with two STI strategies, a CD4-guided strategy (treatment interrupted at CD4 > 350 cells/µl and restarted when it dropped below 250 cells/µl) and a 2-month-off/4-month-on therapy strategy. Endpoints were death and serious morbidity (WHO stage 3 or 4 conditions). At the interim analysis the DSMB recommended stopping the CD4-guided STI arm, and the analysis of this arm versus continuous therapy was presented at CROI. Patients in the study had a median nadir CD4 of 272 cells/µl and median CD4 at entry of 460 cells/µl. A more than 2-fold higher rate of serious morbidity was demonstrated in the STI arm (IRR 2.6, 95% CI 1.3 -5.6). This was mainly accounted for by invasive bacterial infections (IRR 15.9, 95% CI 2.6 - 64.8). The common bacterial infections were *Salmonella typhi* and *Streptococcus pneumoniae*. There was also a non-significant trend to more tuberculosis and oropharyngeal candida in the STI arm. There were more hospitalisations and outpatient visits in the STI arm. There were no significant differences between the two arms in terms of mortality, drug side-effects or emergence of viral resistance.

ISS PART[5]

There were two arms in this study: a continuous treatment arm and an STI arm in which there were planned interruptions of 1, 1, 2, 2 and 3 months with a 3-month period of continuous HAART in between each of these interruptions; 70% of patients were on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens, and when interrupting they stopped the NNRTI 3 - 6 days before the other drugs. Those on protease inhibitor (PI) regimens were mainly on unboosted PIs. All patients were on their first regimen and all had VLs < 400 copies/ml at study entry. The mean CD4 at study entry in the STI arm was 714 cells/µl and the mean CD4 nadir 418 cells/µl. The primary endpoint was the proportion of patients with CD4 > 500 cells/µl at 24 months. More patients achieved the primary endpoint in the CT arm (87% v. 69%), making the STI strategy inferior to continuous treatment in this regard. There were more protocol discontinuations in the STI arm. Rates of virological failure (defined as VL > 400 copies/ml at 24 months) were the same in both arms (8% in CT arm v. 9% in STI arm). Thirty per cent of patients in the STI arm demonstrated at least one resistance mutation during treatment interruptions and these were associated with a greater risk of virological failure. The emergence of resistance mutations was associated with the presence of archived mutations in proviral DNA at baseline and the use of unboosted PIs. The investigators concluded that potential STI candidates were patients with:

- high pre-HAART CD4
- absence of archived mutations
- absence of residual viral replication (VL < 2.5 copies/ml),
- and not on unboosted PIs.

There were 14 serious adverse events in each arm – none were drug side-effects.

WINDOW-ANRS 106[6]

Patients with nadir CD4 > 100 cells/µl on HAART with CD4 > 450 cells/µl and VL < 200 copies/ml for at least 6 months were randomly assigned to either continuous therapy or an 8 week-on/8 week-off strategy for 96 weeks. Patients on nevirapine were excluded and if patients were on efavirenz this was stopped 7 days before other drugs in their regimen. At baseline the median CD4 was 741 cells/µl and nadir 280

cells/µl and 8% had AIDS. The primary outcome was immunological failure defined as reaching CD4 < 300 cells/µl; 3.6% v. 1.5% reached this primary endpoint, demonstrating that this STI strategy was not inferior to continuous therapy in this regard. The median loss of CD4 cells was 155 cells/µl in the STI arm over 96 weeks. The interruption strategy was also clinically safe. There were 2 HIV unrelated deaths (1 violent and 1 from alcoholic cirrhosis) in the STI arm and no AIDS-defining illnesses in either arm. There was no difference in drug side-effect rates between the two arms. More patients in the STI arm had VL > 400 copies/ml at 96 weeks (19% v. 10%, $p = 0.02$). There was no significant difference in resistance patterns in patients experiencing virological failure between the two arms. Over the 96 weeks those in the STI arm were spared 49% of drug exposure.

OTHER ISSUES TO CONSIDER

STIs are also associated with thrombocytopenia (< 5% in all studies) and acute retroviral syndrome (up to maximum 6% in the Staccato study).

Nadir CD4 count is the best predictor of how long patients can spend off HAART. Pre-HAART CD4 nadir was the only independent predictor of time off HAART in ACTG 5170.

After stopping HAART the CD4 declines to the pre-HAART nadir within weeks. The ACTG 5170 study demonstrated a rapid decrease in CD4 count in the first 2 months after stopping HAART (by 198 cells/µl), reflecting a fall back to pre-HAART nadir. Thereafter there was a more gradual decline (1.7 cells/µl/week), reflecting natural progression of immuno-suppression. There is also a rapid VL rebound after stopping HAART: VL setpoint was reached 4 weeks after stopping HAART in this study.

Another important issue to consider when interrupting HAART is the potential for the development of viral resistance. This applies particularly to interruptions in an NNRTI regimen, as NNRTIs have much longer half-lives than NRTIs and therefore persist in the plasma after the regimen is stopped, resulting in effective monotherapy and the selection of NNRTI drug resistance mutations. To help avoid this it is advisable to continue the NRTIs for 5 - 10 days after the NNRTI is stopped to 'cover the NNRTI tail'.

On a public health level it must also be considered that STIs, by resulting in episodes of viraemia, may contribute to an increased risk of HIV transmission. Another issue to consider is that in patients with chronic hepatitis B, stopping HAART regimens that contain lamivudine (3TC), emtricitabine (FTC) or tenofovir may result in hepatitis flares and is therefore not advised.

CONCLUSION

Key messages to emerge from these studies are:

- The largest study on this issue (SMART) demonstrated a clear increase in the risk of morbidity and mortality using an STI strategy. This particular STI strategy is therefore not advised in clinical practice. Other studies have shown STI to be safe, and this may result from differences in study design and patient population. Further studies to confirm whether STI strategies may be safe in less immunologically advanced patients using more conservative strategies are needed. Until then they are generally not advised in clinical practice.
- Some feel that STIs may still have a role in patients who started HAART early with CD4 counts higher than 350 cells/µl and where a threshold of 350 cells/µl for recommencing HAART during STI is set. Certain studies (Staccato and ACTG 5170) support this. However, in the SMART study even patients with a CD4 nadir > 400 cells/µl had excess morbidity/mortality in the STI arm.
- It is important to remember that most of the HIV-related morbidity associated with STIs in the SMART study occurred when the CD4 was between 250 and 350 cells/µl, and on the basis of SMART STIs that allow CD4 decline into this range therefore seem inadvisable.
- The best predictor of outcome using an STI strategy is nadir CD4. STIs are most risky in patients with low CD4 nadir.
- The setting is also an important consideration. The one study done in Africa showed unique risks, in particular invasive bacterial infections.
- An unexpected outcome of the SMART study was an increase in cardiovascular, hepatic and renal complications in the STI arm. It was speculated that HIV replication and the resulting immune activation during STIs may play a role in inflammation-mediated cardiovascular effects.
- Most studies showed no increased risk of viral resistance using an STI strategy apart from ISS PART. The HAART regimens patients were on and the staggering method of stopping drugs may have influenced this. In the ISS PART study interruptions of an unboosted PI regimen was a particular risk factor for resistance.

It is important to note that the risks associated with progression during STI may well be different from those in naïve patients, and the findings above therefore do not apply to decisions about when to start HAART in naïve patients. The data above are useful for clinicians managing a patient on HAART who requests a self-initiated 'drug holiday'. There are many findings here that allow for an evidence-based discussion regarding the risks associated with this for an individual patient. Clearly the nadir CD4 is the most important factor to consider in such discussions.

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THE PRICE OF POLITICAL INACTION – AND WHAT NEEDS TO BE DONE TO END IT

Plenary Presentation to XVI International AIDS Conference, 17 August 2006, Toronto, Canada

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'We now have the means to reverse the global pandemic and to avert millions of needless deaths.'[1]

In June 2006 governmental leaders met for the second time under the auspices of the United Nations General Assembly Special Session on AIDS (UNGASS). The Political Declaration on HIV/AIDS, which was the main outcome of this meeting, was criticised by many civil society activists for its refusal to set targets, or to state expressly the measures needed to protect vulnerable groups from HIV infection.

However, the vital admission above, tucked away in paragraph 14, inadvertently reflects both the progress that is behind us – and the challenge ahead.

Implicitly the Declaration accepts that since 2000 many of the barriers that blocked access to HIV prevention, treatment and care have been removed. As Piot points out in a recent article in the *Lancet*, across the world large parts of society are now mobilised against AIDS; some essential medicines have become more affordable; interventions to prevent MTCT could halt hundreds of thousands of infections; there is much more money – albeit still insufficient.[2]

So, 'We have the means' – then what stops us from acting? And what should be done about those in power who refuse to act? These are the most pertinent questions facing the next stage of the AIDS epidemic.

Early in 2006, in preparation for the high-level meeting on AIDS (UNGASS II), a report by the UN Secretary General assessed states' progress with implementation of the 2001 UNGASS Declaration of Commitment. The report identified many areas of failure, particularly of HIV prevention programmes to reach populations most at risk.[3] But the Secretary General avoided analysis of the reasons for these failures or to hold governments accountable for their actions – or lack of them. The report thus became complicit in covering up human rights violations with huge political and social significance.

The rest of this lecture follows the path untravelled by the SG. It does so not in order to assign blame but because, mid-way through the AIDS epidemic, millions of lives still rest on a forthright assessment. The key charges of this analysis are that political failures on HIV have distinct but overlapping consequences for (a) development and (b) human rights. Therefore identifying and overcoming political failure is a crucial test of the United Nations.

The flip side of political failure is political leadership. But unfortunately, for the past two decades, despite the frequency with which it has been invoked, political leadership (meaning leadership by those elected to govern us and trusted with our countries' resources, as well as business, trade union, faith, academic, civil society and media leaders) has remained largely elusive.

To describe the price of political inaction, so as to prevent it in future, this presentation focuses on two of the nations that are at the epicentre of the global HIV epidemic, South Africa and China. The crux of its argument is that:

- In the absence of political leadership, the South African HIV epidemic exploded along a course that was predictable and to some measure preventable, driven by a set of social factors that were understood as early as 1990.
- If the lessons of South Africa are not learnt then in countries like China, which are on the cusp of similarly explosive HIV epidemics, there will be millions of avoidable HIV infections, which will be a blow to Chinese people and to global control of HIV.
- Without political leadership, truth-telling and a commitment to the human rights HIV prevention and treatment will continue to be stymied at great human cost.

SOUTH AFRICA

South Africa is a society in transition. In the last 12 years it has offered the global community examples of the best and worst responses to political and social challenges of the late 20th and 21st century. The best practices are numerous – the worst practices relate mainly to the response to HIV/AIDS.[4]

For half a decade activists in South Africa have been calling for HIV to be declared an emergency. But, to the extent that it has

responded at all, the government has said that there are more pressing social problems, poverty in particular, to which the nation must be directed. The contradiction, as activists have pointed out continually, is that progressive social reforms are being undone by its simultaneous failures in HIV prevention, treatment and care.

When reasons are sought for the failure to respond effectively to the AIDS crisis, the government cannot feign ignorance. In 1990, four years before the end of apartheid, Chris Hani, a senior leader of the ANC, warned that: 'We cannot afford to allow the AIDS epidemic to ruin the realisation of our dreams. Existing statistics indicate that we are still at the beginning of the AIDS epidemic in our country. Unattended, however, this will result in untold damage and suffering by the end of the century.'[5]

In the same year, Peter Doyle, an actuary for an insurance company, made public a scientific method for modelling the likely course of the HIV epidemic in South Africa.[6] A year later, based upon research into the influence of apartheid policies on patterns of sexually transmitted disease and epidemiology, researchers explained how the migrant labour system had 'institutionalised a geographic network of relationships for spreading STDs.'[7]

> 'This network suggests that once HIV enters the heterosexual mining community it will spread into the immediate urban area, to surrounding urban areas, from urban to rural areas, within rural areas, and across national boundaries.'[8]

This presentation does not chart the detailed course of the next 16 years.[9] Suffice to say that throughout this period there has been an absence of moral, political and strategic leadership from the ANC and the government, which has been unique in the way it has sought to make a virtue out of its refusal to be pressured into responding to AIDS. This has very directly facilitated the spread of the HIV epidemic. Today, Hani's worst fear has been confirmed. In 2005, HIV prevalence among women attending antenatal clinics (Fig. 1) rose for the fifth consecutive year to 30.2%.[10]

As was predicted by Doyle, adult and infant mortality have also increased significantly. The estimates of death due to HIV made in the Doyle model (between 429 000 and 525 000 per annum by 2005) were made in the era before the advent of combination antiretroviral treatment, which only became available after 1996. Theoretically, that should have given South Africa 10 years to disprove Doyle's projections on death. But unlike the Brazilian government, which introduced a treatment programme in 1996, South Africa did so only in mid-2004 (and even then only under pressure). But by 2004 it was estimated officially that 1.5 million people in South Africa had already died of AIDS. In the same year it was reported that the number of recorded deaths per annum, due to all causes, had risen from 316 505 in 1997 to 567 488 in 2004. It is still rising.

The dramatic increase and change in ages of death is reflected in Fig. 2, taken from the Statistics South Africa report (p. 11).[11]

Statistics South Africa, the source of this information, is a government department. Yet its findings have still not given rise to any public recognition by SA's most senior political leadership, and President Mbeki in particular, that there is now a massive crisis of death among young adults. Instead, the South African government continues to worsen the often paralysing confusion and stigma around HIV by publicly questioning whether these deaths are taking place[12] as well as the role that medicine and access to the highest attainable standard of health care can play in overcoming illness. For example, Manto Tshabalala Msimang, the Minister of Health, repeatedly promotes and juxtaposes the value of traditional medicine as opposed to 'Western medicine', creating a pseudo politics around 'Western versus African' traditions of health care by citing the fact that 80% of South Africans' first port of call is a traditional healer.[13] This may be true. The reasons for it are complex and historical. But, as Fig. 2 above shows, it is obvious that traditional healers do not have in their arsenal the means to prevent HIV infection or to stop people dying of HIV disease.

Recently there are signs that the South African government has begun to accept that there has been a rise in mortality. A report published in July 2006 by the Presidency refers to 'an increasingly pronounced and unnatural hump in death' and the existence 'of a pandemic in silent attack'.[14] But although the report acknowledges that it is of 'critical importance' to

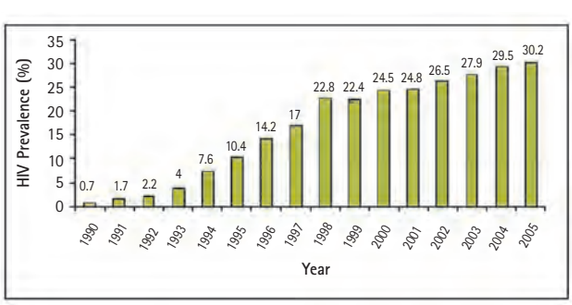


Fig. 1. HIV prevalence among women attending antenatal clinics, 1990 - 2005.

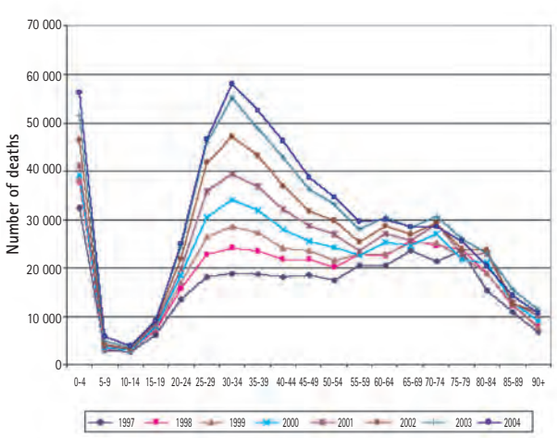


Fig. 2. Distribution of deaths by age and year of death, 1997 - 2004.

contain the HIV and AIDS epidemic it does not say how, or set any tangible targets to ensure that treatment reaches all those who require it clinically and that policies are put into effect to urgently mitigate some of the social consequences of illness and death in poor families.[15]

Indeed, despite this information and a large budget for HIV prevention and treatment, South Africa's response to HIV is currently in chaos. Its Strategic Plan for HIV prevention has not been revised for 6 years; despite substantial capacity to provide ARV treatment in the public and private sector only 17% of people with AIDS are receiving therapy; and an outbreak of multidrug-resistant tuberculosis in KwaZulu-Natal is being unmanaged.

Tragically, in South Africa, governments can find an example of the cost of not providing political leadership on HIV. This cost will be a huge burden on government and society in future.

CHINA

In the last 5 years the AIDS epidemic in Africa has drawn the lion's share of political attention. This has had justification, but must not obscure other regions of the world on the cusp of similarly explosive epidemics. For example, in China the government is in much the same position today as South Africa was a decade ago. According to UNAIDS/WHO: '… it is projected that *without concerted prevention and treatment efforts*, the number of people living with HIV/AIDS in China will exceed 10 million by 2010. …'[16] [my italics].

China is receiving a deluge of media attention as an awakening giant in the world economy and politics. But, outside of those who work at HIV prevention, it is receiving almost no attention as a possible additional epicentre of the global AIDS epidemic. This may not be surprising. Viewed cynically, it seems that industrialised countries, the G8 in particular, are far more concerned with those infectious diseases that threaten to come out of China, SARS and H5N1 in particular, than with inward transmission of HIV.[17] Or, put another way, has there been a crude calculation that even if 10 million more people are infected with HIV in China in the next 4 years, there will be no impact on China's economy because HIV prevalence will still be less than 1%?

The question governments should immediately be compelled to answer is whether we value these 10 million lives. Do we consider people in China with HIV to be human beings with human rights or politically and economically insignificant statistics when measured against the total Chinese population?

The Chinese government (like the South African government 12 years ago) has enough information about the epidemiology of HIV and the probable trajectory of new infections to allow it to act decisively and effectively.

Obviously, there are major differences between China and South Africa, but there are certain vital common denominators which may heavily impact on patterns of HIV infection.

Like South Africa, China is a society undergoing a rapid transition that affects many areas of life and behaviour. One startlingly similar fact to the South African political economy of HIV/AIDS is the impact of population movements. In China it is estimated that there are 120 million internal migrants[18] – people moving from the impoverished rights-less rural areas to the rapidly developing cities. One critical difference is that many of the migrants are young women.

Like South Africa, there are deep historical inequalities between men and women. While not in the past a cause of physical violence and abuse of women, there are reports that the contemporary social turmoil is leading to an increase in risky sexual relationships, sex work and violence against women.[19]

Looking further ahead, it is also clear that the Chinese public health system (which suffers massive underinvestment from the Chinese government) does not have the capacity to care for millions of poor people who will need access to ARV treatment if they are to stay alive.[20]

Some might argue that it is premature to express concern about the lack of political leadership on HIV in China. Indeed, there is some evidence that the HIV epidemic is being taken more seriously by the Chinese government.[21] However, statements of good intention need to be tested against independent information about what is actually happening. In addition, it is vital to see how China's resolution of its human rights issues is also tied up with how effectively it responds to HIV.

From this viewpoint, China's record so far raises concern. Three issues stand out.

Firstly, between 1985 and 1995 one of the major causes of HIV infection in China was the trade in blood and the failure to ensure safe blood products, particularly for haemophiliacs. The Chinese government was aware of the risk to blood. Indeed, in 1987 it stopped the importation of factor 8. However it took a further 10 years to pass and implement laws that set safety standards for locally produced factor 8. During this time, haemophilia activists estimate that up to 3 000 people may have been infected with HIV. Added to this was the blood-for-sale scandal in Henan, Anhui and Hubei provinces which, official estimates suggest, caused up to 69 000 people to be infected with HIV. However, Human Rights Watch estimates that as many as 1 million people were in infected. But to date, only a tiny number of people infected in these ways are aware of it. An even smaller number have been compensated. Instead, those who have sought compensation have sometimes been imprisoned, intimidated and transported back to rural areas. Apart from the obvious injustice, the effect of

China's policy of refusing to take responsibility is to discourage people with haemophilia from finding out their HIV status, thus increasing the risk to their sexual partners (in what would otherwise be a traditionally 'low-risk group').

Secondly, in 2006 China again pledged in the Political Declaration on HIV/AIDS 'to eliminate gender inequalities, gender-based abuse and violence …'.[22] But despite recognised efforts to take concrete steps towards women's equality, this commitment is severely tested by, for instance, the laws and policies China practises in relation to sex work.

Ironically, another parallel with South Africa exists here. In both countries political reform is driving progressive legal changes in the status of women. However to survive the economic transition millions of women engage in sex work or are in disempowered sexual relationships with men whose income they depend upon. Marital migrancy, often as a means of gaining economic security, is an evolving phenomenon.[23]

While the latter is not illegal, sex work is. Between 1995 and 2004, for example, official statistics record that two million women were 'found guilty' of prostitution[24] and sent to labour re-education camps. Given China's promise at UNGASS to protect and promote the human rights of women, and our knowledge of the risk of HIV infection associated with sex work, laws that criminalise and punish women involved in sex work should be scrapped as an imperative of HIV prevention and human rights.[25]

Finally, China's response to independent non-governmental organisations seems to be based on harassment and imprisonment.[26] This is not in keeping with international norms or with established knowledge of the importance of an independent civil society in HIV prevention and treatment. Thus, as recently as July 2006 an HIV-positive woman was detained for trying to petition the government for compensation for her HIV infection.[27] The UN Human Rights Council, UNAIDS, the Secretary-General and international activists must demand an immediate end to the detention of HIV-positive petitioners and activists.

HUMAN RIGHTS

The examples of South Africa and China show again that responses to HIV must be based on both the protection of civil and political rights and the promotion of the right to health. Global recognition of this link between human rights and health – as well as the ill-health and the denial of human rights – has been one of the lasting 'benefits' of the HIV epidemic.[28]

But what is immediately relevant is the fact that inherent in an acceptance of human rights, and their embodiment in global norms[29] and covenants, is the duty of solidarity with victims of human rights violations and truth-telling where rights are violated. This duty applies to all levels of society: between men and women, between communities, within countries and between countries.

However, while many governments appear willing to speak out against violations of civil and political rights, the history of AIDS is demonstrating a great reticence when it comes to speaking out about violations of the right to health and dignity. This seems to be all the more so if the violation is by an otherwise democratic government, like South Africa, or a strategically important government like China.

In this vein, the greatest tragedy for people vulnerable to, or living with, HIV is that the political response to AIDS is directly influenced by global geo-politics and rules of 'diplomacy' which in many instances disallow truth-telling.

A stark example of this has been the silence of UN Secretary-General Kofi Annan about South Africa's governmental failures on HIV. When Annan addressed a joint sitting of the South African Parliament on 14 March 2006, not one word of criticism was levelled at the South African government's response to HIV. Instead, his speech elaborated on the theme that 'the kind of things South Africa is doing at home, and promoting on the wider African scene, may show us the best way for developing countries in general to respond to today's world.'[30]

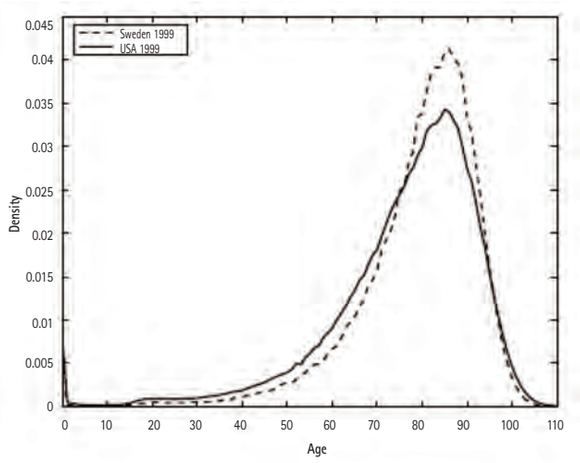
Annan is aware of the HIV crisis in South Africa and of the crisis of governmental denial. He has privately met with Treatment Action Campaign (TAC) and other activist leaders. Stephen Lewis, his Special Envoy on HIV/AIDS in Africa, has spoken out powerfully of the crisis.[31] But Lewis, obviously, does not have the political influence of the Secretary-General, who seems to have been intimidated by the South African government's complaints about his turbulent and honest envoy.

Human rights must begin to trump diplomacy in the UN system. This is because implicit in the very existence of institutions such as UNGASS and UNAIDS, built as they are on the foundations of the Universal Declaration of Human Rights, is an understanding that ensuring access to health is a human right and a governmental duty. Therefore the way in which a government responds to an epidemic such as HIV cannot be solely a matter of national jurisdiction – certainly not when it is characterised by a stubborn and deliberate refusal to take steps that will save lives.

Henceforth, it should be the norm that the adequacy of a state's response to HIV (or any other disease threat) is measured by human rights standards and against the duties that the ratification of a variety International Covenants (the Convention on the Elimination of all forms of Discrimination Against Women, the Convention on the Rights of the Child, the International Convention on Civil and Political Rights) have created on states. Governments must be compelled to take measures to ensure for all 'the highest attainable standard of health' and, in particular, access to life and equality.

If this approach is not adopted and practised by UN agencies, the African Union, European Union, etc., then the inevitable

result will be the deepening of fundamental inequalities between high-prevalence (developed) and low-prevalence (industrialised) countries. If proof of this is required, contrast, for example, the pattern of mortality in Sweden and the USA (Fig. 3)[32] with that of South Africa (and many other sub-Saharan countries (see Fig. 2).



Notes: Data are the $_nd_2$ densities from life tables for both sexes combined provided by the Human Motality Databases.

Fig. 3. Distribution of ages at death in Sweden and the USA, 1999.

The tolerance of such inequity in the 21st century is itself a human rights violation. It is also an acceptance of a violation of numerous other rights. It has a profound impact not only on the individuals directly affected, but also on social development – a fact that is now making itself evident with regard to the probable non-attainment of the Millennium Development Goals.

POLITICAL LEADERSHIP

In the last sentence of the report of the UN Secretary-General it is stated that: '… leadership commitment is the key to ultimately putting an end to AIDS'. The question, therefore, is how to define 'leadership commitment' and to ask what responsibility the global community has to ensure that South Africa, and other governments characterised by state failure in relation to HIV, comply with their duty to abide by international norms for 'leadership commitment' on HIV/AIDS. Alternatively, what steps can be taken against countries that continue along a deadly path of obfuscation and AIDS denial?

Based on the commitments made at UNGASS in 2001 and 2006, as well as duties arising from international covenants signed by states, we would argue that 'political leadership' requires at a minimum:

- An express, visible and ongoing commitment by governments to reverse the HIV epidemic. This must be based on the explicit understanding that HIV is an exceptional social, economic and political crisis because it profoundly affects affected people's rights to life, equality, dignity and access to health and social services.
- Identifying the major social barriers to openness, prevention, treatment and care and devising concrete measurable plans to remove them.
- That governments co-ordinate all societies' efforts to prevent and treat HIV and mitigate its impact on individuals and society as a whole. This includes agreeing clear lines of accountability at every level of society – government, business, labour and civil society – with the encouragement of critique that does not undermine programmes. It must include agreed sanctions for stakeholders who fail to do what is in their capacity.
- The setting by governments and the UN of time-bound targets and independent monitoring of their attainment, or not, with weekly updates to Cabinet and regular reports on progress by the President and relevant Ministers, to Parliament and civil society forums.
- Actively promoting and protecting human rights and integrating the response to HIV into all strategies for development.
- That governments of industrialised and developed countries take exceptional measures to commit, find and sustain the resources needed – human, financial and material – at national and regional levels of the response.
- Finally, political leadership is essential for, but not limited to, government. It must include the sustained, independent leadership by individuals and collectives of business, labour, faith and civil society leaders.

This presentation has focused on South Africa and China. The UN, G8, EU, AU and others have stood by and watched with puzzled bemusement the unfolding of the South African government's response to the HIV epidemic. There has been much whispering and little shouting. This has contributed to the difference between 20% and 30% HIV prevalence among pregnant women – that is, it has cost hundreds of thousands of lives. But in differing degrees, the consequences of political inaction concerning HIV are similar across the world. In China, India, Nigeria and South Africa millions are placed at risk by political failure. In other countries the numbers are smaller. But any failure that is based on either a refusal to act or policies that violate human rights must be condemned.

Political leaders must not fail again in China. Or India, Nigeria, Mexico. Where there has been political leadership, such as in Brazil, the UN must find ways of supporting the government to sustain its prevention and treatment programmes while it also supports the neglected regions of Latin America and the Caribbean.

Finally a word to AIDS activists: According to Jim Yong Kim, 'AIDS activism has changed our society indelibly'.[33] This may be true. But it is a double-edged sword, because a great deal of AIDS activism has been necessitated by state failure. AIDS activism needs to grow and get louder. But it also needs to find new paths. Much more must be done to inform and mobilise whole populations, particularly in industrialised countries, of the humanitarian crisis caused by AIDS. Like the share holders of pharmaceutical companies, ordinary citizens of countries need to be mobilised to build pressure on their

governments to do more than pay lip service to the AIDS crisis. This will not be easy.

The start of the 21st century has normalised human rights violations. Electronic proximity to pictures of tragedy via television and the Internet has, ironically, created detachment. In a political culture that offers selective impunity for gross human rights violations, such as those recently witnessed against people in Lebanon, there is a danger that the response to HIV will be a further casualty.

That is why the Treatment Action Campaign (TAC) calls on activists, health workers and governments to continue and strengthen the struggle against AIDS by:

- Organising a global day of action on 1 December to demand that the governments of South Africa, China, India, Mexico, Brazil, Nigeria and Russia give a commitment to political leadership. We urge the new Secretary-General to endorse this demand of political leadership.
- Continually mobilising for the political commitment to meet the needs of prevention and treatment, particularly in those countries worst affected by HIV, and for donor governments in particular to make public commitments about how they will meet the funding targets set in the Political Declaration[34] as well as how they will fund the Global Fund for AIDS, TB and Malaria.
- Building a culture of truth-speaking within governments, across governments and to governments.
- Devising a plan to ensure that universal access by 2010 is attained, including an emergency plan to get health care workers and treatment to where they are needed.
- Endorsing the targets for HIV prevention and treatment set by the African Union in Abuja in May 2006[35] and ensuring that a similar set of national and global targets are developed by the end of 2006 as promised in the UNGASS Political Declaration (2006).

There should be no going back from the UN's collective admission that 'we have the means', nor from the Secretary-General's statement that 'leadership is the key'. The question should not be whether these statements will one day haunt those political leaders who did not take advantage of medicine, modern technologies and available social and economic resources to try to save lives. Recriminations may come later. Rather, what can be done now and how?

Millions of lives depend on the answer.

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20. The crisis of the health system in China is as severe, if not more, as in any other developing country. According to the World Health Report, 2005, per capita total expenditure of health was only US$61 in 2003. South Africa by comparison was $US 295. Even more startlingly, out-of-pocket expenditure on health was 87% of private expenditure on health, with general government expenditure on health only 36.2% of total expenditure.
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22. Paragraph 30, Political Declaration on HIV/AIDS.
23. It has been noted that marital migrancy takes women away from tradition support networks increasing their vulnerability to sexual and physical abuse. See footnote 19 above.
24. In fact human rights activists say that little due process is followed in respect of women suspected of being prostitutes, who are often rounded up to meet quotas, physically and sexually abused by police and then sent for 're-education' in labour camps.
25. Despite the fact that the suppression of sex work might be a significant driver of the HIV epidemic, the Chinese government is unlikely to come under major pressure from the United States Government, with which it finds common cause on this issue.
26. Human Rights Watch, 'Locked doors: The human rights of people living with HIV/AIDS in China', August 2003, Vol. 15, No 7.
27. 'Chinese HIV victim detained after asking government for help' July 20, AFP. According to the report: 'A Chinese woman who contracted AIDS from a hospital blood transfusion was detained on suspicion of a serious crime after she asked the health ministry for more compensation'.
28. The human rights approach to HIV ought to guide the public health response to other infectious diseases, particularly TB. In this respect, critics of 'AIDS exceptionalism' make the mistake of wanting to pull the response to HIV down to the threshold of care for other diseases, usually overlooking patient dignity and autonomy, rather that raising standards of care across to the levels we demand for HIV. This argument is resurfacing in proposals from the WHO to dispense with proper pre-test counseling for HIV, see: Draft Guidelines.
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BOOSTING PROTEASE INHIBITORS WITH LOW-DOSE RITONAVIR – UNRAVELLING THE MYSTERY

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The advent of highly active antiretroviral treatment (HAART) has had the dramatic effect of changing HIV infection from a relentlessly progressive disease with inevitable death to a disease that is chronic and manageable. The goal of HAART is to suppress HIV replication maximally, and thereby restore immunological function, reduce HIV-related morbidity and mortality, and improve quality of life.[1] HIV-infected persons who qualify for treatment can be treated with a HAART regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI).[2]

In the presence of subtherapeutic drug levels, viral replication persists, resulting in the formation of mutations and resistant variants.[3] There are various reasons for failure to suppress viral replication to undetectable levels.[4] Non-adherence is one of the major reasons for incomplete suppression.[3] Non-adherence can be due to high pill burden, high frequency of dosing, dietary restrictions, and lack of tolerance of adverse effects.[4]

Pharmacological factors also play an important role in treatment failure. Pharmacodynamic drug-drug interactions can change the pharmacological effect of a drug. The pharmacological effect of two or more drugs can act additively or antagonistically.[4] Pharmacokinetic drug-drug interactions are associated with inappropriate plasma concentration of drugs. Changes in plasma concentration of drugs can be the result of inadequate absorption, inadequate transport, inadequate metabolism, or inadequate elimination.[4]

Antiretroviral drugs and antibiotics used for opportunistic infections are metabolised by various isoenzymes in the cytochrome P450 (CYP) enzyme system, which consists of a superfamily of haemoproteins.[4] These isoenzymes catalyse the oxidative metabolism of a wide variety of exogenous chemicals such as therapeutic drugs, carcinogens and toxins; and endogenous compounds such as steroids, fatty acids and prostaglandins.[5] The CYP enzyme family plays an important role in phase 1 metabolism of these drugs.[5] The biotransformation of these drugs and chemicals is responsible for the clinically significant drug interactions during multiple drug therapy.[6] Each isoenzyme of the CYP family is a specific gene product with characteristic substrate specificity.[5] Although there are many types of isoenzymes, only six isoenzymes, namely CYP3A4, 1A2, 2C9, 2C19, 2D6 and 2E1, are important in the hepatic metabolism of the drugs. Many drug interactions are the result of either induction or inhibition of the CYP isoenzymes.[7] CYP3A4 is the most predominant isoenzyme in the liver, accounting for 30% of CYP proteins in the liver, and metabolising 30 - 40% of drugs, including the PIs and the NNRTIs.[7] Substantial levels of CYP3A4 are also present in the small-intestinal epithelium, and play a role in the presystemic elimination of orally administered drugs.[7]

Another protein, the P-glycoprotein, plays an important role in actual body and tissue sanctuary site penetration and this remains important for the oral bioavailability of certain drugs.[8]

ENZYME INHIBITION

The majority of clinically important drug interactions are based on inhibition of the CYP isoenzymes, thus causing a decreased metabolism of medications. A drug may inhibit a CYP isoenzyme whether it is a substrate of that isoenzyme or not.[6] Inhibition of CYP isoenzymes causes a dose-related increase in plasma concentration of substrate within minutes to hours of the first dose, thus potentially causing toxicity.[4] Drugs with a long half-life and a narrow therapeutic index can potentially cause serious side-effects.[4]

For the sake of completion enzyme inducers increase the production of CYP isoenzymes, and thus accelerate the metabolism of various medications. It is worth noting that the antiretroviral drug efavirenz is both an inducer and an inhibitor of CYP isoenzymes.[4]

RITONAVIR-BOOSTING EFFECT ON PIs

HAART regimens that include a PI have had a dramatic impact on HIV-related morbidity and mortality. Following their

introduction into clinical practice, there has been a sharp decline in AIDS-related deaths by 47% in the USA.[9] However, the limited bioavailability of, and lack of adherence to, PIs because of high frequency of dosing, high pill burden, dietary and fluid restrictions and intolerance of adverse effects, can lead to the development of resistant strains and virological failure.[10] Any strategies that reduce the collective impact of the adherence–limiting factors mentioned above will improve the patient's motivation and willingness to adhere to therapy.[11] In this section the authors will limit the PI drugs to those currently and readily available in South Africa.

Some PIs (lopinavir and saquinavir) undergo extensive first-pass metabolism via the CYP isoenzyme system, primarily via CYP3A4 in the liver and the small intestine.[3] Of all the PIs, ritonavir is the most potent and most effective inhibitor of CYP3A4, and is therefore also a potent inhibitor of the metabolism of the other PIs.[3] Ritonavir also inhibits CYP3A4 in areas of the body outside the liver and the intestinal tract.[12]

Co-administration (boosting) of a PI with low-dose ritonavir (100 - 200 mg) can increase the total area under the concentration versus time curve (AUC) of the primary PI, as well as the minimum concentration (C_{min}). The maximum concentration (C_{max}) of the primary PI is also increased, although to a lesser extent than that for AUC and C_{min}.[3] Plasma peak and trough levels of the primary PI in a boosted PI regimen is generally higher than when the primary PI is given without boosting with ritonavir. The antiretroviral activity of the primary PI is consequently enhanced in terms of intensity and duration.[12] The pharmacokinetics of the different PIs varies, as does the effect ritonavir has on their pharmacokinetics.[13]

Two distinct patterns of PI boosting are seen, namely

- the C_{max} boosting effect with a modest $t_{1/2}$ boosting, or
- the $t_{1/2}$ boosting with a modest AUC level boosting.[13]

Table I divides the relevant PIs into C_{max} and $t_{1/2}$ boosting patterns.

TABLE I. TWO DISTINCT PATTERNS OF PI BOOSTING ARE PRESENT AND THE PHARMACOKINETICS OF THE RELEVANT PIs ARE DIVIDED BELOW

C_{max} boosting	$t_{1/2}$ boosting
Saquinavir	Amprenavir
Lopinavir	Indinavir
Nelfinavir – effect unknown	

Saquinavir is removed by first-pass metabolism in the small intestine, limiting its bioavailability. Ritonavir improves the efficacy of saquinavir by inhibiting first-pass metabolism and thereby increasing AUC, C_{min}, and C_{max}.[14] Indinavir has relatively good bioavailability, but has a comparatively short $t_{1/2}$. Ritonavir improves indinavir efficacy primarily by inhibiting hepatic metabolism, and decreasing systemic clearance.[15] This leads to larger increases in C_{min} than AUC, while having less effect on C_{max}.[16] Trough indinavir levels are maintained above the IC_{95}.[17] The effect of ritonavir boosting on nelfinavir pharmacokinetics is less than on other PIs, as nelfinavir is metabolised by several CYP isoenzymes, and has relatively good bioavailability.[18] Larger increases are observed in the AUC, C_{min} and C_{max} of nelfinavir's M8 metabolite, but the increases are generally no larger than 1-fold.[13] Lopinavir is only available in combination with ritonavir, and, like saquinavir, benefits from ritonavir's inhibition of first-pass intestinal metabolism.[13] Ritonavir's effect on amprenavir appears to be similar to its effect on indinavir, with inhibition of hepatic metabolism leading to larger increases in C_{min} than AUC.[16]

Low plasma levels of PIs are strongly related to virological failure, but it is ultimately the amount of free drug within the HIV-infected cell, where HIV replication actually occurs, that will most closely influence antiretroviral activity.[17] Drug efflux transporters play an important role in establishing and maintaining HIV sanctuary sites by lowering the intracellular drug concentrations via an efflux mechanism.[18-20] P-glycoprotein and multidrug-resistant protein (MRP) are two such drug efflux transporters whose substrates include PIs and NNRTIs. High levels of expression of these proteins may be found in patients treated for HIV infection, thereby reducing drug absorption from the intestinal tract and enhancing drug elimination in bile and urine.[20-22] P-glycoprotein and MRP efflux transporters in the endothelial cells of the blood-brain barrier may also prevent the transport of PIs into the central nervous system.[20,21,23] Evidence has been presented that ritonavir inhibits functional activity of P-glycoprotein and MRP efflux transporters, allowing a second PI to pass through cellular boundaries.[16,23-25] Thus ritonavir inhibition of efflux transporters combined with the bioavailability of higher plasma levels of the primary PI, appears to facilitate PI penetration into the HIV sanctuaries.[15,16,21,26] The inhibition of P-glycoprotein and MRP by ritonavir not only helps retain PI levels intracellularly, but also increases the oral bioavailability, systemic exposure and central nervous system penetration of the primary PI and ultimately decreases the secretion of the circulating drug into the intestinal lumen.[17,18,27]

ADVANTAGES OF PI BOOSTING

INCREASED POTENCY AND EFFICACY

HAART regimens containing an unboosted PI result in trough drug levels that are likely to be only slightly higher than the 50% inhibitory concentration (IC_{50}).[3] However, boosting with low-dose ritonavir results in primary PI trough levels becoming substantially higher than the IC_{50} or IC_{95}.[3] The addition of low-dose ritonavir to amprenavir, fosamprenavir or indinavir produces substantial increases in C_{min} and AUC, with more moderate or minimal increases in C_{max}.[13] Low-dose ritonavir substantially increases C_{min}, C_{max} and AUC of both lopinavir and saquinavir.[28] However, there is little effect on nelfinavir pharmacokinetics.[13]

DECREASED RISK OF DRUG RESISTANCE

The high peak and trough levels of the primary PI that are achieved with low-dose ritonavir boosting exceed the IC_{50} and

IC_{95} so that there is a high genetic barrier against the development of resistance.

REGIMEN SIMPLIFICATION

PI boosting with low-dose ritonavir results in greater oral bioavailability and longer half-life of the primary PI. Patient adherence is promoted by less frequent dosing, a lower pill burden, and the elimination of food and fluid restrictions.[3]

BOOSTED PI REGIMEN IN TREATMENT-EXPERIENCED PATIENTS

Treatment-experienced patients can also benefit greatly from PI boosting. In patients in whom previous regimens have failed, adequate virological suppression afforded by PI boosting can delay the emergence of new viral mutations that confer further PI resistance and cross-resistance, thereby helping to preserve future treatment options.[3]

DISADVANTAGES OF PI BOOSTING

ADVERSE EFFECTS

As a result of the higher peak levels reached with PI boosting, an increased frequency of PI-related adverse effects has been observed.[3] Indinavir-associated **nephrolithiasis** in PI-boosted regimens may increase in incidence.[29]

Dyslipidaemia, with elevated levels of total cholesterol, low-density lipoprotein cholesterol or triglycerides, is a PI-related adverse effect that has to be monitored closely because of the increased cardiovascular risk.[30] Dyslipidaemia, in the form of increased triglycerides, appears to be more severe with ritonavir than with other PIs.[31] Elevated serum lipid levels have been observed when indinavir, lopinavir or saquanavir is boosted with low-dose ritonavir.[32-39] **Gastro-intestinal** side-effects are common, especially diarrhoea. PI boosting with ritonavir cannot be used in patients who are allergic to ritonavir.

DRUG-DRUG INTERACTIONS

Since all the available PIs are metabolised by, and are inhibitors of, CYP3A4, and since ritonavir is a particularly potent inhibitor, numerous drug interactions can potentially occur with an inducer, an inhibitor or a substrate of this isoenzyme.[40]

Ritonavir metabolism also involves the CYP2D6 and 1A2 isoenzymes, so that co-administration of drugs that are metabolised by these isoenzymes may result in altered drug activity.[3]

Ritonavir also inhibits, although to a lesser extent, CYP2C19, which is important in the metabolism of nelfinavir, and the metabolism of its active metabolite, M8.[13]

Further, ritonavir can induce some P450 isoenzymes and this inhibiting effect may in some instances help to overcome other drugs that interact by induction.[13]

THE FUTURE

In view of the pharmacokinetics of low-dose ritonavir-boosted PIs with high AUC, high trough and peak levels, high C_{min}, good bioavailability, and high genetic barrier to mutations and resistance, is it not an opportune time to have a paradigm shift from the traditional triple therapy consisting of a backbone of two NRTIs together with a NNRTI or a PI, to monotherapy with low-dose ritonavir-boosted PIs such as LPVr (Kaletra)?[41]

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A REVIEW OF THE EXPANDED USE OF CO-TRIMOXAZOLE IN HIV-INFECTED AFRICANS

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The HIV/AIDS epidemic affects large numbers of people in sub-Saharan Africa. Most are unaware of their HIV status. Despite two decades of scientific advance, the education of communities and the provision of antiretroviral medication to some, many still succumb to the virus. Can this situation be changed? Antiretroviral (ARV) drugs have been shown to be effective in both poor and rich communities.[1,2] But for the majority, these agents remain unaffordable and difficult to access. After 2 years, the public-sector ARV rollout programme in South Africa remains under-subscribed and under-utilised.[3] Diets, vitamins, micronutrients and herbal concoctions have been advocated.[4] But none has provided the survival benefit, freedom from opportunistic disease, and completeness of recovery, of antiretroviral therapy.[5]

In recent years, research in developing countries has suggested that the daily use of the sulfonamide combination antibiotic, co-trimoxazole (CTX, trimethoprim-sulfamethoxazole, TMP/SMX), enhances the survival of infected adults and children.[6-8] Co-trimoxazole (CTX) use in patients with advanced HIV infection became widespread in the 1980s when efficacy against *Pneumocystis jiroveci* pneumonia (PJP) was demonstrated. In this context, prophylactic CTX was commenced at CD4 levels of 200 cells/µl or less or following an AIDS-defining condition including PJP itself, prolonged and unexplained fever and weight loss. It was discontinued once the CD4 count rose to and remained above 200 cells/µl for at least 6 months.[9]

But the landscape for prophylactic CTX use in Africa appears to be changing. Recent World Health Organization (WHO) Guidelines have recommended expanding CTX use to all HIV-infected persons – where CD4 levels are unknown – with symptomatic WHO stage 2, 3 or 4 disease and where CD4 counts are available, to all with counts below 350 cells/µl. All HIV-infected persons with TB - pulmonary and non-pulmonary – are to be placed on CTX prophylaxis irrespective of their CD4 cell count. A 'universal option' of 'CTX to all' is offered to those who live in regions of high HIV prevalence and inadequate health care support.[10] When is CTX prophylaxis stopped? 'The general view is to continue CTX prophylaxis in adults – in resource-poor settings – indefinitely.'[10]

Much of the data behind these recommendations come from Africa itself: Cote d'Ivoire, Uganda, Malawi, Zambia and South Africa[6-8,11-12] (and see Fig. 1 in Anglaret *et al.*[22]). How ought health workers and planners to interpret these suggestions for their region?

CTX USE AND THE DEVELOPMENT OF ANTIMICROBIAL RESISTANCE

RESISTANCE TO REGIONAL BACTERIAL PATHOGENS AND MALARIA

The sulfonamide antimicrobials were discovered in 1932. A sulfonamide-trimethoprim combination was first registered in 1968.[13] Sadly the general efficacy of CTX has been curtailed by the rapid emergence of drug resistance. Among the enteric bacteriaceae and the pneumococci, resistance to CTX is a global phenomenon.[14-16] Indeed, the level of CTX resistance in many parts of central and southern Africa is high.[11,14,17,18] Resistance is not confined to the bacterial kingdom. Point mutations in the dihydrofolate reductase (*dhfr)* and dihydropteroate synthetase (*dhps*) genes of *Plasmodium falciparum* have rendered the malarial parasite resistant to sulfadoxine-pyrimethamine (Fansidar), a sulfonamide anti-malarial used widely throughout Africa.[19,20]

Sulfonamides prevent the conversion of para-aminobenzoic acid to dihydrofolate via the inhibition of dihydropteroate synthetase, DHPS. Trimethoprim blocks the subsequent formation of tetrahydrofolate through blocking dihydrofolate reductase (*dhfr*). All organisms require folate for their metabolic needs. Mutations in and altered function of these genes form the basis of much of the resistance to these drugs. It has been noted that strains of *Escherichia coli* isolated in the developing world are more often resistant to CTX than are strains in developed regions. Climate, poverty, poor hygiene, a weak health infrastructure, and the indiscriminate use and abuse of antimicrobials have contributed to this.[13] With regard to sub-Saharan Africa, these factors are unlikely to change soon. Drug resistance is transferable between microbial kingdoms. The use of Fansidar in Malawi has been linked to the local increase of CTX resistance in *Streptococcus pneumoniae*.[21]

RESISTANCE TO *P. JIROVECI*

Despite inconsistent reporting, *P. jiroveci* is an important African pathogen.[24-26] Sulfonamide use has been followed by *dhps* gene mutations in this organism. The gradual accumulation of more and more resistant genes is likely to lead to the high-grade sulfonamide resistance that has become 'usual' in other microbes.[27-32]

Despite the high level of background bacterial resistance, the use of CTX in HIV-infected Africans appears to confer survival benefit against regional pathogens, not just at traditional CD4 levels below 200 cells/µl, where it would be expected to prevent *P. jiroveci* pneumonia (PJP), but at levels in excess of 500 cells/µl.[22,23] What then is CTX doing that is benefiting the HIV infected? And were CTX to be used more widely in Africa, what will this mean for further resistance to, and the use of, this antimicrobial in the future?

THE CLINICAL STUDIES

THE COTE D'IVOIRE STUDIES[6,7]

Two randomised placebo-controlled clinical trials evaluated the role of CTX in subjects who either had a WHO stage 2 and 3 HIV diagnosis or presented with smear-positive pulmonary tuberculosis (TB).[6,7] The studies were performed by two groups of investigators based in Abidjan, Cote d'Ivoire. Enrolment ran from 1995/6 to 1998 with a median follow-up of approximately 10 - 12 months. Patients were not provided with ARV therapy. Primary end-points included the occurrence of severe events, particularly death or hospital admission. Secondary outcomes measured morbidity. Both studies were discontinued prematurely in the light of significant benefit in the CTX arms. Few adverse events were recorded in those subjects receiving CTX. In the TB study, benefit was shown to be greater in those whose CD4 level was below 350 but above 100 cells/µl. Anglaret *et al.*[6] noted benefit across all CD4 strata: below 200, between 200 and 499, and above 500 cells/µl. Fewer episodes of pneumonia, isosporiasis, malaria and 'acute unexplained fever' were reported. Subjects enrolled in the TB study and taking CTX experienced fewer enteric and bacteraemic infections. Importantly, the authors note that at that time, many pathogens (including the pneumococci and salmonellae) in the Abidjan area were still sensitive to CTX.

In a subsequent letter to *AIDS*[22] these researchers point out that an Ivoirean consensus statement now recommends the prophylactic use of CTX in all HIV-infected persons with a WHO clinical stage 2, 3 or 4 diagnosis or who have CD4 cell counts below 500 cells/µl. This view is endorsed by 'the Global AIDS Policy Model Investigators', who in addition conclude that prophylactic CTX is cost-effective in a developing world scenario when started at or after WHO stage 2, i.e. at an early stage of HIV infection.[33]

THE UGANDAN DATA[12,23,34,35]

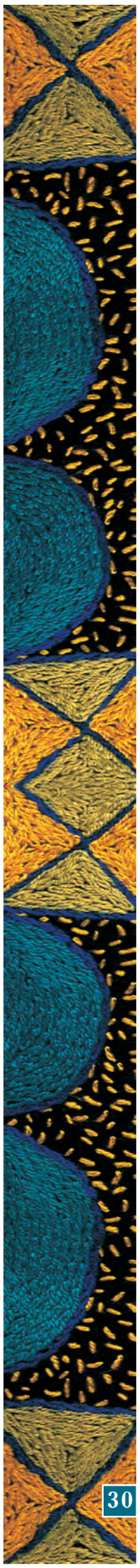
Since 2001, Mermin and co-workers have been researching a stable population of rural HIV-infected Ugandans. Subjects were provided with 'safe' drinking water and CTX. In subsequent follow-up studies ARVs were added, and later still, mosquito-repellant impregnated bed nets. Overall mortality and morbidity rates were examined in addition to rates of occurrence of malaria, diarrhoea illnesses, the numbers of clinic visits and hospital admissions. Participants provided their own 'internal' controls: subjects were monitored for 5 months before commencing CTX therapy.

Of bacterial isolates from study subjects 76% were found to be resistant to CTX. Nonetheless, the use of CTX was associated with a reduction in the number of episodes of diarrhoea and fewer deaths. Daily CTX use was associated with a 72% decrease in the rate of malaria among study subjects. Parasite levels were lower. Although the death rate among the HIV-infected was 28 times higher than that of uninfected Ugandans, the use of CTX conferred a 46% reduction in death in the former. Improved survival on CTX was significant only for those whose CD4 levels were below 200 cells/µl or who had a WHO stage 3 or 4 entry-level diagnosis. However, in a further letter to *AIDS*[23] the authors note that in a sub-analysis of their patients with CD4 levels in excess of 500 cells/µl, the annual rate of decline of cells was less than that for the period prior to the start of CTX prophylaxis. They argue for considering commencing CTX prophylaxis at levels above 500 cells/µl.

In a related study the prophylactic use of CTX in HIV-positive household members – usually parents – gave some degree of protection to their uninfected children. Mortality was reduced and there were fewer episodes of malaria or diarrhoea in these children.[34] Before and after CTX-resistance patterns of stool pathogens appeared to remain unchanged and the benefit was attributed to the improved survival of the index case (adult) within the family.

The researchers took their work further with an assessment of the potential benefit of ARV therapy and mosquito-repellant impregnated bed nets in subjects already taking prophylactic CTX. Cumulative benefit was demonstrated with both interventions: fewer episodes of malaria. Benefit for other morbidities such as pneumonia, diarrhoea and bacteraemia was not measured.[35] These later sequential studies lacked contemporaneous control groups and were observational in design. The median duration of actual follow-up while on ART and CTX was short, a mere 126 days. These studies took place in a rural setting in Uganda.

Similar results have been achieved in two peri-urban clinics in Uganda: reduced mortality and fewer episodes of malaria.[36] The latter study was non-randomised, used historical controls and took place between August 1999 and March 2002. The primary benefit seems to have been in malaria control, whereas the incidence of diarrhoea with fever, herpes zoster and oral thrush actually increased on CTX. Worryingly, subjects on CTX had a greater decline in their CD4 cell counts while on CTX. Likewise total white cell counts and mean neutrophil counts were significantly reduced during this period. The fall in CD4 cells and blood counts while on CTX is not discussed in detail.



The Ugandan studies support those from the Ivory Coast and indicate that the role of CTX prophylaxis extends beyond just the prevention of PJP in subjects whose CD4 counts are below 200 cells/µl. Much of this benefit reflects improved malarial control. These clinical trials are not all alike: some have been randomised and placebo-controlled while others have been less tightly structured. The context – urban and rural populations, differing target of primary pathogens and differing resistance patterns – has not been identical. But nonetheless the work has reflected the situation on the ground and has been extremely valuable. The preventive value of CTX appears to vary with regard to respiratory and enteric infections. Its role against malaria is very convincing.

ZAMBIA[11]

Researchers based in Lusaka, Zambia, have evaluated CTX prophylaxis in HIV-infected children. Bacterial pathogens in this region are mostly resistant to CTX. The study was double-blind, randomised and placebo-controlled. It started in 2001 but ended prematurely in 2003 when data confirmed benefit to those children on CTX. The median follow-up was 18.9 months. A small but equal number of children (4 - 5%) in both groups were able to afford ARV therapy (ART). Fewer children in the CTX arm died, and there were fewer hospital admissions in this group. Mortality benefit was independent of age or CD4 category. Pneumonia was strongly associated with mortality and was less frequent in the CTX arm. Somewhat surprisingly, *P. jiroveci* was isolated in only 1 child. An earlier autopsy study based in Lusaka revealed a high prevalence of PJP in this community, 27.5% of children dying with lung disease.[37] South African and Malawian researchers have confirmed a high prevalence of PJP in this part of the subcontinent.[24,25,38] *Pneumocystis* infections are notoriously difficult to nail. The possibility remains that some benefit from CTX may have been accounted for by occult *Pneumocystis* infections. Malaria was not a significant pathogen in this group. Survival benefit appears to be related to the reduction in respiratory disease.

Chintu *et al.*[11] recommend that 'all children with clinical features of HIV-infection should receive cotrimoxazole prophylaxis irrespective of age and CD4 count', 'irrespective of levels of background resistance to the drug'. In a region with cost constraints and where only 5% of children are accessing ART it would seem ill advised to contradict this opinion.

An adult CTX prophylaxis study, the LUCOT trial, has been submitted for publication. The subjects are Zambians with newly treated or previously treated pulmonary tuberculosis. Results demonstrate a 45% reduction in mortality in the CTX arm. The findings are discussed in the WHO Guidelines paper.[10] A further Zambian study noted birth outcomes in pregnant women given CTX prophylaxis. Results indicated reduced chorioamnionitis, prematurity, and neonatal mortality in children born to mothers on the CTX arm. The women had CD4 counts below 200 cells/µl.[39]

SOUTH AFRICA[8]

Grimwade *et al.*[8] looked at the effectiveness of CTX on the mortality of adults with TB in the Hlabisa district of rural KwaZulu-Natal. The study utilised previously diagnosed TB patients (1998 - 2000) from the community as historical controls. HIV seroprevalence in the area – via anonymous testing – had increased from 36% (1993) to 78% in 2001/2. Despite counselling, only 5% of the 1 173 subjects recruited for the study from 2001/2 agreed to be tested for HIV status; 80% tested positive. The researchers found a significant reduction in death at 6 months in those given CTX. Despite continuing with the trial, there was no change in mortality after this period. Adherence to daily CTX had in fact dropped to 43% by 6 months. Malaria was infrequently diagnosed and was felt to be an unlikely reason for CTX-related benefit. The authors admit that there were significant differences in 'type of TB' between the historical cohort and the study subjects. In addition no CD4 levels are given, nor was the degree of immunological suppression of the subjects reflected in any other data provided by the authors. Without this, it is difficult to exclude benefit from *Pneumocystis* prevention as a contributing factor.

CURRENT WHO RECOMMENDATIONS AND USE OF CTX IN HIV-INFECTED PERSONS IN RESOURCE-POOR REGIONS[10]

GENERAL REMARKS

Patients with a history of severe reactions to CTX or other sulfonamides and children with glucose-6-phosphate dehydrogenase (G6PD) deficiency ought not to receive CTX prophylaxis. Dapsone 2 mg/kg once daily orally (100 mg daily in adults) is an alternative. Inhaled pentamidine for *P. jiroveci* prophylaxis is expensive and generally unavailable in resource-constrained areas. Neither dapsone nor inhaled pentamidine possess the breadth of antimicrobial efficacy of CTX.

The continued requirement for CTX prophylaxis in patients who are receiving highly active antiretroviral therapy (HAART) is probably limited to those in whom reconstitution of the immune system is adequate or who experience treatment failure and subsequent regression of CD4 levels. In adults on ART, CTX is stopped after a CD4 count above 200 cells/µl has been achieved and maintained for at least 6 months after starting HAART.[40] This may take some time. The Development of Antiretroviral Therapy for Africa (DART) Study examined the CD4 cell response following the start of HAART in Ugandans. Where subjects initiated ART with CD4 levels above 100 but below 200 cells/µl it took a median of 24 weeks to return levels to above 200. If the initial CD4 level was below 50, the median time to achieve a level above 200 was 72 weeks[10] (as quoted, reference not given). Even on HAART, some patients fail to achieve a level above 200 cells/µl, particularly where initial CD4 levels were extremely low; prudence recommends continuing CTX prophylaxis in such patients.[41]

INFANTS AND CHILDREN

In children aged under 1 year, CTX prophylaxis is provided from 4 - 6 weeks of life and throughout this period, irrespective of CD4 percentage or the use of HAART. Opportunistic infections are common and life-threatening at this age. There are no available data on the value of both

HAART and CTX use in children in resource-poor areas. European and USA guidelines discourage the continuous use of both CTX and HAART in children provided immune reconstitution has taken place[9,42,43] (Table I).

TABLE I. WHO RECOMMENDATIONS WITH REGARD TO THE INITIATION OF CTX PROPHYLAXIS IN INFANTS AND CHILDREN[10]

Situation			
HIV-exposed infants and children	Confirmed HIV infection in infants and children		
	< 1 year	1 – 4 years	> 5 years
CTX prophylaxis is universally indicated, starting at 4 - 6 weeks after birth and continuing until cessation of risk of HIV transmission and the exclusion of HIV infection **[A-III]**	CTX prophylaxis is indicated regardless of CD4% or clinical status of child	WHO stages 2, 3 and 4 regardless of CD4% **OR** any WHO stage with a CD4 < 25% **[A-I]**	Follow adult recommendations

Universal option: Prophylaxis for all infants and children born to confirmed or suspected HIV-infected mothers. This strategy may be considered in settings with high prevalence of HIV, high infant mortality due to infectious disease, and limited health infrastructure. **[C-IV]**

Note that the grading of recommendations as indicated in this WHO Table is based upon the following:

Strength of recommendation:

A. Highly recommended. Should be followed.
B. Consider: Applicable in most situations.
C. Optional.

Level of evidence to support the recommendation:

I. At least one randomised controlled trial with clinical endpoints or several relevant high-quality scientific studies.
II. At least one randomised controlled trial with surrogate markers, at least one high-quality study or several adequate studies.
III. Observational cohort data, one or more case-controlled or analytical studies adequately conducted.
IV. Expert opinion based on evaluation of other evidence.

ADOLESCENTS AND ADULTS

Should the initiation of CTX preventive therapy be restricted to patients with CD4 counts below 200 cells/µl or AIDS-defining diagnoses? Clearly the data that emerge from the studies discussed in this paper suggest not. Mortality and morbidity benefit occurs in those with CD4 counts above 200 cells/µl, possibly even above 500, and/or with early WHO stage 2 and 3 disease.[6,12,23] What is the upper level at which further benefit cannot be demonstrated? Does CTX preventive therapy need to be continued despite successful immune reconstitution on HAART?

Most of the African data reflect a rather specific context: poverty, little or no access to HAART, endemic malaria and/or invasive enteric and respiratory infections. Can these results be applied uniformly to the cities and rural districts of southern Africa?

Poverty exists in these cities, as do other determinants of poor health outcomes: informal settlements, overcrowding, contaminated and insecure water supplies, failing health and hygiene structures, uneducated, displaced and disempowered people. HIV/AIDS is defining the context of life lived in modern Africa. In these ways the cities and rural regions of southern Africa are not too different from the social environment described in the above studies on CTX. However, there are differences too. Malaria is less prevalent in the south of the continent than in central and west Africa. Other organisms that may respond to CTX therapy have variable regional expression in Africa or variable resistance patterns to CTX – *S. pneumoniae*, isosporiasis, non-typhoidal salmonellae, toxoplasmosis and possibly even common enteric pathogens such as *E. coli*. The local prevalence of these conditions may influence the regional effectiveness of CTX prophylaxis.[26]

The rollout of ARVs in South Africa, Botswana and Namibia is generally more widespread than in countries to the north and the influence of immune reconstitution with ARV treatment is likely to significantly diminish the need for CTX prophylaxis in patients on HAART (Table II).

TABLE II. WHO RECOMMENDATIONS WITH REGARD TO THE INITIATION OF CTX PROPHYLAXIS IN ADOLESCENTS AND ADULTS IN RESOURCE-POOR REGIONS[10]

Based on WHO clinical staging criteria alone where the CD4 count is not available	Based on WHO clinical staging and CD4 cell count criteria
WHO stage 3 or 4 **[A-I]**	CD4 below 350 cells/µl **[A-III] OR** WHO stage 3 or 4 and any CD4 level **[A-I]**
WHO stage 2 **[A-III]**	

Universal option: Countries may choose to adopt a Universal CTX for all HIV-infected persons irrespective of CD4 or clinical stage. This strategy may be considered in settings with a high prevalence of HIV and limited health infrastructure **[C-III]**

For grading of recommendations see Table I.

These new WHO Guidelines suggest that where CD4 counts are available, CTX should be given to all with a CD4 count below 350 cells/µl, particularly in resource-poor settings where malaria and invasive bacterial infections are common. Similarly it is suggested that all patients with any form of TB should start CTX prophylaxis irrespective of their CD4 cell count. Long-term adherence to CTX is emphasised and may well be difficult to implement widely, particularly where a 'universal CTX-for-all-and-taken-indefinitely" approach is followed. Women who require CTX prophylaxis and who fall pregnant are urged to remain on CTX. The CTX is continued even while breastfeeding.

Discontinuation of CTX is suggested in the context of immune recovery or toxicity. However, in the absence of CD4 count monitoring 'no consensus was reached' regarding stopping CTX therapy. Discontinuation is suggested after a year on CTX provided the patient is on HAART, has had no symptomatic WHO stage 2, 3 or 4 events and has displayed reliable adherence. CTX is to be restarted when the CD4 count again

falls below the starting value and/or when WHO stage 2, 3 or 4 events occur.[10] In an attempt to avoid confusion as to the cause of hepatic and skin toxicities, it is recommended that CTX prophylaxis be started 2 weeks before commencing HAART where the latter is available. Should the patient develop breakthrough invasive infections, antibiotics other than CTX are advised. This would also apply to the active management of malaria, where a patient currently on CTX would not be expected to derive benefit from sulfadoxine-pyramethamine (Fansidar). Alternative antimalarials must be used.

CONCLUDING REMARKS

The current WHO recommendations for the use of CTX in resource-poor regions focuses on communities where invasive infections are frequent and are accompanied by significant morbidity and mortality in the HIV infected. Southern Africa is a kaleidoscope of developing and developed worlds where some, but not all, access ARV medication and clinical support. The fact that an inexpensive antimicrobial can provide survival advantage must be taken seriously and this benefit should be offered to patients whose CD4 count exceeds 200/µl and who are not on ARVs. However, thorough research into the appropriateness of such a course of action will be required – who to give it to, when to stop, and whether benefit is maintained in the context of the antiretroviral rollout in southern Africa. Invasive bacterial disease is sufficiently important in the southern African context to warrant review in relation to CD4 cell count in much the same decisive way the Cote d'Ivoire investigators have done (see Fig. 1). Answers would inform the issues of whether local patients need to be on CTX when this CD4 count is above 200 cells/µl. Would CTX prophylaxis benefit those on ART? This question requires an answer, which will involve clinical research and evidence-based data. At this time the question in relation to southern Africa remains unanswered.

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COMMENTARY ON JUDGE CAMERON'S SPEECH

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In May 2006, Judge Edwin Cameron, probably the most high-profile South African living openly with HIV, delivered a lecture at the University of KwaZulu-Natal in honour of Professor Ronald Louw. Professor Louw, a lecturer in the Faculty of Law at the university, a member of the Treatment Action Campaign and a human rights activist, had died a few weeks earlier of an AIDS-related illness. Despite his access to information about HIV, and to adequate resources to manage his illness, Professor Louw had not tested for HIV, and by the time his HIV status was discovered he was too ill to benefit from treatment.

Judge Cameron, himself a well-known advocate for the human rights of people with HIV, suggests that the time has arrived to re-assess HIV testing procedures, in particular whether the current protocol, which includes access to both pre- and post-test counselling, informed consent and guaranteed confidentiality, is acting as a barrier to the scaling up of HIV testing, and contributing to further self-stigmatisation of people with HIV. While acknowledging the continued prevalence of external stigma, he expresses a profound and moving concern that the safeguards around testing are now reinforcing 'the inner fears and dread – the inner sense of self-contamination – of those who suspect that they may have HIV'. He controversially suggests that the exceptionalisation of HIV, including the strict requirements regarding testing, now constitutes a source of risk and harm to people with HIV.

Judge Cameron advocates routine testing. He suggests that where antiretroviral treatment is available and can be offered to the patient, where the patient is assured that he or she will not be discriminated against if they have HIV and where adequate safeguards exist to ensure confidentiality of the test and its outcome, HIV testing must take place unless the patient expressly refuses the test. He acknowledges that counselling is useful, but that it should only be provided if 'a health care facility is able to offer it without sacrificing the time and energy of its health care personnel'. That time, says Judge Cameron, 'is urgently required for diagnosis and treatment of HIV'.

Judge Cameron's lecture coincides with increasingly loud calls by public health authorities, including the World Health Organization (WHO), for a move away from the traditional voluntary counselling and testing (VCT) model. Options being debated range from routine offers of testing to all patients at all points of contact with the health system, to routine testing where patients must expressly state that they do not wish to be tested, the so-called 'opt-out model'. Some countries, e.g. Botswana, have already introduced a policy of routine testing. Public health officials arguing for this approach reiterate many of the arguments articulated by Judge Cameron and specifically point to the high costs of providing VCT in resource-poor settings. They argue that in high-prevalence countries there is great urgency to scale up HIV testing to facilitate access to antiretroviral treatment.

Human rights activists, however, continue to advocate for VCT, arguing that other models, where consent and counselling are not central to the process of testing, will violate basic human rights norms and expose unprepared and vulnerable individuals to stigma, discrimination and prejudice.[1] An international symposium on HIV testing and human rights in September 2005 concluded that 'Informed consent, counseling before and after a test, and confidentiality of test results are all grounded in human rights norms. Forms of HIV testing that significantly curtail these elements are not acceptable.'

There is currently a lack of empirical data confirming the effectiveness of any of these approaches, and there is clearly a need for research that will develop a detailed understanding of the benefits and disadvantages of different models of testing. Data regarding the experiences of people who are tested, and their responses to the process and the test result, must be gathered and are crucial to building an understanding of what the best model is to encourage testing and knowledge of HIV status. Attention should be paid to the specific needs of vulnerable groups, including women, gay men and sex workers, and their experiences of testing.

In the absence of such research, however, there is little to suggest that VCT does not work, and in my view it has much to recommend it, especially for women. I do not mean to suggest that VCT is not equally important for men, merely that

The Tshwaranang Legal Advocacy Centre to end violence against women is an NGO that aims to make the legal system a vehicle of social change for women by influencing policy and legislation through advocacy, training and education, research and information dissemination.

there is a specific context for women that must be carefully considered when assessing which models of HIV testing will be most effective.

Despite a plethora of laws and policies that provide for equality and non-discrimination, South African society continues to be characterised by high levels of inequality between men and women, and disturbingly high levels of violence against women. This context suggests that programmes intended to facilitate greater access to HIV testing and treatment for women, especially poor women who rely on the public health system, will not be successful unless they take these realities into account. In the context of sexual violence, research internationally and locally has affirmed the importance of access to adequate psycho-social care for survivors of gender-based violence, and activists and service providers continue to emphasise the importance of this access as part of the healing process for women. The lack of resources committed to providing this care has been a source of ongoing advocacy and lobbying. The value of counselling is starkly illustrated by research[2] conducted into adherence to post-exposure prophylaxis (PEP) after sexual assault, in Gauteng hospitals and clinics. This research reveals that PEP services are significantly undermined and weakened if they are not supported by access to counselling and properly integrated into other services for women. The research also shows that women themselves see counselling as necessary and important to their health and well-being.

The provision of counselling should be therefore be seen as an essential part of a package of care for poor women who may suspect that they have HIV. For many women, this fear is exacerbated and reinforced by additional fears of violence, abandonment and loss. Although there is also little empirical research regarding the true extent of HIV-related stigma and discrimination, there is sufficient anecdotal evidence to show that it continues to be a major problem that must be addressed. Pre-test counselling represents one of the very few opportunities for poor women to access any form of psycho-social care where they can discuss their fears and concerns regarding their health status and the consequences of a positive test result for themselves and their families, and where they are able to develop strategies to cope with HIV and its potential impact on their lives. Post-test counselling plays an equally important role – for those women who are negative, it is a chance to receive and discuss information that could save their lives; for those who are not, it is a safe space to begin the process of coming to terms with having a life-threatening illness.

For many poor women, VCT may also have an important symbolic value. Living in deeply sexist societies, for many it is the first opportunity where their rights to autonomy and agency are respected and encouraged.

So, rather than eliminating VCT, it should adequately resourced so that it is more widely accessible and effective – some research has suggested that the quality of counselling is weak. It should also be integrated more holistically into health services so that it can support and strengthen health services generally.

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PERSONAL STORY

LIVING POSITIVELY WITH HIV/AIDS

Geddes M Nala

In 1985 my employer, Scaw Metals, appointed me as a candidate to attend a course as a non-departmental advisor. The course was run by the Department of Health and Population Development at their training centre in West Fort, Pretoria. The objective of the 2-week course was to train both departmental and non-departmental advisors in hygiene, high blood pressure, diabetes, family planning, obesity, STDs, communicable diseases and HIV/AIDS. After completing the course successfully, I would then impart the knowledge to my co-workers.

Together with the nursing sister who was in charge of our medical centre, we gathered as many teaching aids as we could lay our hands on. We borrowed a range of videotapes from Chris Hani Baragwanath Hospital and acquired audio-visual materials, booklets and posters from various health centres. We then played the self-explanatory videotapes on the medical centre TV for employees who had come to see the doctor, while they were waiting. We also conducted health sessions at the company's hostel after work.

Never did it dawn on me that I would be the carrier of the virus one day. Today I am living with HIV. The reason why I disclose my status is that I know what I am talking about. In 1999 I became very sick. I was losing weight drastically and always felt tired. I also had night sweats and was short of breath. I had

become very thin and very dark. I ate very little and preferred fruit when I did eat.

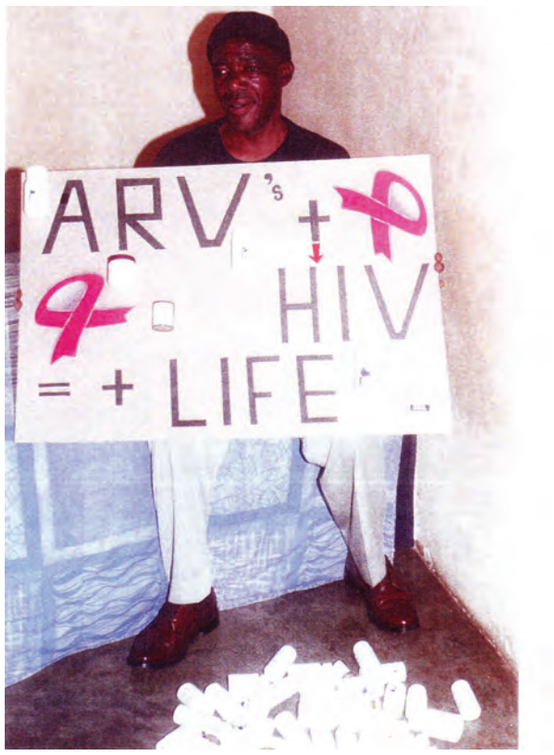
During this time my younger brother phoned to inform me of the death of my elder sister's sister-in-law. The funeral would take place on the Saturday of that same week at the local Methodist Church at about 8 am, and we would leave for the cemetery at 1 pm. I left early on Saturday morning and arrived by 9 am. I did not see any of my family, as the church was jam-packed, and it was only at the cemetery that I saw my younger brother and sister standing side by side. I went to join them, but to my surprise it took them longer than usual to recognise me. Tears began to roll down my younger sister's face.

I was driven home immediately after the funeral. My brother took me to the doctor, who examined me and, through a syringe, took two watery samples from my back (between the shoulderblades) and poured them into two small bottles. He told my brother that he suspected TB and warned him to take me and the samples to hospital no later than the following Monday. He then gave me treatment to help me through the weekend.

On Monday morning at the hospital, X-rays and further tests were conducted. I did indeed have TB. I was hospitalised, and further tests revealed that I was HIV positive; I only knew this through a counsellor before I was finally discharged. I want to give credit to this gentle lady and thank her, for after putting me at ease, she said, 'To be HIV positive is NOT A DEATH SENTENCE. You must read a lot about issues relating to HIV/AIDS. This will help you to cope with the situation, and if you find other problems, remind the virus - THIS IS MY BODY THAT YOU ARE LIVING IN. I WILL KICK YOU OUT IF YOU MISBEHAVE.' It really did the trick, and I believe contributed towards my acceptance of my situation. She was a true professional.

After this intensive and sincere counselling, she gave me a letter referring me to the clinic. I decided to take the letter to the company's medical centre for convenience. The doctor then referred me to another health centre, where further X-rays and other tests were done, before I was finally put on treatment. I was told that this treatment would last for 9 months.

I returned to work exactly 4 months later. The doctor recommended that I be put on a much lighter job. I then helped in the HR department with some filing and other personnel duties. After a few months I found a permanent position as a clerk in the Design and Development Department. Although I completed my TB treatment. I continued to fall ill from time to time. It would be pneumonia one day and influenza the next. I was in and out of hospital most of the time. My time-keeping also deteriorated. I could not sleep well because of night sweats and coughs. I would doze off at dawn and wake up late. I decided to disclose my status to my colleagues and boss. This required a lot of courage, but I had to do it. It would in turn relieve me of the stress of having to account for poor time-keeping and performance.



Word went around that the company would be rolling out ARVs in the near future. The doctor had informed me about it and had promised to put me on the ART programme once it was implemented. But when the clinic sister gave me the consent form to read and sign, I had chickened out and declined the treatment. I was not going to be a 'guinea pig'. I would not be the first one to experiment with a drug that had become so notorious for its toxic and other side-effects.

In 2003 I had to change my mind. In July I became so sick that everyone had written me off. I could not walk as much as 3 metres. I had lost a lot of weight. I was a skeleton and very, very dark. One would not even take a second look at me. I was finished … The doctor informed me that I had pneumonia and referred me to hospital. There I was wheel-chaired to the consulting rooms and once examined, I was admitted immediately.

I was taken to Ward 2. There was something interesting about this ward. It looked like a club-house. All of the patients there looked exactly like me. They were very thin, very dark and every one was on a drip. Eventually when I sat on my bed I thought. 'Well this is a club all right, I just wonder which position I am going to fit into'. So much was happening in this ward: patients using food trolleys to carry them to the toilet, patients refusing to eat because of sores in their mouths, patients refusing to take a bath because of being powerless. Saddest was the mortality rate in the ward.

I do get along with my ex-wife, although we are divorced. I had phoned to inform her and my son that I was in hospital. She in turn passed on the message to my mom. She visited me often thereafter, bringing me food and prayers. She was also there when the rest of my family visited as well. I was having a good time. My niece had brought me food and fruit. As usual

I was my jovial self and everyone was laughing. Then it was my sister's turn. She said, 'Geddes, my brother, you must get me correctly. I do not say that it will be like that, but there have been problems before. We are still struggling to sort out problems regarding my sister-in-law who recently passed away as we did not ask for her financial details while she was alive. Please understand we would not want to repeat the same mistake. Now, in case you die, where would you like to be buried? We would also appreciate it if you could provide us with your banking details and company benefits.'

Although it was not surprising, I did not expect it so soon. After taking a deep breath to settle down, I obliged and gave her the information and referred her to a friend and colleague for other benefits such as the NUMSA membership. Before they left, we said a prayer after which I accompanied them to their car and said goodbye. I returned to the ward and threw myself on my bed and my sister's words came back to me loud and clear, 'YOU ARE ABOUT TO DIE!' I jumped up and said aloud (to the surprise of other patients and nurses), 'NOT I, NOT NOW!'

On Friday in the second week of August I was discharged from hospital. I went straight to our medical centre and asked the sister to give me the consent form, and signed it. I did not have to waste time and read it now. I had nothing to lose. I had tasted death, so why not ARVs this time? Blood samples were taken and sent to the laboratory for analysis. After my final examination at the hospital, I was put on the ART programme on 28 August 2003. I have been on Combivir and efavirenz treatment ever since.

Before I took the treatment, my CD4 count was below 50 and my weight was below 40 kg. I was dead, dead 'finish and klaar'. Today my CD4 count is well over 250 and my weight ranges between 73 and 76 kg. I am healthy and strong. It is interesting to note that before I took the treatment I was treated for high blood pressure, but for unknown reasons since I started taking ARVs my BP is normal and I have been taken off its treatment.

What has actually prompted me to come out and talk is that I know what I am talking about. I felt guilty about remaining silent while other people were suffering and even dying from a situation that I had miraculously survived. I believed that it would haunt me until the last day of my life if I did not talk. That is why I appeal frankly and sincerely to all of you to go for VCT. Let our motto be 'TAKE ACTION NOW, KNOW YOUR STATUS'.

The most dangerous thing about HIV/AIDS is the stigma. People refuse to go for testing for the following reasons:

- Stigmatisation
- They are to afraid to know that they are HIV positive
- They do not believe that there is such a thing as HIV/AIDS
- They believe that HIV/AIDS is taboo
- Culture and religion
- Many years ago HIV-positive people were isolated and even killed.

There is nothing wrong with HIV/AIDS. A speaker once said, 'There are over 127 "viruses" like TB etc. and HIV is one of them.' People prefer to admit that they suffer from TB or pneumonia rather than accept that they are HIV positive. Is it because the first two are curable, or is it because celebrities like or former state President Nelson Mandela and Bishop Desmond Tutu have publicly admitted to have been treated for TB, and it's not bad to suffer from what great men have once suffered from?

As Madiba himself once said, 'AIDS is no longer is a DISEASE but a HUMAN RIGHT.' We must put all the resources that we have together and intensify our fight against HIV/AIDS, just like we did in our Struggle against Apartheid. We must unite in the war against this pandemic in this country. We bury people who die from AIDS-related ailments daily. This is far above the statistics we receive through the media regarding the Middle East. What makes our battle even more complex is that it is abstract in nature.

Let us all go for VCT. This process is not time-consuming. Before testing you are put at ease through counselling, and after the test you are once more comforted. Your test results are strictly confidential. Your employer cannot force you to go for a test, and at the same time cannot victimise you for your status. If you test positive, do accept it, and leave with a positive attitude to your status. As one doctor said to his patient after testing positive, 'Two situations occur when you test HIV positive. The first one is that you *deny* and die long before you are buried. The second one is you *accept* and takr it as a wake-up call.'

It is therefore very important for us to encourage people to go for testing and know their status. We should convince them that being HIV positive is not a 'DEATH SENTENCE'. For those who test negative, we must encourage them to remain so by maintaining good lifestyles and practising protected sex.

In conclusion, I would like to thank my company for its compassion towards its employees. I would also appeal to other companies and public sectors to join in this campaign for the betterment of our country and all who live in it.

CARING FOR HOME-BASED CARE WORKERS

Understanding the needs, fears and motivations of front-line care workers in South Africa

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Home-based care has emerged as a service delivery model to cope with the devastation caused by the HIV/AIDS epidemic in sub-Saharan Africa, where medical and traditional care infrastructures have been overwhelmed. In these communities home-based care workers provide critical services, which include physical, psychosocial, and palliative care activities.[1] A quantitative and qualitative study of home-based care workers in South Africa was conducted in 2005 to better understand the needs, fears and motivations of front-line care workers at Thembalethu Home Based Care (THBC), located within the Nkomazi region of South Africa's Mpumalanga province. The objectives of this study were to:

- Describe the socio-demographic background of home-based care workers to better understand worker demographics, workers' finances and job characteristics
- Assess THBC care workers' willingness to undergo voluntary counselling and testing (VCT) to determine their HIV status
- Explore the emotional impacts of care work for THBC frontline care workers to determine what mechanisms could be put in place in order to support and expand the current care work infrastructure.

Findings suggest that THBC care workers value the emotional support from weekly group meetings and use this time to process the emotional impacts of their care work. Although rates of testing are low, 83% of participants would consider undergoing VCT to learn their HIV status. Specific strategies to ensure that care workers receive appropriate medical care and supportive services are discussed.

Sub-Saharan Africa has 25 million, or 60%, of the world's HIV-infected population. Many communities within this region are facing two fundamental obstacles making them especially vulnerable to the effects of HIV and AIDS: HIV infection rates as high as 39%[2] and extreme levels of poverty.[3] The challenges created by these two coinciding factors include caring for large numbers of sick and dying adults and children, orphans, psychological distress associated with the stigma around HIV/AIDS, and managing the symptoms of opportunistic infections such as tuberculosis. Poverty, unemployment, underdeveloped utilities and lack of infrastructure exacerbate the care responses of many resource-poor communities. The deleterious impact of HIV/AIDS has overwhelmed traditional familial and communal care-providing structures, making home-based care (HBC) the emerging service delivery model to cope with the physical, psychological and social devastation of the AIDS epidemic. Particularly in non-urban communities, the traditional and limited medical care infrastructures have been inundated resulting in a severe lack of basic medical services, including access to antiretroviral therapy (ART).[2]

A THBC worker in her garden. Seeds are provided by THBC and are given to patients, orphans and care workers to provide sustainable agriculture within the communities THBC serves.

Home-based care is defined as any form of care given to ill people in their homes in order to 'promote, restore and maintain a person's maximum level of comfort, function, and

A team of THBC care workers meet in THBC's outdoor auditorium area to discuss a question together. Separate groups of care workers were set up throughout the site to facilitate private group discussion.

health; including the right to a dignified death'.[1,4] The goal of HBC is to provide hope through high-quality and appropriate care that helps ill people and families to maintain their independence and achieve the best possible quality of life through physical, psychosocial, spiritual and palliative care activities.[4] Staffed by care workers who give their time, services and often personal resources to improve the lives of those infected and affected within their communities, care workers offer a vital resource within the communities they serve. While there has been literature citing the programmatic difficulties HBC agencies face,[5] additional research on the emotional impacts of front-line caregiving is still needed.

Throughout southern Africa, HIV/AIDS continues to impede the already struggling health care sector. Absenteeism caused by sickness and death results in inefficiency resulting in less care for community members and lost time recruiting additional personnel.[6] Simultaneously, burnout and emotional exhaustion threaten the existing structure. One strategy to buttress the current situation includes offering and encouraging VCT services for HBC workers and access to ARVs as roll-out programmes are implemented throughout the region. According to UNAIDS/WHO, HIV status provided through VCT remains critical to the effectiveness of HIV prevention.[7] Care workers aware of their HIV status can help reduce transmission of HIV/AIDS among their own families and clients by serving as change agents within their communities to promote the importance of VCT and the benefits of ARV adherence.

THE STUDY

The purpose of this paper is to illustrate the needs, fears and motivations of front-line care workers from THBC, a community-based organisation that serves terminally ill patients and orphans within 16 villages in the Mpumalanga province of South Africa and neighbouring areas of Swaziland and Mozambique. Mpumalanga, one of South Africa's nine provinces, is situated in the north-east of the country. It was formerly part of the Transvaal province and borders both Swaziland and Mozambique. Mpumalanga, South Africa's seventh most populous province, occupies 6.5% of the land surface area of the country and is inhabited by approximately 7% (or 2.8 million) of the country's population.[8] Census data indicate that in 1999, 30% of the population was infected with HIV.[9]

The objectives of this study were to:

- Describe the socio-demographic background of HBC workers in order better to understand worker demographics, finances and job characteristics
- Assess THBC workers' willingness to undergo voluntary counselling and testing (VCT) to determine their HIV status
- Explore the emotional impacts of care work for THBC front-line care workers to determine what mechanisms could be established in order to further support and expand the current care work infrastructure.

METHODS

A mixed research methodology was used to capture both quantitative and qualitative components of care workers' demographics, attitudes regarding VCT and HIV testing and emotional impacts of care work during June - August 2005. Approval of the project was provided by the THBC Management Team in accordance with Harvard Medical School's Office of Research Subject Protection. All participants provided consent before participating in the survey and were compensated for their participation with lunch and a pen.

QUANTITATIVE COMPONENT

A survey was administered to two-thirds of THBC's South African care worker population (N = 138). All care workers from Swaziland and Mozambique were excluded from participation owing to the researchers' inability to travel to sites in other countries. The survey instrument was piloted beforehand with seven care co-ordinators who oversee the home-based care programme at THBC on a daily basis. Participation was based on care worker attendance at regularly scheduled care workers training sessions at one of three THBC sites.

The piloting of the survey with THBC's director and founder Sally McKibbin and care co-ordinators. Each care co-ordinator oversees an aspect of the THBC's functioning: HBC team, child and orphan care, administrative responsibilities, and gardening projects.

Items on the survey included demographic information including number of children and orphans in their care, caseload and work-related questions, views on VCT, disclosing HIV status, burnout and motivation for care work, and financial security including type of dwelling and access to electricity and running water. Each participant was randomly assigned a participant ID number. All data were inputted into SPSS statistical software which was used to store and analyse quantitative data.

QUALITATIVE COMPONENT

Qualitative methods included focus group responses, site visits with HBC workers and field observation. Focus group interviews explored, in greater depth, home-based care workers' attitudes to VCT and the emotional impacts of their work (*N* = 37). Participating care workers were divided into small groups and asked four questions relating to VCT and their fears around HIV testing. Each group recorded and presented their responses to the other groups, which facilitated an open yet guided discussion.

RESULTS AND DISCUSSION

SOCIO-DEMOGRAPHIC BACKGROUND

All surveyed care workers were women and natives of South Africa. The mean age was 39 years. Nearly half (46%) had up to a standard 6 (grade 8) education level, similar to provincial census figures (Table I). Almost three-quarters of respondents (72%) were either married or partnered and had a mean number of 5.4 biological children. Additionally, 38% of surveyed care workers had taken in an orphan (related or non-related) into their homes. The investigators noticed a discrepancy between total numbers of orphans when care workers were asked to specify how many of these children were related or not related to the care worker. One explanation for this discrepancy is that respondents do not consider family members as 'orphans' (Table I).

On average there were 2.7 adults in the surveyed care workers' households, of whom 55% were not employed. Although some of these adults may be absorbing some of the household responsibilities, caregiving and/or financial, it is evident that many care workers have significant responsibilities in their homes, with dependent children and orphans in addition to their caseloads within the organisation. Financially, over half (52%) of respondents received a Child Grant from the South African government, yet 23% reported not receiving any additional funds from any kind of government grant or pension and reported lacking financial support if a family member was to die and funeral assistance was needed. These figures suggest high levels of financial insecurity and reflect the general poverty levels in the region. The majority of the sampled care workers (66%) would be dependent on THBC or some other form of charity if a death occurred in their family. Owing to a lack of other resources, it is necessary for HBC organisations to recognise that the expense of funerals will become an increasing responsibility of the organisation, especially when considering the rate of family deaths reported by care workers. Nearly 60% of care workers had experienced the death of at least one immediate family member within the past 6 months alone.

The care workers had a median length of service with the agency of 4 years, responses ranging from 6 months to 6 years. Collectively the sample provided services to 1 038 patients, of whom 507 were in critical condition, and 1 436

TABLE I. SOCIO-DEMOGRAPHIC CHARACTERISTICS OF THE THBC CARE WORKERS

Variable	%	Mean	Median	Provincial %[10]	National %[10]
Age (range 21 - 65 years)		38	39		24.86*
Highest level of education completed (*N* = 138)				33.1	17.9
No schooling (n = 16)	11.6			33.1	17.9
Some primary school/ elementary (n = 12)	8.7			16.5	16.1
Completed primary/elementary (n = 23)	16.7			6.1	6.4
Some secondary schooling (n = 37)	26.8			25.1	30.2
Standard 10/Grade 12 (n = 46)	33.3			15.1	20.4
Higher (n =4)	2.9			4.2	9.0
Marital status (*N* = 137)					
Single or never married (n = 30)	21.9			50.8	
Married: civil/religious or traditional (n = 90)	65.7			28.5	
Partnered or living together (n = 8)	5.8			10.3	
Divorced or widowed (n = 9)	6.6			2.3	
Other (n = 0)				8.1	
Number of biological children (*N* = 138) (range 1 - 9 children)		5.4	3.0	–	2.8 children
Care workers who care for non-biological children/orphans in their home (*N* = 52)	37.6	1.5	0		1.7 children†[10]

*This figure reflects the national median age of South African females since all THBC care workers are female.
†National figure represents general population caring for orphans.

orphans. On average, each care worker had 8.2 patients under their care, 3.7 of them in critical condition, and cared for 10.5 orphans.

EMOTIONAL IMPACTS OF CARE WORK

When asked how often care workers find themselves upset or sad about patient-related issues when they come home from work, 69% of respondents reported feeling sad or upset either 'every day' or 'a few times each week'. Two illustrative responses from the focus groups include:

'I find myself sad when I come home from work because sometimes I find my patients very critical [critically ill] and there's no way to help them. Sometimes I go to visit them and there's a need to go to the clinic or hospital but they don't have the money to go and I don't have it. So all these things are very serious problems.'

'It is too sad. I am sad. Sad about orphans ... Orphans that are orphan-headed households are living a bad life because there's no one to teach or counsel them about their ways. And this course leads to dropout in school at an early age and unwanted pregnancy.'

Despite these emotional challenges, 51% of respondents reported that they 'never' consider stopping their care work and remain motivated because of satisfaction from helping others, training and skill building and religious beliefs (Fig. 1).

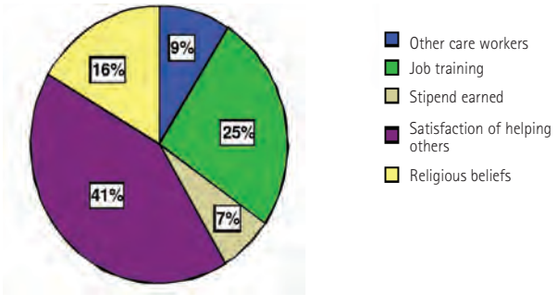

Fig. 1. What motivates care workers?

Generally care workers felt adequately trained by THBC, but 28% requested more training and specified the following:

- Counselling on disclosure and HIV counselling in general
- Basic first aid and medical training
- Information on ARVs (how they work within the body, and where to get ARV medication)
- Palliative care.

Nearly all (91%) of care workers surveyed found the weekly care worker meetings helpful to their problems and concerns, especially in terms of processing their experiences with others who can relate to the work they do. One care worker stated:

'Sometimes we feel like crying because there is nothing that care workers can help our patients with. We need to talk with others, like other care workers, in order to reduce our stress. They understand what my family do[es] not.'

VCT AND HIV TESTING

Despite the increasing prevalence of HIV in the Mpumalanga region, only 16% of the care workers had undergone VCT within the last year. However, a key finding from the survey was that 83% of respondents would consider being tested for HIV if THBC could ensure confidentiality. Forty-six per cent of surveyed care workers cited 'scared to know results' as the number one reason preventing community members from getting tested for HIV. However, the group interviews highlight how stigma associated with HIV-positive status is a main reason preventing community members from learning their HIV status (Table II).

TABLE II. WHY DO PEOPLE IN THE COMMUNITY NOT GET TESTED?

- 'They are afraid of being rejected by their families'
- 'Women are fearful of their husbands' reaction if they are HIV positive'
- 'The community might ignore them'*
- 'The community might stigmatise'
- 'They would feel ashamed if they were HIV positive'*

* Indicates that a quote was repeated during group interviews.

About a quarter (26.8 %) of surveyed care workers reported that someone in their household had gone for an HIV test, while 72% did not know of anyone from their household who had gone for a test. This suggests that HIV testing is not being spoken about openly among family members, despite their connection to a community-based organisation with available educational resources. During the group interviews care workers elaborated on the reasons why they do not undergo VCT. Fear was a salient factor and can be categorised into fear of family and fear of illness (Table III).

TABLE III. REASONS CARE WORKERS HAVE NOT PERSONALLY UNDERGONE VCT

Fear of family disruption:

- 'My husband will reject me or not support me'
- 'How would I tell my husband I am HIV positive?'
- 'I am afraid of divorce'*
- 'My family will not accept me'

Fear of illness:

- 'I will die soon if I am HIV positive'
- 'I am scared of taking pills for my whole life'
- 'Lack of knowledge/information on HIV'
- 'I don't know enough about antiretroviral therapy'

* Indicates that a quote was repeated during group interviews.

IMPLICATIONS

Local-level strategies that HBC organisations can implement in order to address the needs revealed from survey and group interview results are outlined below. Although the information from the survey and group interviews is specific to THBC, the strategies have been written to be applicable to similar organisations offering comparable HBC services in regions with a high HIV/AIDS prevalence.

In spite of the financial insecurity described above and the large families that care workers are already responsible for, 68% of care workers reported that if given more space, they would be willing to take additional orphans into their homes.

To help demystify the testing process, THBC care workers observed how a fingerprick HIV test is administered and how the results are interpreted. It was the first time many of the HBC workers had seen what an HIV test entails.

This is a significant finding for THBC, since more than two-thirds of care workers would be willing to care for orphaned children in the surrounding area. As the HIV epidemic continues to result in increasing mortality, especially among parents, more children will be orphaned in the region.[9] It is critical to identify caregivers willing to absorb some of the orphan burden from these HIV/AIDS-related deaths in Mpumalanga province and other regions facing similar circumstances.

The hardships care workers are experiencing in their homes, both from their familial caregiving burden and from grief normally associated with death in the family, are important findings. Recommendations such as those suggested below need to be implemented to ensure that care workers feel supported and remain nurtured as much as possible by THBC. As a community-based organisation, it is essential for THBC to continue to sustain their care worker population by understanding the typical household composition, financial security and family structure that comprise their home environments.

The findings of this study have important implications for the care workers at THBC and similar HBC organisations. The following recommendations, which aim to improve the care worker programmes in southern Africa, will ultimately result in improvements for the patients, orphans and communities being served.

- HBC organisations should seize upon care workers' willingness to raise orphans as a viable placement option for children who would otherwise live in orphan-headed households or group-home settings. It is imperative that building funds are specifically procured for the purpose of building additional rooms in the homes of care workers who are willing to take orphaned children into their homes.
- It is critical for HBC organisations to explore additional funding streams that specifically target the transportation of patients in a critical condition. This tangible strategy will address a primary source of frustration and disempowerment that many of the care workers expressed during the group interview.
- Based on the responses of questions regarding government grants, it is likely that many of the surveyed care workers are eligible for welfare grants that could ease their personal financial burden. The number of eligible care workers may increase, particularly if care workers continue to take orphans into their homes. HBC organisations should consider extending their administrative infrastructure to assist care workers in accessing government services. An alternative strategy would be to create a training module to assist care workers with the logistical information about government grants, including eligibility requirements and application procedures, to ensure a minimal financial safety net.
- Since care workers have expressed desire for training in all aspects of HBC, THBC and other HBC organisations should have a rotating schedule so that each care worker completes training in all areas related to their work.
- Care workers expressed a consistent appreciation for the value of weekly care worker meetings. Opportunities for expanding additional care worker support groups, especially after patient deaths, should be explored further.

CONCLUSION

As the AIDS epidemic continues to ravage the populations of sub-Saharan Africa, the number of sick individuals and orphaned children will continue to increase. Those infected and affected by HIV/AIDS will continue to rely on HBC workers, further stressing an already overburdened care network in resource-limited settings. Understanding the needs, fears and motivations of front-line care workers is necessary to inform public policy and care-providing programmes at the local level throughout many regions in southern Africa. Assessing care workers' willingness to undergo VCT to determine their HIV status and exploring the emotional impacts of care work in the front line allow HBC community organisations and non-governmental organisations to determine the mechanisms needed to support and expand the current care work infrastructure. Care workers are simply too valuable to the community to be lost to premature death from a manageable HIV infection.

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CASE STUDY

VIROLOGICAL RESPONSE WITHOUT CD4 RECOVERY

A case of disappearing soldiers – can basic science help?

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The objective of antiretroviral therapy (ART) is to suppress viral replication so that immune restoration can occur. Failure of immune restoration is usually associated with poor virological suppression. In children a good immunological and clinical response to ART is often achieved despite incomplete viral suppression. However, we have recently managed a number of children in whom immune restoration did not occur despite excellent virological suppression. We present a case, discuss possible causes and speculate on the appropriate course of action.

CASE DISCUSSION

A 5-year-old boy with WHO stage 3 HIV disease attends the Community Health Centre in Grabouw, approximately 100 km from Tygerberg Academic Hospital. He has been on appropriate doses for body weight of stavudine, lamivudine and efavirenz for the past 14 months. At baseline his plasma HIV RNA was 87 000 copies per ml (log 4.94) and the CD4 count was 263/µl (6.6%). He weighed 16 kg and his weight-for-age Z-score (WAZ) was –0.69. He had just completed his second month of antituberculosis (TB) therapy. TB was suspected because his mother had TB and he had a persistent cough.

Six months after starting HAART and 2 months after completing anti-TB therapy:

- The patient's weight remained 16 kg.
- Notably, he had features of chronic lung pathology and a chest radiograph showed generalised bronchiectasis.
- He had no intercurrent illnesses.
- He had attended the clinic for follow-up regularly, and although there was no objective means of measuring this, his compliance with medication (ART) seemed good and his mother (a seasonal farm worker) confirmed this. His TB treatment card showed good compliance with TB treatment.
- His viral load was undetectable.
- His CD4 count was now 258/µl (0.36%).
- A full blood count (FBC) and biochemistry (transaminases) were normal.

Two months later, **8 months** into highly active antiretroviral therapy (HAART), the tests were repeated:

- The patient had now lost a kilogram in body weight.
- His mother reported that he had been admitted to the regional hospital for 5 days for a 'chest infection'. He had received intravenous antibiotics but did not require supplemental oxygen. There was no letter documenting clinical findings, investigations or management during that episode.
- He had no constitutional or pulmonary symptoms, and had no excessive losses (e.g. diarrhoea). His appetite remained good and his nutritional intake at home had not changed in any form (he was also receiving nutritional supplements from the clinic).
- The only new finding was a crop of molluscum contagiosum on his left lower eyelid.
- On history, there were no known TB contacts in his immediate environment.
- The CD4 count was 181/µl (6.1%), and the total lymphocyte count (TLC) 4 700 $\times$ 10^6 cells/l.
- The viral load remained undetectable.
- The rest of the FBC was normal.

At this time the patient was **re-investigated for TB:**

- The tuberculin skin test was non-reactive
- A sputum smear for acid-fast bacilli was negative and TB cultures were negative after 42 days.
- A chest radiograph showed no new changes.

Over the following few months his weight increased to 17 kg. Treatment was adjusted to stavudine 20 mg capsules, lamivudine 75 mg (half a tablet) twice daily and efavirenz 250 mg capsule at night (reduced as he was no longer receiving rifampicin). His mother was shown how to use a pillbox in an

effort to assist with adherence to ART. Nutritional supplements were provided in an effort to improve his nutritional status.

Four months after the last set of tests and 12 months into HAART:

- There are no new clinical symptoms or signs, and the patient has had no serious illnesses during that period.
- Compliance with clinic visits and medication (as well as could be ascertained by means of pill counts and recall) remained good, and his mother is concerned and reasonably informed about his well-being and his CD4 count!
- His weight is 17 kg (WAZ –1.07) and height 104 cm (height-for-age Z-score –1.72, weight-for-height Z-score 0.09).
- The CD4 count is 164/µl (5.02%) and the TLC 5 900 × 10^6 cells/l.
- The viral load is undetectable.

Table I shows these results in chronological order.

TABLE I. LABORATORY AND ANTHROPOMETRIC RESULTS

Date	Viral load (copies per ml)	CD4 (cells/µl)	TLC (× 10^6) cells/l	Weight (kg)	WAZ
Baseline	87 000 (log 4.94)	263 (6.6%)	– –	16 kg	–0.69
6/12	Undetectable	258 (6.4%)	–	16 kg	–1.13
8/12	Undetectable	181 (6.1%)	4 700	15 kg	–1.29
12/12	Undetectable	164 (5.0%)	5 900	17 kg	–1.07

All the specimens were processed in the same laboratory, and with the exception of baseline samples were all taken by the same person.

Why is there no immunological recovery and worsening immunosuppression after one year of ART, although there is full viral suppression?

Why has the patient shown no improvement in growth at all?

POSSIBILITIES

- We did not suspect **hyperlactataemia/lactic acidosis**, so did not test for it. Also, the patient would need to travel about 60 km to the centre where this can be done.
- Does he have **incompletely treated TB** or resistant TB, which is contributing to his state of persistent immunosuppression? There is no evidence of radiological deterioration and he remains asymptomatic
- Does he have **an occult opportunistic infection or malignancy** that is contributing to his immunosuppression? Which one? Where? Nothing is clinically obvious. No palatal Kaposi's sarcoma lesions were seen. *Mycobacterium avium-intracellulare* infection is possible, yet there is no focus of infection. He has remained on co-trimoxazole throughout.
- His total lymphocyte count has remained normal. What's going on?

Where, oh where, have his soldiers gone?

DISCUSSION

This case illustrates the problem of **discordant immunological and virological response** to ART in a child. After 12 months he has shown a good virological response. Clinical response has been moderate. He has had no significant weight gain, but there have been no significant intercurrent illnesses. His CD4 count has declined persistently and significantly.

The usual response to HAART is viral suppression and immune reconstitution. Some patients, however, show discordance between virological and immunological responses. In children, a rise in the CD4 count despite detectable plasma HIV RNA occurs fairly commonly. The converse, virological response and the absence of immunological response, as in our patient, has been described in adults. Poor CD4 responses can occur with previous therapeutic failure, low baseline CD4+ T cells, advanced disease, poor adherence to HAART, long duration of therapy, and previous treatment interruption. So far there is no evidence that patient age or viral or genetic factors are implicated.[1]

Jevtovic and colleagues[2] in Serbia recently conducted a retrospective survey of discrepant values in a cohort of 446 adult patients. Almost half showed dissociation, with 39% not reaching a CD4 count of 400 cells/µl and 11% not reaching a count of 200 despite adequate viral suppression. The most important risk factor was a baseline CD4 count below 100/µl. They did not associate discordant results with adverse outcome. Protease inhibitors appeared to be protective, as they prevent CD4 loss through inhibition of apoptosis of CD4 cells.[3]

The situation in Serbia is analogous to that in South Africa where until recently lack of access to health care has resulted in initiating ART in patients with advanced disease, as described in the above case report.

As a means of evaluation, we ask and attempt to answer a series of questions about this case.

WHAT COULD ACCOUNT FOR SUCH A RESPONSE?

1. Poor adherence to HAART seems an unlikely cause. We think that the patient would not have achieved viral suppression if he had not been receiving his therapy.
2. Is his immunological response to HAART perhaps simply slow or delayed? This is uncommon in children, who in contrast to adults usually have good CD4 recovery in the face of incomplete viral suppression, with their thymic response and naïve T-cell recovery rate being 10 - 40 times

faster than that of adults in the second phase of immune restoration.[4] However, responses to ART show individual variation. In older children and those with baseline CD4% significantly below 10%, immunological recovery on HAART can be slow. Individuals who do not experience significant increases in CD4 cell levels may have initiated therapy after significant destruction to the thymus had already occurred.

3. Is the patient harbouring an occult opportunistic infection, leading to ongoing immune activation and thus poor clinical and immunological response? He was re-investigated for TB to exclude the possibility of incompletely treated or resistant TB. Another consideration was atypical mycobacterial infection, particularly *M. avium* complex (MAC). So far three sputa remain negative by smear and culture. There is no apparent clinical evidence of opportunistic malignancies such as Kaposi's sarcoma or lymphoma. Could bronchiectasis be playing a role? Recruitment of activated CD4 cells in bronchoalveolar lavage fluid has been observed in patients with pulmonary disease.[5]

4. Could immunosuppressive or myelosuppressive drugs have caused disturbance of bone marrow T-cell progenitor production? If so, why would it be a selective lymphocyte problem? There seems to be no evidence of myelosuppression; all the patient's blood cell indices, including his total lymphocyte count, were in the normal range. We did not ascertain whether the lymphocytes were T or B cells. If they are primarily B cells, it could mean that the thymus is severely impaired by HIV. The combination of tenofovir and didanosine has been associated with poor CD4 response but resolves with dose reduction of TFV. We are unaware of this type of response to other antiretrovirals.[6]

With no clear answers for the cause of this discordant response, we speculate on management options.

COULD THERE BE AN IMMUNOLOGICAL REASON?

It would seem that the patient has good HIV-specific immune responses, in that he has managed to suppress HIV replication to undetectable levels. He would probably then be a candidate for agents that enhance general immune activity, particularly those that induce T-lymphocyte differentiation and stimulate function, for example recombinant cytokines: interferon alpha (IFN), particularly pegylated IFN alpha-2, tumour necrosis factor (TNF) and interleukin-2 (IL-2). Cytokine dysregulation has been described in HIV-infected patients. Diminished IL-2 receptors on CD4 cells were described in 1991.[7] IL-2, a cytokine that stimulates the production of CD4 cells, has been proposed for patients who are unable to replenish CD4 cells, despite adequate viral suppression on HAART.[8] A number of trials have shown improvement in CD4 responses in adults with mild immunosuppression.[9] A possible mechanism for this response could be a diminished loss of CD4 cells through apoptosis.[10]

In anticipation of specific therapy, we continue to monitor the patient and seek to optimise his care.

WHAT CAN WE DO?

Immediate strategies that could help are to improve pulmonary care through physiotherapy, suppressive antibiotics, and excluding gastro-oesophageal reflux. This will reduce pulmonary inflammation and potential loss of activated CD4 cells in the lung. We will re-evaluate for reactive airways disease, where inhaled steroids may be very helpful. We will also consider switching from efavirenz to a protease inhibitor in the hope of diminishing CD4 apoptosis. A single drug switch is appropriate in a patient with undetectable plasma HIV RNA.

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SAHCS HYPERLACTATAEMIA MANAGEMENT GUIDELINES

To the Editor: The guidelines for the prevention, diagnosis and management of nucleoside reverse transcriptase inhibitor (NRTI)-associated symptomatic hyperlactataemia and lactic acidosis are most welcome, and as pointed out may change as better evidence may become available.

I would like to share the experience of the ACHIVA (Augmented Community HIV Action) Project, a partnership between Bristol-Myers Squibb – Secure the Future, the KwaZulu-Natal Department of Health, Ladysmith Provincial Hospital, and Mpilonhle, an NGO. This project commenced in April 2004 at Ladysmith Provincial Hospital in collaboration with Mpilonhle, in the Uthukela district in north-western KwaZulu-Natal.

At Ladysmith Provincial Hospital a tragic situation opened our eyes to the importance of timeous diagnosis of lactic acidosis in patients receiving antiretrovirals and prompted a thorough review of how we identify and manage such patients.

A 36-year-old female volunteer at our chronic disease clinic clinic, weight 130 kg, height 167 cm and body mass index (BMI) of 46, was commenced on the highly active antiretroviral therapy (HAART) regimen of stavudine (d4T) 40 mg bd, lamivudine (3TC) 150 mg bd and efavirenz (EFV) 600 mg daily. Her concomitant medications were co-trimoxazole bd and vitamins.

Findings on clinical examination were normal and baseline investigations 1 week after the start of treatment showed a haemoglobin value of 10.8 g/dl, a gamma-glutamyl transpeptidase (GGT) level of 52 IU/l (normal 37 IU/l), a CD4 count of 149/µl and a viral load of 4 700 copies/ml. The results of the rest of the investigations were normal.

The patient presented 6 months after the start of treatment with abdominal pain, nausea and tiredness. She was asked to stop taking the co-trimoxazole. Why? However, a vigilant nurse requested a full blood count, measurement of urea and electrolytes and liver function tests. The results showed a low bicarbonate level of 14.6 mEq/l (normal 19 - 27 mEq/l), a GGT level of 113 IU/l and a lactate dehydrogenase level of 831 IU/l (normal 220 - 500 IU/l); the transaminases were mildly raised. These features raised a suspicion of lactic acidosis, and a lactate level of 9.08 mmol/l (normal 0.5 - 2.2 mmo/l) confirmed this diagnosis. She was admitted to the intensive care unit and HAART was stopped. Intravenous fluids, bicarbonate infusion, antibiotics, thiamine and vitamins were commenced. She was ventilated but died within 48 hours.

A total of 50 cases of symptomatic hyperlactataemia or lactic acidosis have been diagnosed at Ladysmith Provincial Hospital from January 2005 to March 2006. Of the patients 49 were female and 1 male. The mortality rate was 20%, and all those who died had low bicarbonate levels. Major problems faced have been lack of space and of staff, and inadequate laboratory preparedness and health care worker vigilance. Although all health care workers are aware of hyper-lactataemia/lactic acidosis, it is still being missed (as demonstrated in our first case). The number of patients being seen by a single doctor (in our clinic a doctor may see up to 96 patients a day, i.e. 8 per hour) can lead to compromise of care. After our first case we sent out an alert to all doctors in our hospital and the surrounding area, and we also educate our patients after their 3rd month visit. We have noted that the rise in the anion gap precedes a drop in the bicarbonate, and this may be a useful warning that the patient may be developing lactic acidosis.

For patients with a lactate level below 5 mmol/l we do not stop treatment but monitor them on a weekly basis, and if the level rises to above 5 mmol/l treatment is stopped. The decision to stop treatment must include assessment of the patient's symptoms. When marked symptoms are present discontinuation of the regimen may be considered. All treatment is stopped in patients with lactate levels over 5 mmol/l, and zidovudine (AZT) is commenced once the lactate level is below 2.5 mmol/l. Unfortunately being in the public sector we do not have the luxury of covering the non-nucleoside reverse transcriptase inhibitor tail.

The ACHIVA project highlights the reality of hyperlactataemia/lactic acidosis. The KwaZulu-Natal Department of Health policy on HIV management states that after 6 months of therapy all patients on antiretrovirals should be managed at clinics by nursing sisters. This is of major concern because inexperienced nurses may continue to miss lactic acidosis.

Once lactic acidosis develops mortality is high and therefore prevention is crucial.

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To the Editor: The Perinatal HIV Research Unit (PHRU) commends the Society for its production of hyperlactataemia guidelines. We have some comments and suggestions to offer.

There is little debate concerning management of severe hyperlactataemias and lactic acidosis. The topical area is the management of the 'middle of the road' mild and moderate cases, and our comments refer to this.

SYMPTOMS

While we understand that the intentions of the guidelines are to provide an outline of management, we feel that a term such as 'minimal symptoms' is too vague, and therefore impossible to interpret. This term needs to be sharpened and clarified.

The guideline emphasises grading hyperlactataemia on the quantification of lactate. We propose that patient symptoms, which hold the key in suspecting the diagnosis, should hold greater significance for management and equal importance in the decision to stop drugs, reduce dose or switch therapy.

In turn we propose that clarification of symptom duration be added to the guidelines: for example, peripheral neuropathy and lipodystrophy may be long-term toxicity effects that are temporally distinct from the acute hyperlactataemia symptoms such as vomiting, heartburn and weight loss. When determining whether to restart highly active antiretroviral therapy (HAART) this needs to be borne in mind, otherwise clinicians may hesitate to restart therapy in a patient with resolution of acute symptoms but persisting neuropathy.

DIAGNOSIS

We know that asymptomatic hyperlactataemia occurs in a significant proportion of patients on nucleoside reverse transcriptase inhibitor (NRTI) regimens,[1] and there is a danger that inexperienced clinicians may be quick to diagnose symptomatic hyperlactataemia without first excluding other causes. The guideline, as well as providing a differential diagnosis, needs to include a list of basic investigations that may help to rule out contributing causes – e.g. sputum acid-fast bacilli/microscopy, culture and sensitivity, chest X-ray, full blood count, erythrocyte sedimentation rate, liver function tests (LFTs), blood culture.

The guidelines run the risk of further adding to the confusion, emphasising the diagnosis as one of exclusion but later making the statement that the 'presence of infection therefore does not exclude the fact that the lactic acidosis is contributed to by the NRTIs.' The guidance needs to be clearer on this point.

LACTATE MEASUREMENT

There is a concern of sampling errors and variability, particularly at primary care level. We suggest a repeat lactate measurement to rule out artefactual causes of elevated lactate,[2] before making any decision to alter therapy in mild cases.

We accept that hand-held lactate monitors offer a cost-effective screening tool to primary health settings, but have concerns around its reliability. Planche *et al.* stated that 'while the instrument is sensitive and specific for the detection of lactates above 5.0 there is machine variability for detection of lower levels',[3] whereas von Duvillard *et al.* recommended caution in the use of the hand-held lactate meter for higher levels as these varied significantly from a standard laboratory control.[4]

We propose that any patient with symptoms of tachycardia or tachypnoea may benefit from either a bicarbonate and pH measurement or a U&E (urea and elecrolytes) to measure the anion gap, even if the lactate is < 5 mmol/l.

MANAGEMENT

A recommendation to 'consult an expert' is often unhelpful and very frustrating for the primary care clinician, and the guidelines therefore need to offer as many options and as much information as possible, while maintaining simplicity.

The guidelines suggest monitoring of LFT to exclude hepatic steatosis, but there is a poor correlation between the extent of liver dysfunction and liver enzyme elevation,[5] and we recommend that all facilities that have access should not only do LFTs but also refer patients with moderate or severe hyperlactataemia for an ultrasound assessment of the liver.

Switching to a less mitochondrial-toxic NRTI in mild cases (i.e. zidovudine (AZT), abacavir (ABC) or tenofovir (TDF)) while having merit in terms of continuing therapy and preserving drug sensitivity, poses problems particularly for management in a primary care setting. With the phenomenon of 'cruising' (where lactates may fluctuate and continue to rise even after discontinuation of the supposed offending drugs), switching drugs may add to management difficulties.

An example is a patient who is switched to AZT/lamivudine (3TC)/efavirenz (EFV) after a lactate level of 4.2 mmol/l. Three days later, if the lactate is 5.0 mmol/l, how is the clinician expected to manage the patient? The guidelines recommend that an expert be consulted, yet a significant number of our cohert of patients have fluctuations in their lactate levels, and primary care clinicians would therefore regularly require expert assistance.

Once again, the emphasis in the guidelines is on the lactate level determining management, rather than the clinical response of the patient. We suggest that in primary care facilities, where expert care is not readily available and it is often not possible to measure bicarbonate levels, it is safer and more prudent to temporarily discontinue HAART until the

lactate level is below 3.0 mmol/l and then restart on a safer regimen as suggested by the guidelines.

In the management of moderately severe hyperlactataemia the suggestion is made that 'when it [the lactate level] is falling the patient can be discharged for outpatient follow-up provided he/she is clinically stable'. In this situation our recommendation would be to discharge a patient only when serial decreases (3 levels acceptable) in the lactate level are noted, given the possibility of fluctuating lactate levels.

The guidelines recommend restarting HAART only 'when the lactate is normalised'. It is acknowledged that this may take months, and in our opinion the most important factor to consider here is the patient's symptoms – if there is marked improvement clinically but the lactate level is hovering around 3.0 we would restart the patient.[5,6]

Furthermore, it is important to consider the patient with comorbidity (tuberculosis, herpes), in whom the lactate may well remain at a higher level than desired for reasons other than drug toxicity. Our recommendation is to restart when the lactate falls to below 3.0 mmol/l, the serum bicarbonate or anion gap returns to normal, and the patient demonstrates clinical recovery.

The guidelines recommend that in some patients with persistently elevated lactates and a low nadir CD4 count, a non-nucleoside reverse transcriptase inhibitor (NNRTI)/Kaletra or dual boosted protease inhibitor (PI) regimen be commenced before the lactate level has normalised. Presumably the intention is to change the patient onto an NRTI-containing regimen when the lactate has normalised (to preserve future regimen options), but as this is not stated, patients may be left on this regimen indefinitely.

Finally, we disagree with the recommendations to use $NaHCO_3$ in profound acidosis, as there is great controversy regarding its potential harm. In critically ill patients severe acidosis may reduce anoxic damage to cells, while $NaHCO_3$ has variable, unreliable effects on intracellular pH, shows no added benefits to haemodynamics than normal saline and has potential deleterious effects on fluid and sodium balance.[5,7]

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CPD QUESTIONS

Journal 24

Two CPD points are awarded for the correct completion and submission of questionnaires.

Please complete and post/fax to: Southern African HIV Clinicians Society, Suite 233, PostNet Killarney, Private Bag X2600, Houghton, Johannesburg, 2041, or fax (011) 453-5059

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1. **In the article 'Caring for home-based care workers', the authors propose which ONE of the following to ensure a minimal financial safety net for home-based care (HBC) workers?**
   (a) raise HBC workers' stipend
   (b) procure additional funds through grant-writing efforts
   (c) determine HBC workers' eligibility for accessing government grants
   (d) establish micro-financing projects within the HBC organisation.

2. **Various isoenzymes in the cytochrome P450 (CYP) enzyme system metabolise antiretroviral agents, including the enzyme CYP3A4, which:**
   - **is the most predominant isoenzyme in the liver**
   - **accounts for 30% of CYP proteins in the liver, and**
   - **metabolises 30 – 40% of drugs. Indicate which ONE of the following is also TRUE:**

   (a) substantial levels of CYP3A4 are also present in the renal epithelium
   (b) substantial levels of CYP3A4 are also present in the mucosal epithelium
   (c) substantial levels of CYP3A4 are also present inthe small-intestinal epithelium.

3. **With regard to the role of co-trimoxazole (CTX) in the management of the HIV-infected patient, indicate whether EACH OF the following statements is TRUE OR FALSE:**
   (a) Prophylactic use of CTX in sub-Saharan Africa has not been found to be of benefit because background bacterial resistance to CTX is at a very high level.
   (b) Current WHO Guidelines recommend giving CTX prophylaxis to all HIV-infected persons in resource-poor areas whose CD4 cell counts are below 350/µl provided they are not on antiretrovirals.
   c) In general, the higher the CD4 cell count, the greater the toxicity of CTX when used in the HIV-infected.
   (d) Despite the presence of sulfadoxine-pyramethamine (Fansidar) resistance in Central Africa, the use of CTX prophylaxis in the HIV-infected has led to decreased morbidity and mortality from malaria.
   (e) CTX should only be given as prophylaxis to exposed newborns once their HIV infection has been confirmed.

4. **With regard to hyperlactataemia, indicate whether EACH OF the following statements is TRUE OR FALSE:**
   (a) Asymptomatic hyperlactatemia occurs rarely in patients on NRTI-based regimens.
   (b) The HIV Clinicians Society hyperlactataemia guidelines recommend switching to a less mitochondrial-toxic NRTI in mild cases (i.e. AZT or ABC or TDF).
   (c) Comorbid illness such as TB may contribute to a raised lactate level.
   (d) Peripheral neuropathy and lipodystrophy resolve relatively quickly once NRTI drugs are withdrawn.

5. **Indicate which ONE of the following is TRUE. A major concern regarding STIs is:**
   (a) risk of disease progression during interruptions resulting in new infections and death
   (b) promotion of viral resistance
   (c) possible acute retroviral syndrome
   (d) all of the above.

6. **Indicate which ONE of the following is FALSE. Research into adherence to PEP after sexual assault has shown that:**
   (a) PEP services are significantly undermined and weakened if they are not supported by access to counselling.
   (b) Women accessing PEP are concerned mostly with the time the visit takes.
   (c) PEP services should be properly integrated into other services for women.
   (d) Women accessing PEP services see counselling as necessary and important to their health and well-being.