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FROM THE EDITOR



The rate of co-infection with HIV and tuberculosis (TB) leaves local doctors in no doubt as to the importance of secondary preventive therapy against tuberculosis. Gavin Churchyard's study, described in this issue, showed that isoniazid reduced the incidence of recurrent TB in miners by 55% compared with no prophylaxis. He suggests that international guidelines be expanded to include recommendations for secondary preventive therapy in settings where TB prevalence is high, such as in South Africa.

A lot has been said about the Bangkok Conference particularly regarding the prevention of mother-to-child transmission and the related issue of resistance when nevirapine is used as a single agent. Neil Martinson and Steven Miller cover this topic thoroughly and eloquently in two separate articles, followed by an informative overview of the entire conference by Francois Venter, who hopes that papers presented at the 2006 Toronto Conference will offer more analysis of raw data as opposed to anecdotal experience.

Beset by problems, including disclosure on birth certificates, trends in AIDS mortality are difficult to determine, but Sudeshni Naidoo and Francis Mburu studied HIV/AIDS mortality among inpatients at Motebang Hospital in Lesotho and found that over a 15-year period AIDS had modified the mortality trend by raising the death rate of younger adults, thereby deviating from the natural trend. Almost 70% of all deaths at the hospital were due to communicable diseases, maternal, perinatal and nutritional conditions, of which 70 - 80% were due to AIDS-related conditions. The researchers believe that their data will serve as a basis on which to evaluate the impact of current and future interventions, e.g. the proposed provision of antiretroviral drugs.



Bloemfontein researchers studied supplementary infant feeding as an important vector of disease transmission and determined the level of microbial contamination in bottle feeds given to infants living in Mangaung. Nearly 85% of bottle feeds tested were classified as unfit for human consumption, leading Fredrick Veldman and Jaco Brink to underline the need to address the content of feeding literacy programmes.

Two interesting case studies are presented in this issue, followed by a legal opinion on the importance of funeral and estate planning by Elsabé Klinck.

Much work still needs to be done in southern Africa to improve the treatment and care of HIV-infected people and their families and communities. It is hoped that the national antiretroviral roll-out will gain momentum and give hope, better health and longer lives to those people who qualify for treatment according to the National Guidelines (CD4+ count < 200 cells/ μ l irrespective of WHO stage, or WHO stage IV disease irrespective of CD4+ count).

In the interim, a national guideline committee of Society experts from both the private and public sectors has compiled a guideline for the management of HIV-infected people not yet requiring or qualifying for antiretroviral treatment. It is hoped that this will assist health care professionals in maintaining the health of infected people for as long as possible prior to the need for antiretroviral therapy. It will be published shortly.

DES MARTIN

*Editor, Southern African Journal of HIV Medicine
President, Southern African HIV Clinicians Society*



THINGS TO THINK ABOUT

Well, the national antiretroviral roll-out is rolling – and we're hearing about activity in just about every province, which is very good news indeed. This journal should be a barometer for how things are going, and perhaps we will undertake to devote half a page or so to monitor progress right across the country. Also we welcome papers on lessons learnt, successes and difficulties from all parts of South Africa – as we share our experiences we will improve our services and make more of an impact.

I know in the Western Cape our AIDS Directorate is very pleased with how things are going, with numbers in current sites increasing weekly and more sites being added monthly. The challenge as initial roll-out takes place is to think one step ahead and anticipate the problems of the future. Just three such problems immediately come to mind, though there are many more to think about and plan for.

The first is recognition that most of the resources are being put into outpatient care. This makes sense when we need to treat many thousands of people, as in our national tuberculosis programme. However, a truly comprehensive health service must offer primary, secondary and tertiary care. While we are treating the sickest of the sick, which will continue for some time as the criteria for starting antiretroviral therapy are AIDS or a markedly reduced CD4 count, we can expect fairly significant mortality and morbidity in the early days of therapy. Aggressive and expert inpatient care for recognition and treatment of the immune reconstitution syndromes, including difficult-to-diagnose TB (often requiring diagnostics not available at primary or even secondary levels), and other opportunistic infections, will enable more people to make it through those troublesome first three months and then have as good a stab as anyone at longer and better lives. And don't forget the small proportion of really adherent patients who develop late side-effects that may need an effective multi-specialist approach to get these 'excellent' patients back to their busy lives.

The other area we are going to have to address as ARV programmes mature is the fact that a large proportion of our patients (70% at Hanan-CRUSAID in Gugulethu) is female and that as viral loads are suppressed and young people begin to feel better, issues around sexuality, fertility and reproduction are raised. A female star on 'Isidingo' has in recent episodes been grappling with just these issues while living with HIV infection. As a health profession we are going to have to work through this one and formulate some appropriate responses. Of course people have a right to children, and I don't think we will be able to decide otherwise! The first prize will be to work with

our patients and ensure that they understand all benefits and all risks and make their decisions with cool heads and with full knowledge. A challenge in a busy ARV clinic! Again, I don't think we are going to be able to have enough doctor and nurse time for these important discussions, so we will need to equip our therapeutic counsellors, foot soldiers, treatment buddies or peer counsellors with the relevant facts so that we get the right messages out there.

What an exciting time to be a health practitioner! HIV and the provision of ART have really brought to the fore patient autonomy and the need for a proper and equal patient-practitioner relationship. A challenge for many of us who haven't experienced this before, but oh! so refreshing!

Finally, Andrew Boulle and Helen Meintjies highlighted a very important third issue to think about as a consequence of the AIDS epidemic and treatment in the 27 August edition of *Mail and Guardian*. They remind us that we have the largest HIV epidemic in the world and will soon have the largest ART programme too. The foster care grant (R530 per month) and the disability grant (R740) have the fastest increase in uptake, and this is a direct consequence of the HIV epidemic. Although not intended to do so, in the absence of adequate social security alternatives each of these grants currently plays a critical role in alleviating poverty in households throughout South Africa. Yet, as Boulle and Meintjies point out, it is discriminatory to provide grants to orphans to the age of 18 years without providing at least equal support to the many other impoverished children whose parents are alive. The child care grant (R170) is of much lower monetary value and only eligible to the age of 11 years. Until the introduction of a national ARV programme where hopefully all eligible HIV-infected persons will be treated with ART, a disability grant awarded to a person with advanced HIV disease was effectively a 'grant for life'. Patients on ART will not sicken to the same extent and therefore never be eligible for the grant, or else may improve significantly, leading to grant withdrawal. In communities where the low employment rate is more of an obstacle to gainful employment than the HIV epidemic, this may have dire effects on the family and indeed on allowing the individual to remain in care. People may delay testing and enrolment in care until they qualify for a disability grant, and then not have the incentive to adhere to therapy once on treatment. Boulle and Meintjies conclude that a possible solution is extension of the child support grant to all children up to 18 years and the implementation of a basic income grant. They argue that it is only with such comprehensive social security that South Africans will be equitably supported through the HIV epidemic.

LINDA-GAIL BEKKER
Managing Editor

EFFICACY OF SECONDARY ISONIAZID PREVENTIVE THERAPY AMONG HIV-INFECTED SOUTHERN AFRICANS: TIME TO CHANGE POLICY?

Gavin J Churchyard^{1,2}, Katherine Fielding², Salome Charalambous¹, John H Day^{1,2}, Elizabeth L Corbett², Richard J Hayes², Richard E Chaisson³, Kevin M De Cock², Badara Samb⁴, Alison D Grant²

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Objective. To determine the efficacy of secondary preventive therapy against tuberculosis (TB) among goldminers working in South Africa.

Design. An observational study.

Methods. The incidence of recurrent TB was compared between two cohorts of HIV-infected miners: one cohort had received secondary preventive therapy with isoniazid and the other had not.

Setting. Health service providing comprehensive care for goldminers.

Participants. 338 men received secondary preventive therapy and 221 did not.

Main outcome measure. Incidence of recurrent TB.

Results. The overall incidence of recurrent TB was reduced by 55% among men who received isoniazid preventive therapy (IPT) compared to those who did not (incidence rates 8.6 and 19.1 per 100 person-years respectively, incidence rate ratio 0.45; 95% CI 0.26 – 0.78). The efficacy of isoniazid preventive therapy was unchanged after controlling for CD4 count and age. The number of person-years of isoniazid preventive therapy required to prevent one case of recurrent TB among individuals with a CD4 count < 200/ μ l and \geq 200/ μ l was 5 and 19, respectively.

Conclusion. Secondary preventive therapy reduces TB recurrence: the absolute impact appears to be greatest among individuals with low CD4 counts. International TB preventive therapy guidelines for HIV-infected individuals need to be expanded to include recommendations for secondary preventive therapy in settings where TB prevalence is high.

The World Health Organisation (WHO) recommendations for tuberculosis (TB) control focus on curing patients presenting with their first episode of TB, with the aim of interrupting TB transmission. In countries with a high TB incidence, recurrent TB accounts for a significant proportion of all cases,^{1,2} and HIV infection is a strong risk factor for recurrent TB³⁻⁶ along with post-TB scarring, cavities, drug regimen used to treat the initial episode of TB and a low CD4 count.^{4,8} In settings of lower TB incidence, recurrent TB occurs more commonly among HIV-infected patients, though the absolute difference in rates is small.⁹ Recurrent TB may result from either recrudescence of disease with the original infecting organism, or reinfection

with a new *Mycobacterium tuberculosis* strain.^{5,10} Reinfection, with rapid progression to disease, has been shown to be an important cause of recurrence among HIV-infected individuals in settings with high rates of TB transmission.⁶

Current international guidelines recommend TB preventive therapy (PT) for HIV-infected individuals who have never had TB previously (primary TB PT).¹¹ However, there is increasing evidence of the efficacy of secondary PT for HIV-infected individuals.^{12,13}

The objective of our study was to determine the efficacy of secondary isoniazid PT (IPT) by comparing the TB incidence rates between two cohorts of HIV-infected goldminers in South Africa with a history of previous TB who had or had not received isoniazid PT.

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STUDY POPULATION AND SITE

The study was conducted at a single goldmining company in the Free State province of South Africa. The mine hospital is the sole source of tertiary care for mine employees and manages the TB control programme. Clinics situated at most of the surrounding mine shafts provide primary health care to miners and dispense TB treatment and IPT.

TB CONTROL PROGRAMME

The TB control programme includes directly observed rifampicin-based short-course chemotherapy regimens, use of combination tablets and active case detection using a miniature radiograph screening programme. Treatment regimens are in line with those recommended by the national TB control programme: four drugs are used for first episodes of TB, and regimens for drug-resistant cases are modified to ensure treatment with two or more drugs to which the isolate is sensitive.

Miners with suspected TB are investigated according to a standard protocol. Three sputum specimens are collected over 2 days. Smears are made from concentrated sputum and stained with auramine for fluorescence microscopy. Positive smears are confirmed with Ziehl-Neelsen staining. Following decontamination with 4% sodium hydroxide, sputum is inoculated onto Lowenstein-Jensen (LJ) slopes and incubated for up to 8 weeks. An initial identification step for *M. tuberculosis* is carried out on LJ slopes with more than five colonies, using a colorimetric ribosomal RNA hybridisation test (Accuprobe, *M. tuberculosis* complex probe kit, Gen-Probe, San Diego, CA). Positive cultures are sent to the National Health Laboratory for drug susceptibility testing of *M. tuberculosis* strains.

COHORT SELECTION

In this study we included miners with HIV infection and a history of previous TB with documented successful completion of TB treatment. Men who failed therapy for the previous TB episode or had an unknown treatment outcome were excluded from the study, as were men treated for non-tuberculous mycobacterial disease.

Participants receiving IPT (300 mg/d) were derived from a cohort of HIV-infected men receiving isoniazid and co-trimoxazole indefinitely as part of a clinical trial. The control cohort comprised men attending a routine HIV clinic who did not receive IPT because of a history of previous TB, an exclusion criterion in accordance with current international and local guidelines. Men in the control cohort received co-trimoxazole prophylaxis if their

CD4+ T cell-lymphocyte (CD4) count was below 250/ μ l if symptomatic or 200/ μ l regardless of symptoms. The incidence of TB recurrence in the two cohorts was compared using a database listing all episodes of TB among company employees since 1979.

TIME AT RISK

At the time of recruitment to their respective cohorts, men had blood taken for a CD4 count and were screened for TB using symptoms, chest radiography and sputum smears and cultures. In order to minimise the risk of including a case of TB diagnosed at the time of screening as a study case, the date of entry into this study was defined as three months after the date of TB screening. Men receiving TB treatment at the time of recruitment, or who were diagnosed with TB at the time of screening, entered time at risk after completing TB treatment. Time at risk was censored at the time of first TB episode during the study, death, loss to follow up or end of study (31 December 2000 for the IPT cohort and 31 July 2001 for the control cohort).

CASE DEFINITIONS

Recurrent TB was defined as *definite* if there were compatible clinical features and sputum or tissue culture was positive for *M. tuberculosis*; *probable* if there were compatible clinical features and two sputum smears were positive for acid-fast bacilli, or sputum or tissue culture was positive for mycobacteria that were not further speciated, or histological examination was positive (acid-fast bacilli present or granulomatous disease); and *possible* if there were compatible clinical features and a response to treatment with anti-tuberculosis drugs.

GRADING OF SILICOSIS AND POST-TREATMENT SCARRING

The standard-sized chest radiographs of study participants, taken at the time of recruitment to their respective cohorts, were assessed for the presence and grade of silicosis using a modified International Labour Organisation (ILO) scoring system. For the purposes of this study silicosis was categorised as none (0/0 or 0/1) or definite (ILO category 1/0 and above). The radiological extent of post-treatment scarring was determined by dividing the lung on each side into three equal zones and allocating a score according to the total number of zones involved. The presence or absence of cavities was also noted.

DATA ANALYSIS

Data were analysed with STATA 6.0 software (STATA Corporation, Texas, USA). Differences between categorical variables were investigated using the chi-square test or Fisher's exact test where appropriate. The differences in length of follow-up between the two groups were assessed

using the Wilcoxon rank-sum test. Poisson regression was used to calculate univariate and adjusted TB incidence and mortality rate ratios for different variables. Overall significance, tests for trends for ordinal variables with more than two categories and tests for effect modification were determined using the likelihood ratio test.

ETHICAL APPROVAL

Ethical approval for the clinical trial from which the IPT cohort was drawn was obtained from the Anglogold Health Services and UNAIDS ethical review boards; all participants gave informed consent. The evaluation of the routine health service clinic from which the control cohort was drawn was given ethical approval by the ethics committees of Anglogold Health Service and London School of Hygiene and Tropical Medicine.

RESULTS

All study participants were HIV-infected black male miners; 338 men who received IPT (IPT cohort) were compared with

TABLE I. SUMMARY OF DEMOGRAPHIC VARIABLES, BY COHORT

	IPT		Control		p-value
	N	%	N	%	
Total	338		221		
Time at risk (yrs)					
Median (IQR)	0.91	(0.60, 1.33)	0.41	(0.19, 0.84)	< 0.001
Age group (yrs)					
< 30	17	5	11	5	0.5
30 - 39	154	46	86	39	
40 - 49	139	41	104	47	
50+	28	8	20	9	
CD4 group (/ μ l)*					
< 200	114	34	65	33	0.2
200 - 499	181	54	95	49	
500+	42	12	35	18	
Time since end of previous TB episode (mo.)					
6 - 12	256	76	131	59	< 0.001
12 - 24	49	14	38	17	
24+	33	10	52	24	
Calendar year of entry					
1998	59	17	0	0	< 0.001
1999 - 2000	279	83	140	63	
2001	0	0	81	37	
Number of previous TB episodes					
1	273	81	173	78	0.5
> 1	65	19	48	22	
Silicosis					
Absent	307	91	206	93	0.3
Present	31	9	15	7	
Cavitation					
Absent	265	78	165	75	0.3
Present	73	22	56	25	
Number of zones					
0	57	17	42	19	0.7
1 - 2	177	52	117	53	
3+	104	31	62	28	

*1 and 26 results missing for IPT and control cohorts, respectively. IPT = isoniazid preventive; therapy; IQR = inter-quartile range.

TABLE II. SUMMARY OF TB EVENTS, BY COHORT

Factor	IPT		Control		p-value
	N	%	N	%	
Total	28		23		
Case definition					
Definite	17	61	18	78	0.2
Probable	11	39	5	22	
Classification					
PTB	22	79	18	78	0.7
ETB	4	14	2	8	
PTB + ETB	2	7	3	13	
CD4 group (/ μ l)*					
< 200	12	43	10	50	0.5
\geq 200	16	57	10	50	

*CD4 group at baseline. CD4 count missing for 3 individuals from the control cohort.

221 who did not (control cohort). The characteristics of the two cohorts are presented in Table I. The two cohorts were similar with respect to age, CD4 count, number of previous TB episodes, silicosis grade, presence of cavitation and extent of post-treatment scarring. The control cohort had their preceding episode of TB significantly longer before study entry than did the IPT cohort, and had a shorter duration of follow-up within the study (median 0.41 v. 0.91 years). Recruitment to the IPT cohort began and ended a year earlier than recruitment to the control cohort.

A log of all treatment dispensed to the primary health care clinic and collected by the study participants on a monthly basis was kept. Of men in the IPT cohort 76% (256/338) collected at least 80% of the isoniazid dispensed; 19/28 (68%) of the TB cases from the IPT cohort collected at least 80% of their prescribed isoniazid. IPT was interrupted, and then restarted, in 4 patients due to skin rash (2), abdominal pain (1) and nausea (1). IPT was stopped and not restarted in a further 3 patients, all due to skin rash. There were no episodes of hepatitis or peripheral neuropathy.

Fifty-one cases of TB were diagnosed during the study period, 28 (8.3%) among the IPT cohort and 23 (10.4%) among the control cohort. The recurrent TB cases in the two groups were similar with respect to the proportion classified as definite, site of disease and CD4 count at baseline (Table II). There was no significant difference in the prevalence of isoniazid resistance between the IPT and control cohorts (20% [2/10] and 23% [3/13], respectively, $p = 1.0$).

Results of incidence rates (IR) of recurrent TB, unadjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) are presented in Tables III and IV. There was a significantly lower incidence of TB among the IPT cohort compared with the control cohort (IRR 0.45; 95% CI 0.26 - 0.78). There was no difference in efficacy of IPT when adjusted for age, silicosis, extent of post-treatment scarring or presence of cavitation, CD4 count and time since

TABLE III. UNADJUSTED INCIDENCE RATES OF RECURRENT TB AND INCIDENCE RATE RATIOS BY NUMBER OF PREVIOUS TB EPISODES, CD4 GROUP, TIME SINCE PREVIOUS TB EPISODE AND TB CASE DEFINITION

		N	Events*/pyrs	IR	IRR (95% CI)
All					
Overall	IPT	338	28/324.3	8.6	0.45 (0.26, 0.78)
	Control	221	23/120.3	19.1	1
Previous episodes of TB					$P_i = 0.03^\dagger$
1 episode	IPT	273	19/268.3	7.1	0.33 (0.18, 0.61)
	Control	173	21/97.2	21.6	1
> 1 episode	IPT	65	9/56.0	16.1	1.85 (0.40, 8.58)
	Control	48	2/23.1	8.7	1
CD4 category (μl)					$P_i = 0.55^\dagger$
< 200	IPT	114	12/87.8	13.7	0.40 (0.17, 0.92)
	Control	65	10/29.1	34.3	1
≥ 200	IPT	223	16/234.8	6.8	0.57 (0.26, 1.25)
	Control	135	10/83.0	12.0	1
Time since previous TB episode					$P_i = 0.86^\dagger$
< 12 mo.	IPT	202	13/183.5	7.1	0.52 (0.22, 1.27)
	Control	111	8/59.3	13.5	1
12 - 24 mo.	IPT	83	10/87.1	11.5	0.37 (0.15, 0.94)
	Control	50	8/26.0	30.8	1
>24 mo.	IPT	53	5/53.7	9.3	0.47 (0.15, 1.47)
	Control	60	7/35.1	19.9	1
Probable/definite*					
Overall	IPT	338	17/324.3	5.2	0.35 (0.18, 0.68)
	Control	221	18/120.3	15.0	1
Previous episodes of TB					$P_i = 0.02^\dagger$
1 episode	IPT	273	11/268.3	4.1	0.23 (0.11, 0.50)
	Control	173	17/97.2	17.5	1
>1 episode	IPT	65	6/56.0	10.7	2.47 (0.30, 20.5)
	Control	48	1/23.1	4.3	

IR = incidence rate per 100 person-years (pyrs); IRR = incidence rate ratio; CI = confidence interval; IPT = isoniazid preventive therapy. *Number of TB recurrences. † P-value for the interaction between variable of interest and cohort group. ‡ See text for case definitions.

completion of treatment for previous TB episode (adjusted IRR = 0.45, 95% CI 0.26 - 0.79). The effect of IPT on TB incidence remained significant when the analysis was restricted to TB cases defined as probable or definite (Table III). Likewise, the effect of IPT remained highly significant if the analysis was restricted to those in whom the previous TB episode had been culture positive for *M. tuberculosis* (IRR 0.19; 95% CI 0.09 - 0.42) (Table IV).

Among men with only one previous episode of TB, the incidence of recurrent TB in the IPT cohort was significantly lower than in the control cohort (Table III). Among men with more than one previous episode of TB, recurrences occurred more often in those on IPT, though the difference was not statistically significant (Table III). The interaction

between the number of previous TB episodes and the efficacy of IPT was significant overall ($P_{\text{interaction}} = 0.03$), when the analysis was restricted to those cases classified as probable or definite ($P_{\text{interaction}} = 0.02$) (Table III) and when the preceding TB episode was culture positive for *M. tuberculosis* ($P_{\text{interaction}} = 0.001$) (Table IV). The effect of IPT was strongest in men with only one previous episode of TB that was culture positive for *M. tuberculosis*, among whom there was an 89% reduction in incidence of recurrent TB (IRR 0.11; 95% CI 0.04 - 0.27).

The effect of IPT was not significantly modified by time since completion of previous TB treatment ($P_{\text{interaction}} = 0.86$) or by CD4 category ($P_{\text{interaction}} = 0.55$) (Table III). However, the incidence of recurrent TB increased with

TABLE IV. UNADJUSTED INCIDENCE RATES OF RECURRENT TB AND INCIDENCE RATE RATIOS RESTRICTED TO INDIVIDUALS WHOSE PREVIOUS TB EPISODE WAS CULTURE POSITIVE FOR M. TUBERCULOSIS

		N	Events*/pyrs	IR	IRR (95% CI)
All					
Overall	IPT	186	10/176.4	5.7	0.19 (0.09, 0.42)
	Control	119	17/58.1	29.3	1
Previous episodes of TB					$P_i = 0.01^\dagger$
1 episode	IPT	155	6/151.1	4.0	0.11 (0.4, 0.27)
	Control	94	17/46.4	36.6	1
> 1 episode	IPT	31	14/25.3	15.8	-
	Control	25	0/11.7	0	

IR = incidence rate per 100 person years (pyrs); IRR = incidence rate ratio; CI = confidence interval; IPT = isoniazid preventive therapy. *Number of TB recurrences. † p-value for interaction of the number of previous TB episodes.

TABLE V. MORTALITY RATES AND RATE RATIOS BY COHORT

		Events*/pyrs	MR	MRR (95% CI)	p-value
All individuals	IPT	33/339.8	10.0	0.70 (0.39, 1.24)	0.22
	Control	18/129.3	13.9		
CD4 < 200/μl, on co-trimoxazole†	IPT	30/93.1	33.3	0.73 (0.39, 1.38)	0.33
	Control	14/31.8	44.1		

MR = mortality rate per 100 person years (pyrs); MRR = mortality rate ratio; CI = confidence interval; IPT = isoniazid preventive therapy.
 *Number of deaths. †114 and 60 individuals from the IPT and control cohorts, respectively.

decreasing CD4 count (CD4 count \geq 500/μl: 6.9/100 person-years (pyrs); CD4 count 200 – 499/μl: 8.6/100 pyrs; < 200/μl: 18.8/100 pyrs; $P_{\text{trend}} = 0.008$) and hence the number needed to treat to prevent a case of recurrent TB was substantially lower for individuals with lower CD4 counts. (The number of pyrs on IPT required to prevent one case of recurrent TB was 10 pyrs overall, 5 pyrs for CD4 count < 200/μl and 19 pyrs for CD4 count \geq 200/μl.)

Overall mortality was not significantly lower among the IPT cohort compared with the control cohort (mortality rate ratio 0.7; 95% CI 0.39 - 1.24) (Table V). In order to control for any possible effect of co-trimoxazole on mortality, the analysis was restricted to those men with a CD4 count of 200/μl or below who were taking co-trimoxazole, but this did not affect the result (mortality rate ratio 0.73; 95% CI 0.39 - 1.38).

DISCUSSION

The concept of TB PT was developed in the pre-HIV era, based on the idea that treatment of asymptomatic latent or recently acquired TB infection would reduce the risk of developing active TB disease.¹⁴ In industrialised countries, the contribution of exogenous reinfection to active disease was declining in the mid-20th century,¹⁵ and PT was thought to have no effect among those who had been previously treated for TB¹⁶ and secondary PT was therefore not recommended. The clinical trials that demonstrated the efficacy of TB PT among HIV-infected individuals were based on this same principle, and hence only included individuals who had no history of previous TB. However, with the development of molecular ‘fingerprinting’ techniques, it has become clear that recurrent TB may occur either as a result of recrudescence of disease from the original infecting organism (relapse) or due to reinfection with a new strain of TB, particularly in settings with a high rate of TB transmission.^{6,10}

In this study, in a setting where the prevalence (and hence also the risk of transmission) of TB is high, secondary IPT was associated with a 55% reduction in the incidence of recurrent TB among HIV-infected individuals. The results are consistent with small prospective randomised trials of

secondary IPT from Haiti¹² and Abidjan,¹³ and a study from the Democratic Republic of Congo that demonstrated a reduction in TB recurrence among HIV-infected individuals in whom treatment was extended by 6 months with twice-weekly isoniazid and rifampicin.¹⁷

The effectiveness of secondary PT is likely to be limited to communities with high rates of TB transmission, such as the South African goldmining industry, where there are high rates of TB recurrence following documented cure, particularly among HIV-infected individuals.^{4,6} DNA fingerprinting data suggest similar rates of relapse between HIV-infected and uninfected individuals, but higher rates of reinfection with rapid progression to TB disease among HIV-infected individuals.⁶ In this setting, secondary PT may prevent acquisition of new infection or treat recently acquired infection that may have occurred following completion of treatment of the previous TB episode.

Our study suggests that the effectiveness of secondary IPT may be limited to HIV-infected individuals with only one previous episode of TB. This may be because individuals who have had more than one recurrence of TB are more likely to have drug-resistant TB than those individuals presenting with their first recurrence;¹⁸ the number of individuals in this study with isoniazid-resistant TB was too small to provide data supporting this hypothesis. Limiting secondary PT to individuals who have only had one previous episode of TB seems rational but requires additional studies to confirm a lack of benefit in those individuals with more than one previous TB episode.

Current WHO recommendations regarding TB preventive therapy for HIV-infected individuals in resource-poor settings have not been widely implemented.¹⁹ In sub-Saharan Africa the majority of HIV-infected individuals are unaware of their HIV status¹⁹ and many discover their status only when an opportunistic infection, often TB, is diagnosed, at which point it is too late for primary PT. Furthermore, owing to limited eligibility criteria and logistical difficulties of excluding active disease prior to commencing PT there is a high attrition of patients during the screening process.²⁰ Consequently, the number of patients who start primary PT compared with the number

screened is small. Secondary TB PT may be easier to implement than primary PT. HIV testing should have been offered at the time of TB diagnosis, a tuberculin skin test (TST) and chest radiograph are not required and exclusion of active TB at the end of treatment, by sputum smear examination, is done routinely according to WHO TB control programme guidelines. For these reasons it seems logical to offer secondary PT to HIV-infected individuals in settings of high TB prevalence where primary TB PT is being offered.

In this study, the risk of recurrent TB increased significantly with declining CD4 count, but the relative effect of IPT was not significantly modified by CD4 count. Hence fewer patients with advanced HIV disease would need to be treated to prevent a case of TB compared to patients with less advanced HIV disease. It may be more cost-effective to target IPT to those with advanced HIV disease, based on CD4 count or clinical staging. Of note, absolute numbers needed to treat depend on TB incidence and hence where TB incidence is lower, the numbers needed to treat will be higher.

In other studies^{12,17} the effectiveness of secondary PT was evaluated in the immediate post-TB treatment period.¹³ Our study demonstrated effectiveness of secondary IPT regardless of the interval between the previous TB episode and commencing IPT. We therefore propose no restriction by time since previous episode for offering secondary PT to HIV-infected individuals.

Although secondary IPT significantly reduced the incidence of TB recurrence in this study, the rate of recurrence in the IPT cohort remained unacceptably high (8.6 per 100 person-years) and mortality was not significantly reduced. In resource-poor settings secondary IPT may be a safe and, at less than \$10 per person per year, affordable way to reduce morbidity among HIV-infected individuals with a history of previous TB. Antiretroviral therapy (ART) is likely to have a greater effect in reducing morbidity and mortality from TB and AIDS-defining conditions in this group of patients.^{21,22} However, TB incidence remains high among individuals on ART with low CD4 counts living in communities with endemic TB,²² and thus TB preventive therapy will remain an important intervention for individuals receiving ART in these settings.

In this study, we were able to include a relatively large number of individuals with a large number of events. Since this was not a randomised controlled trial, there could have been differences between the two cohorts that we were not able to control for. However, we had access to detailed data on potential confounding factors, and the two cohorts had similar baseline characteristics. Although the two cohorts differed in terms of time since last TB episode, there was no

difference in efficacy of IPT when adjusted for time since last TB episode. The risk of recurrent TB in the IPT cohort may have been greater because of the longer duration of follow-up and hence increased chance of disease progression. If so, we may have underestimated the efficacy of IPT.

Secondary IPT was administered indefinitely in this study, which contrasts with current international guidelines of 6 - 9 months of isoniazid for primary PT^{11,23} and other studies of secondary PT.^{12,13} Further work is needed to determine the optimum duration of both primary and secondary TB PT in settings with high rates of TB transmission, and to establish how best to target PT.

There is a growing body of evidence of the efficacy of secondary TB PT for HIV-infected individuals in communities with a high incidence of TB. HIV-infected individuals may benefit from secondary PT, and international recommendations need revision to take this into account.

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Commentary by G J Churchyard and A D Grant

South Africa is classified by the World Health Organisation as one of the 22 high TB burden countries world-wide.¹ Approximately 2 million South Africans are co-infected with TB and HIV, and the estimated incidence of all forms of TB was 509 per 100 000 population for 2002, with 60% of adult cases being HIV-infected.¹

As in other countries with endemic TB, recurrent disease accounts for a significant proportion of all TB in South Africa. HIV infection increases the risk of recurrence following successful treatment of TB.² Risk factors for recurrence of HIV-associated TB are initial treatment regimens with less than 6 months of rifampicin,² post-TB scarring, cavities, and a low CD4 count.

The importance of new infection as a cause of recurrent TB has been clearly shown in a prospective strain-typing study among TB patients in a South African goldmine.³ HIV-infected miners had recurrent TB disease due to a new strain of TB (reinfection) at 18.7 times the rate in HIV-uninfected miners, but there was no increase in their risk of recurrent disease due to the original strain (relapse). In settings of lower TB incidence, recurrent TB still occurs more frequently among HIV-infected patients, although the absolute difference is smaller. These observations suggest that there is little to gain from intensifying the treatment regimens currently used in South Africa, but that consideration should be given to secondary TB preventive therapy in settings of high TB transmission. The article by Churchyard *et al.*⁴ reproduced in this journal contributes to the body of evidence supporting the use of secondary TB preventive therapy among HIV-infected individuals. Although the South African HIV Clinicians Society guidelines recommend TB preventive therapy for HIV-infected individuals who have had an episode of TB more than 2 years previously, the Department of Health's TB preventive therapy guidelines do not advocate the use of secondary TB preventive therapy. Further research is needed to establish how to use secondary TB preventive therapy most effectively among HIV-infected people, and to determine whether secondary TB preventive therapy has a role to reduce TB recurrence among individuals receiving antiretroviral therapy.

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PREVENTION OF MOTHER-TO-CHILD TRANSMISSION

A report-back from the XV International AIDS Conference, Bangkok, 11 - 16 July 2004

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The XV International AIDS Conference was held in Bangkok from 11 to 16 July 2004. The theme of the conference was 'Access for all'. It was an enormous gathering; 10 000 abstracts were accepted for presentation, of which approximately 400 were oral. There were 19 500 attendees from all over the globe with a high representation from Asian countries. South Africa was well represented by a large contingent including politicians, researchers, activists and government officials. The abstracts and presentations which may have an impact on policy and research directions have been reviewed and are summarised.

WHO GUIDELINES FOR PMTCT

New World Health Organisation guidelines for the prevention of mother-to-child transmission (PMTCT) of HIV¹ were presented at an evening satellite session. The guidelines, available at <http://www.who.int/reproductive-health/rtis/MTCT/>, were compiled by a WHO-convened Technical Consultation on Antiretroviral Drugs and the Prevention of Mother-to-child Transmission of HIV Infection in Resource-limited Settings in Geneva, Switzerland in February 2004. The participants considered the available scientific evidence and the programmatic experience and recommended specific antiretroviral (ARV) regimens according to different clinical situations. The guidelines differ from the recommendations issued by WHO in 2000, which focused mainly on the PMTCT of HIV, by acknowledging the greater access to ARV treatment for women and the desirability of providing ARV treatment for women who need it. They complement other guidelines on treatment issued by the WHO and the 3 by 5 Initiative.

Women may receive ARV drugs during pregnancy as part of combination regimens used to treat their HIV infection or

to prevent HIV infection in infants. All efforts should be made to ensure that access to ARV treatment for women is based on their need and eligibility for such treatment. However, ARV regimens for women of childbearing age should be selected considering the possibility of a planned or unintended pregnancy and that ARV drugs may be taken in the first trimester of pregnancy, before a pregnancy is recognised. While triple therapy is widely used in developed countries to prevent HIV transmission in pregnancy, there are concerns about its use for this indication in women where clinical and laboratory monitoring is not readily available.

The key recommendations from the new guidelines are:

1. Women who need ARV treatment for their own health should receive it in accordance with WHO guidelines on ARV treatment. The use of ARV treatment, when indicated, during pregnancy substantially benefits the health of the woman and decreases the risk of HIV transmission to the infant.
2. HIV-infected pregnant women who do not have indications for ARV treatment or do not have access to treatment should be offered ARV prophylaxis to prevent MTCT using one of several ARV regimens known to be safe and effective:
 - Zidovudine (AZT) from 28 weeks of pregnancy plus single-dose nevirapine (NVP) during labour and single-dose NVP and 1-week AZT for the infant. This regimen is highly efficacious, as is initiating AZT later in pregnancy.
 - Alternative regimens based on AZT alone, short-course AZT + lamivudine (3TC) or single-dose NVP (sdNVP) alone are also recommended.

RESISTANCE INDUCED BY NVP

Non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance was a focus of this conference. Specifically the resistance induced by sdNVP to both pregnant mother and the newborn infant attracted much attention. The predominant research method of assessing resistance is to analyse for the presence of viral DNA mutations that are known to confer resistance to specific ARV drugs. The presence of detectable genotypic resistance was reported in three cohorts of women and children. A study of mother-infant pairs recruited from the PMTCT programme in Soweto and Durban who were exposed to single-dose NVP in 2002-2003 was presented.² Previous data from this study showed that 40% of women and 45% of children were found to have genotypic resistance to NNRTIs at 7 weeks after delivery.³ The paper presented at Bangkok reported the fading of genotypic NNRTI resistance to 6 months after the dose of NVP in both mothers and children, and reported the pattern of resistant mutations found. Figs 1 and 2 below show levels of detectable resistance found prior to the NVP dose in pregnant mothers, at 7 weeks after delivery and at 6 months after delivery, respectively. Ninety-eight per cent of the women

were infected with clade C HIV.

This study confirmed previous work showing that not only do detectable resistant mutations fade but also the diversity of the mutations diminishes.

A similar study of NVP-induced genotypic resistance in Thailand assessed the pattern of NNRTI-resistant mutations in a population where the predominant HIV subtype is CRF01_AE.³ Three hundred and ten women with advanced disease who received sdNVP had genotypic resistance assays performed 10 days and 6 weeks after delivery. Overall, the data reported were similar to the work done in South Africa on clade C viruses.³ NNRTI mutations were found in 38% of the women exposed to sdNVP.⁴ Seventy-three per cent of the women with resistance had single-mutation resistance and 27% had at least two mutations. The most common mutation in this study, as in the South African work reported previously, was K103N (65%). However, the second most frequent maternal resistance mutation was G109A (30%), an infrequent mutation in the South African series.

A potential strategy to reduce maternal NNRTI resistance is to not expose the mother to NVP at all. A randomised open label clinical trial was presented that tested two

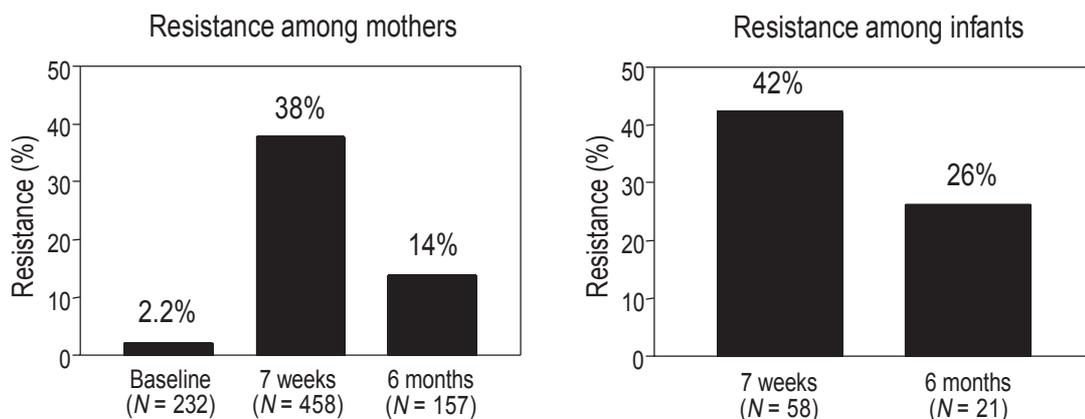


Fig. 1. Graphs of resistance in mothers and infants following single-dose NVP.²

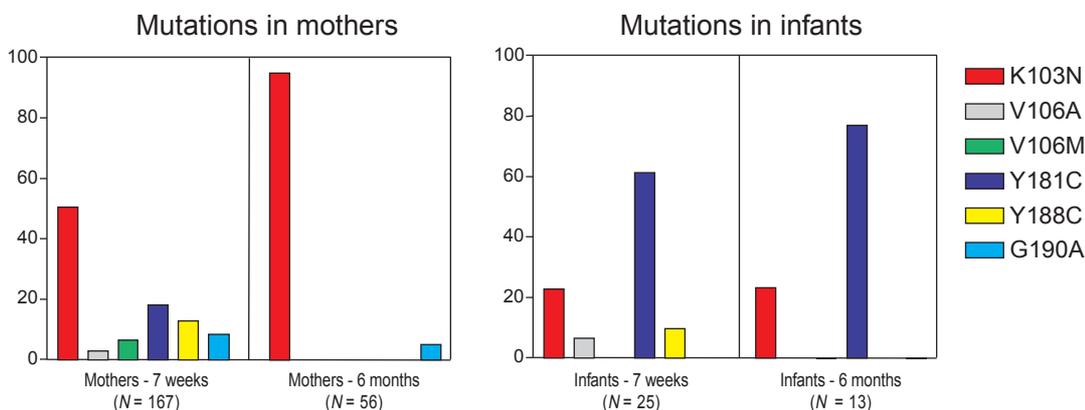
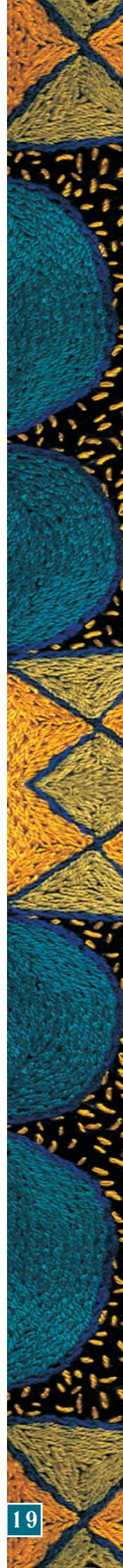


Fig. 2. Pattern of NNRTI mutations detected in mothers and infants with resistance²



interventions to prevent transmission of HIV in infants whose HIV-infected mothers were not able to access antenatal ARVs in PMTCT programmes.⁵ This trial, which recruited 1 051 infants, was undertaken at the Perinatal HIV Research Unit at Chris Hani Baragwanath Hospital. It compared HIV transmission rates in infants whose mothers did not receive ARVs to prevent MTCT for a variety of reasons. Infants were randomised to receive either:

1. A single dose of NVP (2 mg/kg within 72 hours of delivery) or
2. A 6-week course of twice daily AZT commenced within 24 hours of delivery.

Transmission for the entire group at 12 weeks was 16.3% and transmission in the intention-to-treat analysis is shown in Table I.

TABLE I. TRANSMISSION RATES BY ARM AND TIMING OF INFANT HIV PCR TEST^a

Arm	Birth	6 weeks	12 weeks
sdNVP	7	11.9	14.3
6 weeks AZT	5.8	13.5	18.1
<i>p</i>	0.5	0.6	0.4

Overall, sdNVP was better at reducing transmission than 6 weeks of AZT in this group of infants of mothers who had not accessed an antenatal PMTCT programme. Furthermore, the burden on the health service is markedly reduced by giving a stat post-partum dose compared with ensuring that 6 weeks of AZT are provided and ingested by a newborn. An oral paper reported the genotypic resistance induced by the sdNVP arm in this study.⁶ Only 3 of 23 HIV-infected infants whose mothers did not receive NVP and who were randomised to the sdNVP arm were found to have genotypic resistance compared with approximately 45% of infants exposed to maternal NVP *in utero* and then themselves receiving sdNVP after delivery. The patterns of resistance also differed, with those exposed to only their own sdNVP dose having fewer mutations than those exposed to additional maternal sdNVP as part of HIVNET 012 regimen.

The resistance generated by sdNVP may in part be due to its long half-life. A paper presented by a combined Thai/US group showed NVP plasma levels in 61 women who had recently taken sdNVP to prevent MTCT. Although plasma exposure and C_{max} were found to be significantly less in pregnant women than in non-pregnant women and men,⁸ NVP was detected in women who had delivered up to 21 days post partum,⁷ albeit at low concentrations. The median half-life of NVP was 58.3 hours in this study.⁷

PREVENTION OF RESISTANCE

The implications of detection of genotypic resistance are uncertain. However, there is recently published evidence that genotypic resistance induced by sdNVP and exposure to sdNVP without the presence of detectable resistance compromises viral response to triple therapy.⁹ It is generally agreed that where possible resistance should be minimised. One way of doing this is to avoid NVP altogether. An alternative approach presented at the conference is to provide a short course of Combivir, started simultaneously with maternal sdNVP to cover the 'tail' of the prolonged NVP plasma half-life.¹⁰ A study sponsored by Boehringer-Ingelheim, the manufacturers of NVP, and undertaken in South African hospital settings tested the hypothesis that the addition of intrapartum and postpartum Combivir (a fixed dose combination of AZT and 3TC) would reduce maternal NNRTI resistance. Preliminary results of this randomised open-label trial (Table II) providing Combivir post sdNVP to reduce resistance suggest that it is effective in reducing maternal genotypic resistance when compared to sdNVP alone.

TABLE II. MATERNAL RESISTANCE BY TREATMENT ARM^a

Arm	Presence of resistance (%)	
	2 weeks	6 weeks
sdNVP	9/18 (50)	9/18 (50)
sdNVP, Combivir 4 days	120 (5)	4/43 (10)
sdNVP, Combivir 7 days	3/23 (13)	

Owing to the marked reduction of genotypic resistance in the two Combivir-containing arms, the trial was amended and randomisation to the sdNVP-only arm was stopped. The trial will continue to enrol pregnant women into the two Combivir-containing arms in an attempt to determine the better duration of Combivir cover.

NVP, resistance induced by sdNVP and the ongoing interactions between activists, the South African Medicines Control Council and researchers dominated the news reporting of this conference both in South Africa and internationally. The precipitant for this was a media release emanating from the MCC headlined 'MCC no longer recommends the use of monotherapy in preventing mother to child transmission.'¹¹ This was interpreted as a signal of the imminent deregistration of NVP as monotherapy in South Africa for MTCT, and created concern that the PMTCT programme in South Africa was in jeopardy. The Treatment Action Campaign (TAC) then convened a meeting where a

TABLE III. MEASURES OF UPTAKE OF VCT IN LILONGWE, MALAWI¹⁵

Method of HIV testing	Attendance at post-test counselling (%)	
	Acceptance (%)	Attendance at post-test counselling (%)
ELISA	37	78
Rapid testing algorithm	80	98

joint press statement from UNAIDS, UNICEF and the Elizabeth Glazer Paediatric AIDS Foundation was read.¹² This meeting was also addressed by representatives of TAC, Médecins Sans Frontières and the UN Secretary General's special envoy for HIV/AIDS in Africa, Stephen Lewis, who expressed concern that yet another South African NVP spat was diverting attention away from more serious issues of the HIV epidemic. A day later, when the registrar of the MCC clarified the MCC position it became clear that deregistration of NVP was not imminent. Whether this was despite or as a result of the TAC, UN and EGPAF action was unclear.

PMTCT ARVs AND ADVERSE EFFECTS

The impact of maternal AZT on fetal and infant growth in 1 265 infants was assessed in Thailand.¹³ After adjusting for a variety of potential confounders, the researchers reported that the duration of maternal AZT was statistically significantly associated with increased weight and height at birth. This association persisted for up to 18 months of age, independent of gestational age at birth. Maternal AZT was started at 28 or 35 weeks' gestation and babies received either 3 days or 6 weeks of AZT after delivery.

However, the use of ARVs is not without risk. A single case report¹⁴ from the US of an HIV-uninfected baby with extreme hypotonia whose mother was treated with AZT-containing HAART and who was given 6 weeks of AZT after delivery provides isolated evidence of potential toxicity of ARVs. Muscle biopsy showed mitochondrial abnormalities that were attributed to NRTIs.

RAPID HIV TESTING v. ELISA

Rapid testing is gaining acceptability and is of great value in the antenatal clinic where one visit may be the only contact a pregnant woman has with the health service before delivery. A report from Lilongwe¹⁵ confirmed the powerful effect of an immediate HIV result on uptake of VCT. This group compared the acceptance of HIV testing and the rate of attendance at post-test counselling in two groups:

1. Pregnant women who were HIV tested using an HIV-

ELISA with results obtainable some days later.

2. Women who were able to access a rapid testing algorithm with same-day results.

They used the periods before and after the introduction of rapid testing as comparison periods. The results are summarised in Table III.

In another report from Kigali, Rwanda,¹⁶ where rapid tests, infant formula and NVP have been made available in the PMTCT programme, 98% of pregnant women accepted a rapid HIV test of whom 79% attended a post-test counselling session. Of the 21% found to be HIV-infected, 91% took NVP. Notwithstanding the simplicity of the NVP-based PMTCT regimen, an abstract from Malawi¹⁷ showed that despite high uptake of VCT less than half the HIV-infected women in their programme were handed a tablet of NVP by 36 weeks of gestation and only 34% of the newborns of HIV-infected mothers received a dose of NVP.

In keeping with the theme of 'Access for all', it was gratifying to note the large number of abstracts that summarised the experiences of numerous PMTCT programmes documenting the cascade. Several abstracts from throughout Africa reported on the drop-off in the PMTCT cascade from acceptance of counselling to maternal receipt of NVP. All of them reported rates of maternal HIV-infection of greater than 15%.

EFFECTIVENESS OF PMTCT PROGRAMMES

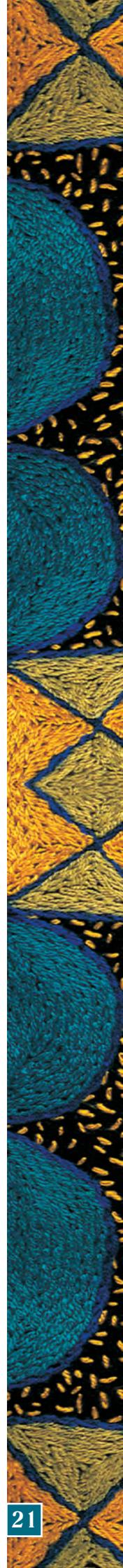
Few data were presented on the effectiveness of PMTCT programmes in preventing HIV transmission when implemented on a large scale. A multi-centre collaborative study from Brazil,¹⁸ where ARVs are provided free of charge to HIV-infected people, reports data from 63 sites in Brazil for the years 2000 - 2002. The overall MTCT rate of HIV was 6.8%. Ninety-two per cent of the infants received AZT. Higher rates of transmission were reported in women who breast-fed, had a vaginal delivery, and took ARVs incorrectly.

These summarised abstracts represent the papers on MTCT which we believe had the most impact at the conference. Further work on infant feeding and programmatic experiences added to the knowledge base. A searchable archive of all abstracts presented at the Conference (eJIAS abstract finder) is available at <http://www.aids2004.org/>.

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ANTIRETROVIRAL RESISTANCE

Highlights from the XV International AIDS Conference, Bangkok,
11 - 16 July 2004

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Over the past decade, the International AIDS Conference has evolved from a purely scientific event into a reunion of the international family of HIV researchers, policymakers and care providers. The recent meeting in Bangkok boasted a wide-ranging programme that attempted to cater for the diverse interests of around 19 000 delegates. Achieving this objective in the limited time available is a daunting challenge for even the most skilled conference organiser. This year it meant that delegates had to be satisfied with small amounts of new information on a multitude of topics.

The worldwide increase in the prevalence of antiretroviral resistance is of particular concern to researchers and practitioners. Since resistance remains one of the most significant threats to the long-term success of any highly active antiretroviral therapy (HAART) regimen, practitioners are anxious to learn from past mistakes, translate new knowledge into appropriate treatment strategies and develop new drugs that retain useful activity in the face of established resistance.

The conference programme emphasised three major areas related to resistance: (i) concerns regarding non-nucleoside reverse transcriptase inhibitors (NNRTIs), (ii) reassuring data on certain protease inhibitors (PIs), and (iii) development of new agents with potential clinical utility for treating resistant virus.

NNRTI RESISTANCE

Considerable emphasis was placed on the selection of resistant virus when using an NNRTI to prevent mother-to-child transmission (MTCT) of HIV. Since nevirapine (Viramune) is the current agent of choice in this setting, the spotlight was brightly focused on this compound. It is important to emphasise three important facts in this regard. Most MTCT prevention strategies currently used in resource-constrained environments employ regimens that are known to have suboptimal virological efficacy. The

selection of NNRTI-resistant virus should therefore come as no surprise. The consequences of suboptimal nevirapine use are probably not unique to this agent, and are very likely to emerge with the suboptimal use of any other NNRTI.

Researchers from the conference's host country¹ presented data on the emergence of resistance among Thai women given zidovudine (AZT) monotherapy from the 28th week of pregnancy followed by single-dose nevirapine during labour. AZT resistance was subsequently documented in 5% and NNRTI resistance in 41%. HIV subtype AE accounted for the majority of infections; the G190A and the K103N mutations were most commonly identified. G190A mediates high-level phenotypic resistance to delavirdine (Rescriptor) and nevirapine, whereas K103N confers high-level phenotypic resistance to all currently available NNRTIs. Of interest was the high proportion of NNRTI-resistant viruses (28%) with multiple resistance mutations.

Until recently, opinion has varied on the long-term consequences of selecting NNRTI-resistant virus by single-dose, or short-course MTCT interventions. Dr Marc Lallement provided sobering information in this regard.² He described the outcome of HAART among 221 women who had participated in the Thai Perinatal HIV Prevention Trial (PHPT). All had previously received nevirapine and were allocated to a regimen of stavudine (d4T), lamivudine (3TC) and nevirapine. After 6 months of medication only 47% had achieved full virological suppression (viral load < 50 copies/ml). Thirty-two per cent of women had nevirapine-resistant virus.

A novel strategy to avoid maternal exposure to nevirapine might be administering the drug to the newborn as post-exposure prophylaxis (PEP). Researchers from South Africa³ reported on the outcome of administering nevirapine as PEP to 23 HIV-infected infants (PEP group); they compared this with the outcome among 30 infants who were given single-dose nevirapine at birth and whose mothers received single-dose nevirapine during labour (standard group). In the standard group, 11/30 (37%) of infants

developed NNRTI resistance (all with the Y181C mutation that causes high-level resistance to nevirapine and delavirdine, and low-level resistance to efavirenz) compared with only 3/23 (13%) in the PEP group. Curiously, only the Y188C mutation (that mediates high-level resistance to nevirapine and delavirdine) was found in the latter group. These results require confirmation in larger studies but suggest that innovative strategies for using nevirapine in a non-HAART setting may result in significantly lower rates of NNRTI resistance, perhaps with different genotypic resistance profiles.

A final aspect of NNRTI resistance is the question of how this phenomenon might affect the success of programmes currently being rolled out in developing countries. HAART regimens comprising AZT or d4T, plus 3TC, plus nevirapine or efavirenz (Stocrin) are recommended as the preferred first-line regimens in many guidelines. These combinations are purported to be safe, effective and affordable, and are often prescribed as fixed-dose, generic drug combinations. The potential weakness of this approach is that both 3TC and the NNRTIs have a low genetic barrier to resistance. Data from our own centre⁴ documented a treatment failure rate (viral load > 1 000 cp/ml) of over 20% within the first 12 months of therapy, despite apparently good treatment adherence. Genotype analysis of these predominantly clade C viruses showed that single-drug resistance was rare. Over 90% of patients failing therapy harboured virus with resistance to multiple drugs including both nucleoside reverse transcriptase inhibitors (NRTIs) and NNRTIs. Since a patient's initial HAART regimen is the one associated with the greatest chance of treatment success, the universal use of NNRTI-based regimens as first-line therapy warrants in-depth evaluation and wider debate.

PIs AND RESISTANCE

Lopinavir/ritonavir (Kaletra) received the lion's share of the scant information on this important topic.

One of the benefits of PIs is their higher genetic barrier to resistance. Long-term follow-up data on patients from several sites in the USA⁵ confirmed the impressive durability of treatment response to lopinavir/r and a remarkably low rate of resistance among patients followed up for over 5 years. Of an original group of 100 patients enrolled in the 720 Study (stavudine, plus lamivudine, plus lopinavir/r) 68 have remained on their allocated therapy for a median of 5.4 years. Thirty-two have discontinued therapy, 13 because of adverse events and 19 for other reasons; none have stopped treatment because of lopinavir/r resistance. Sixty-four of the 68 patients who remain on treatment have viral loads < 50 copies/ml, 3

have viral loads of 50 - 400 copies/ml and only 1 has a viral load of > 400 copies/ml. Resistance testing has confirmed the presence of the M184V mutation in 3 of these individuals (i.e. 3TC resistance). Minor mutations have been documented in the protease gene sequence of 6 individuals. None of the mutations detected are recognised as causing lopinavir resistance.

Because of the dominance of clade B virus in the developed world, considerable attention has been devoted to studying this subtype. Globally, however, the majority of HIV infections occur in the developing world and these are due to viruses belonging to other subtypes. Recently evidence has emerged suggesting that resistance to certain antiretroviral agents might evolve along different pathways among clade B versus non-clade B virus. This is particularly relevant to the clinical use of PIs. Information from Brazil⁶ added to the growing body of knowledge on this important aspect of antiretroviral resistance. Subtype C virus (which is also the most prevalent subtype in southern Africa) frequently has a natural polymorphism at codon 93 in the protease gene known as I93L. This appears to render the virus more susceptible to lopinavir/r. In addition, subtype C virus is unusual with regard to nelfinavir (Viracept) resistance. Among clade B virus, nelfinavir resistance is due to the selection of the D30N mutation; this confers little cross-resistance to other PIs, permitting the practitioner and patient to use PIs in a specific sequence. For this reason, nelfinavir has been widely advocated as the preferred initial PI in Europe, North America and Australia. Clade C virus, however, is much more likely to develop nelfinavir resistance via the L90M mutation. In contrast to D30N, L90M mediates extensive cross-resistance among the PIs. For treating clade C virus nelfinavir is ranked equally with other, older unboosted PIs with regard to its resistance profile.

A disappointing omission from the conference programme was the lack of new data on the novel, once-daily PI atazanavir (Reyataz). Atazanavir has been approved for use in many parts of the world. Registration in South Africa is anticipated later this year, or early in 2005. In treatment-naïve patients, atazanavir resistance has been associated with a distinctive mutation known as I50L. This confers no cross-resistance to other PIs, suggesting that atazanavir could have an important role as first-line PI therapy. To date, however, clinical trial data suggest that atazanavir is less potent than lopinavir/r. Many authorities therefore recommend combining atazanavir with another PI such as saquinavir, or boosting its pharmacological activity by the concomitant administration of low-dose ritonavir. Information is eagerly awaited on the impact that these strategies will have on the evolution of PI resistance.

NEW AGENTS FOR TREATING RESISTANT HIV-1

Data on two new agents, enfuvirtide and F-ddC, brought bad news and good. Enfuvirtide (Fuzeon) is the first entry inhibitor to enter general clinical use. Because of limited manufacturing capacity and cost, enfuvirtide has generally been reserved for treating patients with multi-drug-resistant virus. Data from Canada showed that virus from 40 of 41 patients under treatment with this agent developed a recognised enfuvirtide resistance mutation after as little as 8 weeks of therapy. Several patients had virus with multiple enfuvirtide mutations and/or novel mutations affecting the drug's site of action. This disappointing information suggests that enfuvirtide may be useful only when used as part of a maximally suppressive HAART regimen. The current practice of reserving its use for deep-salvage therapy may need to be revised. By the time the next International Conference on AIDS comes around, there should be early clinical data available on the new oral fusion inhibitors, particularly the novel CCR5-receptor blocker from Pfizer.

F-ddC (Reverset), a new cytidine analogue that inhibits HIV-1 reverse transcriptase, was reported to be effective in early phase II studies that recruited both treatment-naïve and experienced patients.⁷ On average, viral loads dropped by >1 log in the treatment-naïve group and 0.8 log in the treatment-experienced group. Larger studies have been initiated in the USA and Europe. Preliminary results will be released early next year.

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LETTER • LETTER • LETTER • LETTER • LETTER

To the Editor: In response to the overwhelming number of patients presenting with oral lesions associated with HIV infection at our local clinics and hospitals in KwaZulu-Natal, a group of oral hygienists in the public sector have developed a 'mouth care pack' initiative and flip chart training guide.

As the hygienist's scope of practice is limited the initiative is very practical and can be implemented at any level of care, from hospitals to home-based care.

Fundamentally the mouth care pack contains: a toothbrush and toothpaste, bicarbonate of soda (to make a mouthwash), chlorhexidine gluconate (0.2%) mint-flavoured mouthwash, antibacterial soap, disposable cups, and an instruction leaflet in English and Zulu.

An investigation at St Apollinaris Hospital, Centocow, proved that a patient's toothbrush is a vehicle for transmission and re-infection of the mouth with many bacterial and fungal conditions, particularly oral thrush. Disinfecting the toothbrush with chlorhexidine, sodium hypochlorite or antibacterial soap and correct storage are

most important in the management of patients' oral health.

Packs are available for adults and children. The main difference is in the size of the toothbrush, and packs are packaged and dispensed by pharmacies. The packs have been used very successfully, even for babies. The mouthwash is applied using dental cotton wool rolls.

Fresh lemons are an adjunct to the treatment and lemon water is offered to patients as part of their total oral health care routine and to maintain hydration.

A power point and slide presentation have been completed and our oral manifestations of HIV flip chart is being produced and will be utilised in training and distributed to all clinics within the province.

I would be pleased to offer further details.

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THAI ME UP, THAI ME DOWN — THE XV IAS CONFERENCE IN BANGKOK

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A strong Rand, June heat, a beautiful country, and a fun and vibrant city — it doesn't get much better. Nearly 20 000 delegates attended the 15th International Aids Society (IAS) Conference in Thailand. They came to hear the latest updates from the scientists, activists and policy-makers, network with collaborators, sample the local Asian cuisine, and try to get 'One Night in Bangkok' out of their heads.

Bangkok is hot, bustling and polluted, with traffic from hell; it's also fun, vibrant, friendly and safe, with everything from glorious developed-world infrastructure, to a strong sense of culture and vast shopping plazas. Huge numbers of Southern African government health officials, researchers and HIV programme implementers descended on the city, desperately seeking refuge from an African winter.

This review of the conference doesn't do justice to its full depth or breadth, with around 15 different interest streams operating concurrently, but I hope it captures a few of the highlights, especially where southern African researchers contributed significantly to the programme, or where research directly informs our situation.

THE GLOBAL SUPERSTARS

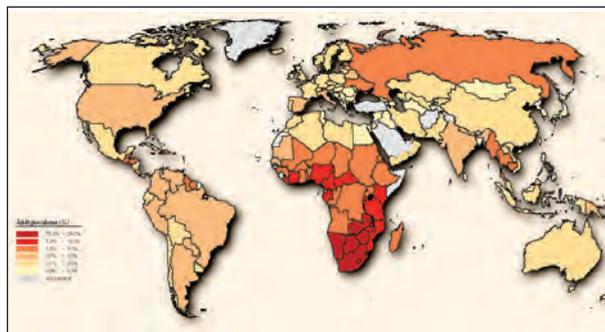
Richard Gere is an unlikely figure to preach safe sex, but that's what he did. The *American Gigolo* star shared a platform with Miss Universe 2004 (Australian Jennifer Hawkins in case you don't follow these things), significantly undermining controversial abstinence programmes, according to many slightly breathless onlookers. Add Ashley Judd, Dionne Warwick and Rupert Everett, and we had a mini-Oscars event.

AIDS conference veteran Madiba, attending his third consecutive conference, laid down the gauntlet, emphasising that he had retired but could not rest until he felt AIDS was being addressed with the urgency it deserved. 'Please let me enjoy my retirement', he pleaded with

delegates, 2 days before his 86th birthday. His wife Graca Machel played an extremely active part throughout the programme, much to the delight of celebrity watchers.

Peter Piot, the charismatic leader of USAIDS, and Richard Feacham, head of the ambitious Global Fund, made upbeat presentations, listing strong, new and novel programmes and partners, and stressing renewed commitment from governments and treatment partners. However, the UNAIDS data were worrying (<http://www.unaids.org/bangkok2004/report.html>), confirming previous data showing limited impact of prevention programmes on a regional level in sub-Saharan Africa, and the disastrous increase in new infections in Asia and Russia. There was also a strong indication that prevention programmes were failing in high-risk groups in developed countries, along with a steady increase in viral resistance to drugs.

No AIDS conference is complete without a nevirapine (NVP) public relations crisis imported from South Africa. The Minister of Health, popping in to open the South African stall at the Conference, was reported as announcing the deregistration of NVP for mother-to-child transmission (MTCT), with a pointed jibe at activists that this confirmed her previous view that the drug should never have been used for MTCT. NVP resistance post-MTCT was the focus of a large part of the Conference, and the spat attracted plenty of international media and research interest. A hastily convened press conference chaired by a visibly



UNAIDS figures revealed little to celebrate, with big increases in Asian and Russian numbers.

weary Zackie Achmat from the Treatment Action Campaign (TAC), recently nominated for a Nobel Peace Prize, provided a vibrant debate on the NVP issue, as well as the status of the national antiretroviral (ARV) roll-out. Many senior government health representatives attended the session, and participated in the discussion. Eventually, it was clarified that there was no plan to deregister the drug, and that the Medicines Control Council (MCC) was simply recommending against monotherapy with NVP for MTCT, a position no one could argue with. Dr Precious Matsotso, the hard-working head of the MCC, clarified the issue of deregistration calmly, saying that it was the MCC's responsibility and not that of the minister to deregister the drug. Other government officials also reassured the audience that there was no plan to stop the NVP MTCT implementation programme. The ideal treatment for MTCT is highly active antiretroviral therapy (HAART) – NVP monotherapy acknowledges that we do not have the human resources or infrastructure to provide HAART to all pregnant women with HIV in southern Africa.

CONFERENCE ACTIVISM

The Conference played host to a huge variety of interest groups, and international governments, pharmaceutical companies and donors were attacked at many levels for not doing enough, doing it wrong, or not doing it in a co-ordinated fashion. The USA in particular provided a lightning rod for many perceived wrongs in the HIV world. One senior journalist bemoaned the fact that he had to keep apologising for being American: 'I feel like a white South African in the 1980s!' A diverse group of activists, researchers and community groups attacked PEPFAR (the Presidential Emergency Program for AIDS Relief), the huge HIV relief fund initiated by President George Bush, with allegations of American protection of multinational pharmacy patent rights, criticism of the focus on abstinence and monogamy, and perceptions of a challenge to the efficacy of condoms. Some issues raised by activists that were not US-related were straight from the headlines, while other activist issues seemed curious to African observers – the demand for access to obscure ARVs, the perceived ethical problems with using tenofovir for prevention of HIV in sex workers highlighted by Paris ACTUP, and the strong focus on intravenous drug abusers. Ugandan President Yoweri Museveni did not help clarify things, in a peculiar plenary speech that seemed to undermine condom use and promote a very old-fashioned view of morality. The head of PEPFAR, Randall Tobias, bravely faced a loud group of protestors, and strongly defended the PEPFAR goals, pointing out that the USA gave more to AIDS than all the other donor nations combined. He defended the allocation of one-third of the PEPFAR

prevention budget to abstinence programmes, pointing out that this approach was successful in Uganda. He said that he knew condoms prevented HIV, which he had been reported as questioning in the past. The National Institute of Health (NIH)'s Tony Fauci, who walks on water among HIV researchers, said that he thought the USA's approach was 'good housekeeping'. This did not stop senior officials, including UN Secretary General Kofi Annan, French president Jacques Chirac and Stephen Lewis, special UN envoy on AIDS in Africa, from criticising the USA on various fronts, including the fact that PEPFAR limits its support to only a few affected countries.

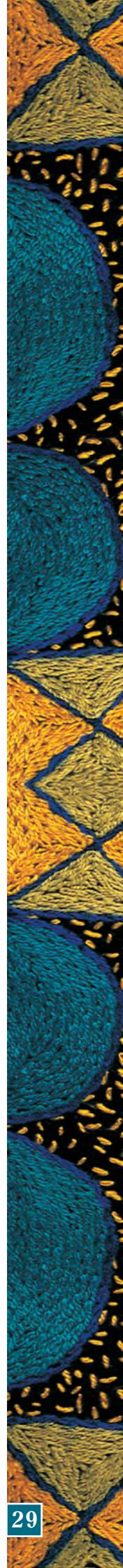
For those interested in the political aspects of HIV, it was a feast. Other attendees grumpily maintained that the science was being undermined by the 'soft' issues. HIV continues to be a showcase for the world's inequalities and social challenges, and solutions to these are not immediately forthcoming. Science purists may have to give future conferences a miss. It's a messy disease to manage, and no organiser was going to please the dozens of interest groups attending.

WHO LET THE DOGS OUT?

Developing-world public health workers breathed a huge sigh of relief as a diminutive investigator (who was later given an award for excellence at the closing ceremony) compared the World Health Organisation (WHO)'s 3 by 5 Initiative-recommended drugs with other regimens used in California (Abstract MoOrB1082). The WHO recommends combinations, using nucleoside backbones of stavudine (d4T) or zidovudine (AZT), with lamivudine (3TC), with either efavirenz or nevirapine. The study demonstrated that the WHO's choices were the best performers, significantly outperforming alternative regimens using other nucleosides and protease inhibitors (PIs) in terms of survival. South African adult treaters sat feeling particularly smug, as the regimen selected for South Africa's roll-out as first-line therapy, d4T/3TC and efavirenz, received the accolade of 'best on test!' However, Harry Moultrie, Baragwanth Hospital's paediatric doyen, correctly pointed out that there was a period where clinicians started patients who were more ill on PIs, which may actually explain the survival difference. The WHO will have to move fast to achieve its goal of treating 3 million people with ARVs in the next 18 months, good drug choices or not, as Jim Kim, head of the WHO's team tasked with this, admitted.

MOTHER-TO-CHILD-TRANSMISSION (MTCT) TAKES CENTRE STAGE

The South African Health Minister initiated the MTCT debate, but hard scientists quickly took centre stage. The



WHO released new and widely welcomed guidelines at the Conference (<http://www.who.int/mediacentre/releases/2004/pr50/en/>). Lynn Morris, from the National Institute for Communicable Diseases and South Africa's leading resistance expert, presented the first long-term data showing that resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) persisted for up to 6 months in women exposed to NVP single dose (sdNVP), particularly those with high viral loads and low CD4 counts (Abstract ThOrB1353). At the end of the talk she stressed that this was not a reason to avoid using the drug, and that the clinical implications of the resistance mutations were yet to be fully documented. The much-quoted Thai trials, showing efficacy of NNRTI-containing regimens in mothers exposed to NVP MTCT (presented at the Conference on Retroviruses and Opportunistic Infections in February 2004) were discussed in a plenary session, and the results appeared to be less alarming than previously thought. James McIntyre showed fascinating data in a late breaker session, demonstrating that adding AZT/3TC for a limited time after NVP monotherapy could reduce the chances of NNRTI resistance (Abstract LBOB09). Prevention of maternal transmission began to launch into the downright peculiar, as breast-feeding grandmothers graced the late breaker presentation as a way of avoiding exposure to infected mom's milk.

As a separate review of the state of MTCT will be published in this issue, it will not be covered further here.

KALETRA, LAMIVUDINE AND MONOTHERAPY/ DUAL THERAPY HERESIES

The quest for simpler and safer regimens continued, with exciting and novel approaches to treatments emerging, challenging the holy grail of 'triple therapy'.

Kaletra (lopinavir/ritonavir – the ritonavir is used in low doses (with minimal antiviral effect) to 'boost' the blood levels of the lopinavir) had the sort of glowing reviews we last saw for efavirenz a year ago at the Paris IAS Conference. Kaletra has a resistance barrier that drug developers dream of. Data presented at the Conference showed no resistance to the drug after 5 years of treatment – patients on regimens containing Kaletra developed resistance to the other drugs in their regimens, but not to Kaletra (Abstract WeOrB129). This is unique in the antiviral world, where all other drugs exhibit distinct resistance profiles. But even resistance to the other drugs was rare in this study. As if things couldn't get any better, it now appears that we may be able to use the drug once daily, and the company has applied internationally for QD registration. The remaining major concerns with Kaletra are its ability to cause lipodystrophy, and the fact that it melts in African heat.

But a Texan dramatically upped the ante (Abstract MoOrB1057). In a fascinating and frankly scary presentation, Dr Gathe from Houston challenged a decade-long heresy – monotherapy for infected patients. He treated 30 patients with Kaletra monotherapy, with CD4 counts from 7 cells/ μ l to over 400 (average 169 cells/ μ l), and many with high viral loads. Ten fell off for reasons of toxicity, non-adherence, etc., but 20 had viral loads of below 400 copies/ μ l after 48 weeks of treatment. Eighteen of these had viral loads below 50. Commentators flocked to urge caution, but a new can of worms has been opened forever. His 24-week data had been greeted at a previous conference with a 'wait and see' attitude. Now may be the time to design the big trials that may change the way we do the business of ARVs.

Other presentations looked at 'deintensification', a treatment concept similar to that used in oncology, where you use aggressive treatment at the start to contain the virus, and then once the viral load is low and viral resistance presumably unlikely, the regimen is simplified to a single drug. Patients with undetectable viral loads on ARVs were randomised to dual therapy with tenofovir/efavirenz or to the same two drugs plus 3TC. No difference between the two arms has yet been seen (Abstract TuPeB4493), although the trial has not been completed. Another used the redoubtable Kaletra as monotherapy in patients on successful ARVs, with excellent results (Abstract TuPeB4577).

The meek and mild 3TC still has not had its role as a viral 'weaker' clarified. The unusual M184V mutation associated with the drug causes the virus to be less 'fit', suggesting a role in deliberately inducing the mutation, by giving 3TC monotherapy, in a bid to decrease the destructive power of the virus. A small Italian study of patients failing conventional ARVs showed that people given monotherapy had slower decreases in CD4 and lower viral loads than those not given it (Abstract WeOrB1286).

But the bottom line remains – this is an exciting but completely unconfirmed area. Do not try this at home! Several clinicians have used Kaletra as monotherapy locally, and the evidence to do this is still very dicey – currently it should not be done outside of a research environment. Several case reports, the first of which came from Johannesburg,² have reported resistance to Kaletra, and particularly worrying is the occurrence of naturally resistant mutations in subtype C virus, the most common clade in southern Africa.

Efavirenz was not to be denied as the ARV poster-child. Data up to 4 years showed it to be a remarkably effective as part of a HAART regimen, even in people with high viral loads, and with very little toxicity (Abstract TuPeB4547).

Despite its low resistance barrier, it continues to be an excellent clinician and patient first choice as part of their ARV regimen.

NEW AND OLD DRUGS, OLD PROBLEMS

It is difficult not to be cynical about the development of new drugs. Every HIV conference seems to have dozens of new candidates paraded, only for them to disappear quietly off the scene when newly recognised toxicity or poor efficacy is realised. However, there were a few interesting developments.

Reverset (D-D4FC), a new nucleoside, shows excellent antiviral activity in a presentation given by Midwestern's Rob Murphy, with potential to be used in patients with resistance, and no side-effects in initial studies. It is now poised to go to phase 2b studies (MoOrB1056). Another PI, fos-amprenavir, showed good efficacy in people with multi-drug resistant (MDR) HIV (MoOrB1055). The much-awaited chemokine receptor-5 (CCR) blockers had a very low-key conference (Abstract WePeB5725).

The new PI, atazanavir, continued its cardiovascular darling status among PIs, with further data that the metabolic concerns afflicting other PIs are less of an issue with this drug (Abstracts ThOrB1355, ThOrB1356). Interestingly, there were still no data showing that metabolic consequences translate into clinical events, although one study showed increased atherosclerosis with PIs compared with NNRTI-containing regimens (ThOrB1355). It has become increasingly apparent that it is not only the PIs that can cause metabolic problems, and a study (Abstract ThOrB1360) demonstrated that the (now rarely used) combination of d4T/didanosine (ddl) causes significant lipodystrophy and metabolic changes previously thought to be specific to the PIs. An alarming study showed that length of time on ARVs correlated with the risk of eclampsia and fetal death, though reassuringly among the over 400 women studied there was no MTCT (ThOrB1359). ARVs seem to spare no organ, and bone came in for a pasting in a study (Abstract ThOrB1358) demonstrating convincingly in a multivariate analysis that length of time on ARVs strongly correlated with the incidence of osteonecrosis. Some commentators have noted that HIV-infected people get a peculiar form of accelerated aging, as part of their clinical profile – strokes, heart attacks and crumbly bones are a concern, although still not yet a clinical reality.

Once-daily dosing of ARVs seems to be the way to go for the developed world, with much attention being given to a regimen of combined tenofovir and emtricitabine taken with efavirenz. HAART delivered by 2 pills taken once daily was the stuff of dreams 5 years ago, but the surrounding

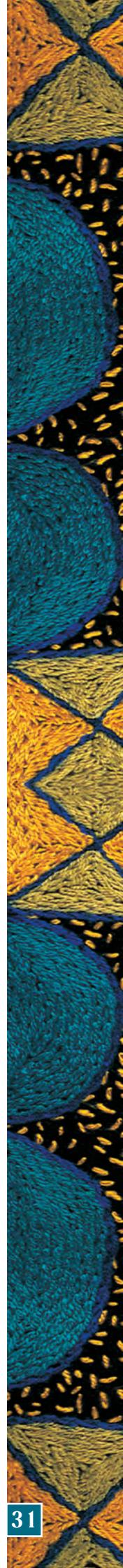
hype seemed slightly unreal given the ARV access issues in Africa.

Resistance continued its bogeyman status, with disturbing data showing resistance occurring in people on ARVs in three-quarters of patients with viral loads below 1 000 copies/ml (Abstract WeOrB1293.). But it is unclear how much clinical panic this should generate, as the gap between viral resistance and clinical outcomes appears to be more complex than previously thought. Studies treading the boundaries of resistance, using off-on approaches to ARVs, had variable results, with one trial having to be stopped because of major resistance.

CLINICAL PROBLEMS AND OPPORTUNISTIC ILLNESSES

This area continues its orphan status in the international HIV conference circuit. Few presentations dealt with African experiences of these diseases, although there was further confirmation that efavirenz 600 mg can be used in conjunction with conventional rifampicin-containing tuberculosis (TB) regimens (Abstract MoOrB1013). Some clinicians have previously used 800 mg, as some studies have suggested that efavirenz levels are decreased in association with rifampicin, but this study showed no difference in blood levels of efavirenz at the different doses, and excellent 38-week viral outcomes. Unfortunately, the study was done in Thais, who are smaller than people in most other nations, with an average weight of 50 kg in the study. Efavirenz's reputation as a 'TB-friendly' ARV continues, although stronger evidence for this and for the use of other drugs would be welcome to people working in high TB prevalence areas.

The thorny issue of smear-negative TB, a huge headache for clinicians in countries where diagnostic resources are lacking, was tackled in a poster looking at using a 'syndromic approach', using clinical and simple laboratory criteria to identify patients with probable TB (Abstract MoPeB3229). The model proved robust, confirming the approach many clinicians are guiltily using – treat patients with symptoms suggestive of TB and see if they get better, before breaking out the expensive or invasive diagnostics. The model may help to formalise this. The prolific Gavin Churchyard, from Aurum Research in South Africa, provided several interesting studies on TB, including one that showed a 5% incidence of TB among mine workers after starting ARVs, despite prescreening (MoPeB3213). Another study from his group showed that oral thrush was a strong predictive factor for immediate severe HIV-related illnesses (MoPeC3392), and that perhaps making it a WHO-4 staging event may be merited.



An interesting study showed that HAART decreases the incidence of opportunistic infections, independent of the CD4 count, suggesting that the CD4 count may not be as robust a marker of immune recovery as it is of immune deficiency (Abstract TuPeC4719).

A remarkably high level of immune reconstitution inflammatory syndrome (IRIS) was seen in a cohort of Thai children commencing ARVs, confirming early anecdotal reports from paediatricians working in South Africa's ARV roll-out (Abstract TuPeB4404). Twenty-four children developed the syndrome out of 95 starting ARVs. The syndrome appeared early (within 3 weeks), and included cases of mycobacteria, herpes and, curiously, cryptococcus, which is reported to be rare in children. Four children died as a result of the syndrome. As expected, the lower the CD4 count, the higher the risk of IRIS.

As has been shown in many cohorts, 'late presenters' (CD4 < 50 cells/ μ l) are still common even in the developed world. A study from the UK showed that these patients place a huge strain on hospital resources in the first 3 months when compared with people presenting earlier, but still did very well on ARVs (Abstract MoPeB3356). The message for us is obviously to redouble efforts to get people tested early and referred quickly to an ARV access point, before they hit the 'late presenter stage'.

Lymphoma treatment for HIV-infected people is much better in the era of ARVs (Abstract ThOrB1403). Patients on ARVs showed a dramatic drop in risk of lymphoma. Those who had lymphomas survived much longer than those who were not previously given ARVs. The thorny question of which drugs to start first (the oncology drugs or the ARV drugs) and what sequencing of treatment should be given, remains a thorny everyday question for clinicians.

A South African study showed increased NVP levels when given with fluconazole, with an increase in hepatotoxicity (Abstract WeOrB1239). This problematic interaction is of concern to southern African clinicians, where use of fluconazole is high. A study comparing amphotericin B with or without an azole (fluconazole or itraconazole) found no benefit in terms of cerebrospinal clearance of cryptococcus or in clinical outcomes (MoPeB3232).

The difficult issue of ARV rationing in Africa was tackled in Abstract MoOrE1072. A distinction was made between explicit rationing (e.g. focusing on specified groups such as skilled workers, students, mothers, households) and the much more problematic implicit rationing currently in force (e.g. 'first come, first served', queuing, not providing transport to distant ARV sites). Implicit rationing creates situations where the elite can queue-jump, undermining efficiency and equity. The need for public debate was

emphasised – the topic will be comprehensively discussed in the *Lancet* later this year.

PREVENTION STRATEGIES

The prospect of a vaccine seemed about as hopeful as the cure for old age. Candidate vaccine corpses have littered the prevention landscape over the last year, and the news that we are years and possibly decades from an effective one was very sobering. Médecines Sans Frontières and a group of scientists headed by the acerbic Robert Gallo, called for the scrapping of the huge Thai vaccine trial currently underway, calling it an expensive flop. Trials of the diaphragm, with and without vaginal microbicides, vaccines, and male circumcision are all interesting but distant public health interventions. Treatment of HSV-2 as an HIV preventive strategy seems very exciting, especially in the light of recent publications suggesting that herpes may be the most significant co-factor driving transmission, with early work starting in South Africa on acyclovir.

CONCLUSIONS

The Conference was frustrating, especially if you don't like the politics or big crowds. More frustrating for us were the surprisingly large number of 'data-empty' presentations, where presenters spoke of their anecdotal experiences rather than presenting analysis of raw data. It does seem that a more rigorous assessment of abstracts is needed, as the good stuff often seems lost in a sea of mediocre presentations, leading frustrated observers to write off the Conference as a waste of time. This would be a pity – this Conference has fundamentally challenged the way we do clinical business. The exciting prospect of simpler and safer ARV therapy seems only a few years away. The next Conference is in 2006 in Toronto. It may not have the buzz of Bangkok, but it will certainly attract the AIDS conference crowd in droves. Here's hoping we won't be discussing NVP this time.

All abstracts, and selected webcasts, are freely available at the IAS website, <http://www.ias.se/>

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IMPACT OF HIV/AIDS ON MORTALITY AMONG THE INPATIENTS AT MOTEBANG HOSPITAL, LESOTHO

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Study design. A retrospective descriptive study of the mortality trend among inpatients at Motebang district hospital in Lesotho.

Aim. To assess the impact of HIV/AIDS on the mortality of Motebang Hospital inpatients from 1989 to 2003.

Rationale. If the hypothesis that AIDS had modified the mortality in a unique way could be confirmed, mortality trends could be used to supplement other methods of estimating the impact of HIV/AIDS such as antenatal and sexually transmitted infections sentinel surveillance.

Methodology. Inpatients' data were collected from January 1989 to December 2003. The 15-year period was split into three 5-year periods (1989 - 1993, 1994 - 1998, and 1999 - 2003) and the diagnoses were grouped into Global Burden of Disease groups I, II, and III. The data were analysed to establish time, gender and age trends.

Results. The mortality rate and number of deaths increased over the 15-year period. Group I (communicable diseases, maternal, perinatal, and nutritional conditions) contributed 69% of all deaths. The rise in mortality was most pronounced in the 15 - 49-year age range, progressively forming a 'bulge' on the death incidence by age curve, with the female peak occurring at the 25 - 29-year age category, 5 years earlier than males. The study found that AIDS-related deaths accounted for 51 - 65% of total deaths and 70 - 80% of group I deaths. Although the number of the inpatients in group II was low, there was evidence of increasing burden from non-communicable diseases. However, the burden from group III (injuries) remained stable.

Conclusion. AIDS modified the mortality trend of the Motebang Hospital inpatients by raising the deaths of younger adults, thereby deviating from the expected natural trend. This implied that mortality data of the hospital provenance can provide information necessary for, *inter alia*, evaluation of the impact of current and future interventions, for instance, the impact of the proposed provision of antiretroviral drugs.

There were 37.8 million people living with HIV/AIDS worldwide at the end of 2003, and 2.9 million had died in the past year. HIV/AIDS is spreading unchecked across Africa and parts of Asia. The African continent has 29.4 million people living with HIV/AIDS, and approximately 4.8 million new infections were recorded in 2003. In Lesotho, national adult prevalence has reached 31%.¹ Lesotho, a developing country in sub-Saharan Africa with a population of 2.057 million, reported its first AIDS case in 1986; however, it had 360 000 people living with HIV/AIDS in 2001.² In 2000, 59% of the reported full-blown AIDS cases were clustered in the 20 - 39-year range and the

majority of HIV-positive cases were young females (aged less than 19 years).³ Estimation of the HIV/AIDS prevalence in Lesotho is based on data from sentinel surveillance of antenatal and sexually transmitted infection clinic attendees,² and reported AIDS cases.³ The estimate could be higher than the actual prevalence according to the Kenya Demographic and Health Survey.⁴

Mortality surveillance using the routine vital statistics and censuses reports can supplement the sentinel surveillance data and methods are available for correcting under-registration and misclassification of deaths,⁵ such as the

Growth Balance Equation by Brass (1975), the Death Distribution Method by Preston and Coale,⁶ and the Age Group Specific Growth Rates Method by Bennett and Hourichi (1984).⁷ Cause-of-death attribution depends on the accuracy of information available at the time of death, postmortem report, diagnostic technology, skills of the clinician assigning the diagnosis, and coding in conformity to a set of specific rules and rubrics such as those specified in the International Classification of Diseases (ICD). The quality of cause-of-death attribution is still of concern.⁸

AIDS-related mortality surveillance proceeds from the premise that there is an increase in the male mortality in the 29 - 59-year range and female mortality in the 20 - 49-year range, with an emergence of a young adult peak, which occurs 5 years earlier among females.^{3,9-11}

METHODOLOGY

The present study was carried out at Motebang Hospital. This hospital, with a capacity of 208 beds and situated in north-western Lesotho, serves Leribe district and is the second largest hospital in Lesotho. From the hospital records, data capture sheets were used to collect data from 1 January 1989 to 31 December 2003. The fields were gender, age, date of admission and discharge, diagnosis and outcome (discharge or death). Medical officers were consulted if abbreviations, representing the diagnoses, could not be deciphered. The data were entered and analysed using the Epi Info 2002 statistical package, and each record was assigned a serial number. The diagnoses were categorised into Global Burden of Disease (GBD) group I (pre-transitional diagnoses consisting of communicable diseases, maternal, perinatal and nutritional conditions), group II (non-communicable diseases), and group III (injuries).

Age was categorised into age ranges that exhibited similar characteristics and were comparable internationally. These ranges were 0 - 4, 5 - 14, 15 - 49 and ≥ 50 years. For the findings to be considered significant, it was predetermined that a trend had to be set and/or each cell had to have at least 150 units. To investigate the time trend, data for each year were used on the death incidence by age curve and a trend was evident. However, for other calculations such as mortality rate, a trend could not be set and most of the cells had less than 150 units. Therefore, the data were grouped into three 5-year periods (1989 - 1993, 1994 - 1998 and 1999 - 2003), which satisfied the predetermined requirements.

The estimate of the 1999 - 2003 mortality attributable to AIDS was computed against the backdrop of the following assumptions:

- The deaths for the period 1989 - 1993 were taken as

baseline as they were assumed to have been largely non-AIDS related.

- Although in absence of HIV/AIDS health improvement gains were expected, it was assumed that difficult economic conditions impacted negatively on social spending, negating these gains.
- HIV/AIDS-related deaths were assumed to be the sum of deaths directly caused by HIV/AIDS, and those that were indirectly related to it. For instance, HIV/AIDS may have shifted substantial focus and resources from other conditions. In addition, children orphaned by AIDS, unlike other children, are more likely to die irrespective of their HIV status.¹²

The study protocol was approved by the Lesotho Ministry of Health and Social Welfare and the University of the Western Cape research ethics committee.

RESULTS

DEMOGRAPHY

A total of 24 328 inpatients were recorded from 1989 to 2003. Females and males accounted for 52% and 48% respectively (Fig. 1). Age was available for 85% of inpatients, recorded as 'adult' for 13.5% and missing for 1.5%. The 0 - 4-year category accounted for the largest proportion (26.5%). The age range decreased to a low level in the 10 - 14-year category before rising to a peak in the 20 - 24-year category and gradually declining thereafter (Fig. 2).

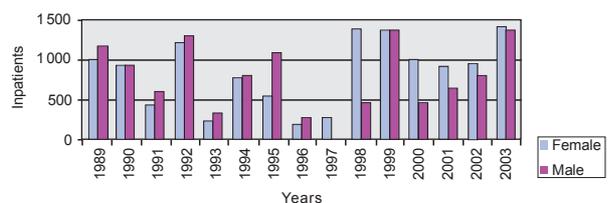


Fig. 1. Motebang Hospital inpatients by gender and year, 1989 - 2003.

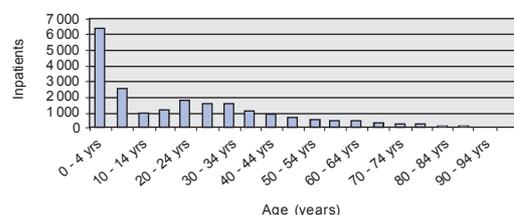


Fig. 2. Motebang Hospital inpatients by age, 1989 - 2003.

MORTALITY

Among all the inpatients, 8.7% died and of these 54.9% were females. The 0 - 4-year category contributed the

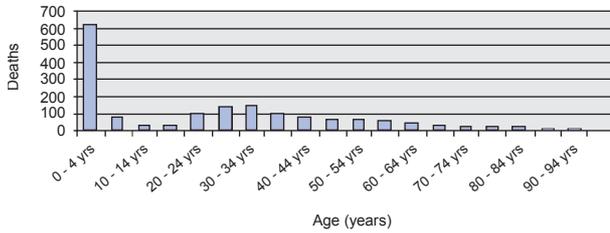


Fig. 3. Motebang Hospital deaths by age, 1989 - 2003.

largest proportion of deaths (29.2%). Mortality then dropped to 1.5% in the age category 15 - 19 years. It then rose to a peak of 7.1% in the age category 30 - 34 before declining gradually (Fig. 3). The 'adult' category contributed 18.7% of the total mortality.

Between 1989 - 1993 and 1999 - 2003, the mortality rate increased by more than twofold (Fig. 4). This increase in mortality progressively caused a bulge between 15 and 49 years. In the first and second periods (1989 - 1993 and 1994 - 1998) the bulge was not as evident as it was in the third period (1999-2003) (Fig. 5). Mortality rate per 1 000 population in the over 50 years category was the highest, followed by the 0 - 4 years, and 15 - 49 years categories. The lowest mortality rate was in the 5 - 14 years category (Fig. 6).

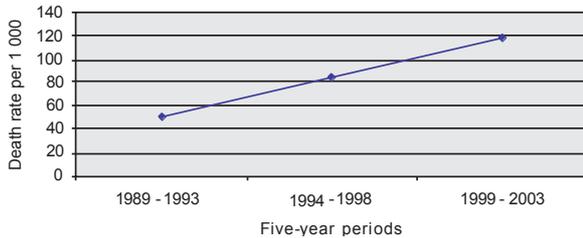


Fig. 4. Motebang Hospital death rate over the three 5-year periods.

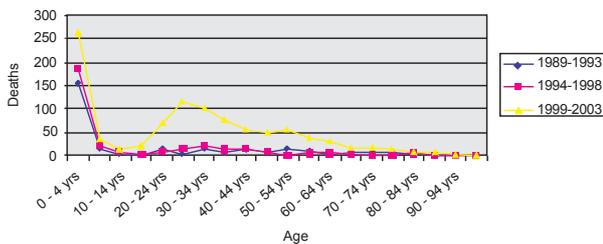


Fig. 5. Motebang Hospital deaths by age and the three 5-year periods.

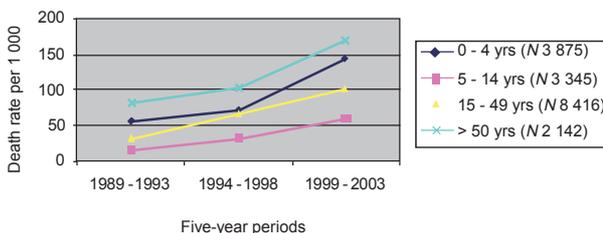


Fig. 6. Motebang Hospital death rates by age and the three 5-year periods.

MORTALITY AND GENDER

There were more deaths among females than males. For inpatients in the 15 - 49-year range, the peak for females was between 25 and 29 years and that for males between 30 and 34 years. The peak for females occurred 5 years earlier than for males (Fig. 7). In the 'adult' category, more males were admitted and there was a correspondingly higher death incidence throughout the study period. Although the mortality rate was higher in the 'adult' category, its male curve mimicked the unique trend of that of males in the 30 - 49-year range. In this range, the male mortality rate curve rose steeply from 1989 - 1993 to 1994 - 1998 and then dramatically declined. The female curves had some similarities in that they were parallel up to 1994 - 1998, and then the mortality rate decelerated (Fig. 8).

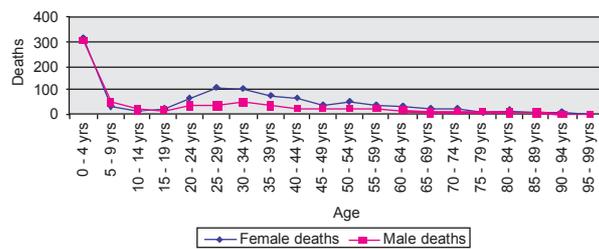


Fig. 7. Motebang Hospital deaths by age and gender, 1989 - 2003.

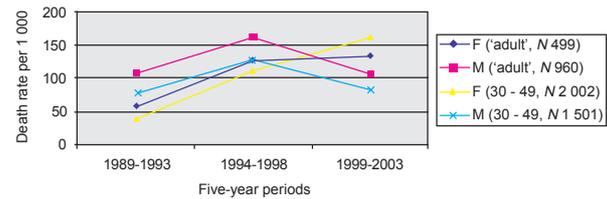


Fig. 8. Motebang Hospital death rates for 30 - 49 years and 'adult' by gender and period, 1989 - 2003.

MORTALITY AND GBD CLASSIFICATION

Groups I, II, and III had 54%, 13% and 30% of inpatients respectively, and the inpatients increased from 1989 - 1993 to 1999 - 2003, except in group III, which showed a slight reduction (Fig. 9). The death rate for group III was the lowest and its increase from 1989 - 1993 to 1999 - 2003 was the least compared with groups I and II. In contrast to

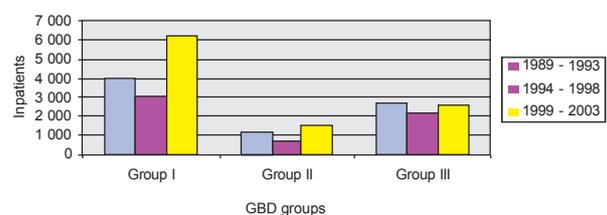


Fig. 9. Motebang Hospital inpatients per GBD group for the three 5-year periods.

the trend in group III, the death rate trends in groups I and II were similar (Fig. 10). When the data for each group in the 15 - 49-year range were excluded from the death incidence graphs, group I exclusion resulted in a deviation from the trend of the total deaths but exclusion of groups II and III did not (Fig. 11).

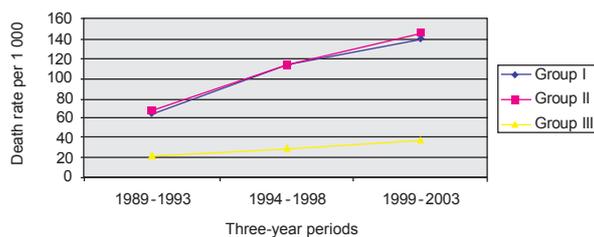


Fig. 10. Death rates in Motebang Hospital groups I, II and III inpatients by 3-year periods.

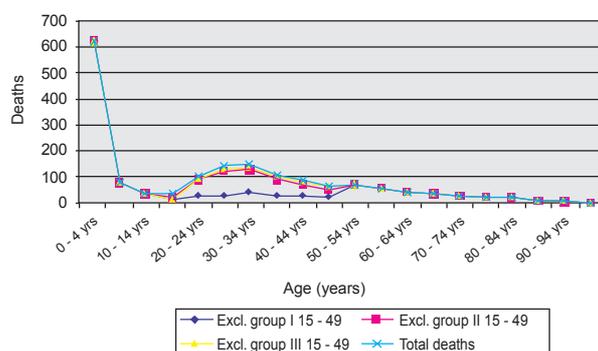


Fig. 11. Motebang Hospital total deaths and deaths excluding the 15 - 49-year group, for each group by age, 1989 - 2003.

DISCUSSION

As was expected, the death incidence was high in the 0 - 4-year category, it then declined through the 5 - 9-year category to a low level in the 10 - 19-year category. However, instead of rising gradually, the mortality rose rapidly forming a bulge on the death incidence curve between 20 and 49 years. Females peaked between 25 and 29 years and males between 30 and 34 years, a 5-year difference. This unusual bulge was completely absent in the period 1989 - 1993, incipient in 1994 - 1998 and clearly evident in 1999 - 2003. In addition, it was limited to group I conditions. The trend exhibited similarities to that of known AIDS-related deaths in Lesotho, Zimbabwe and the ASSA 2000 prediction model, and South African mortality.^{3,9-11} Given that the first case of HIV in Lesotho was in 1986,³ and that HIV-infected people take an average of 10 years (in the absence of antiretroviral therapy) to develop full-blown AIDS,¹³ this peak coincided with the period when AIDS-related mortality had gained momentum. The timing, age range and a trend that mimics that of confirmed AIDS-related mortality in Lesotho³ held AIDS culpable, and this conclusion had been drawn in

South Africa and Zimbabwe, where similar trends have been documented.⁹⁻¹⁰

In this study, the AIDS-related trend was not evident in the first period (1989 - 1993). It started emerging in the second period (1994 - 1998), and was well established in the last (1999 - 2003). The mortality in the first period was therefore assumed to have been largely non-AIDS-related and used as a benchmark. For the period 1999 - 2003, using this benchmark, 51% of all the deaths, and 70% of the deaths in group I, were AIDS-related. These figures rose to 65% and 80% respectively when the deaths were adjusted to account for inpatients discharged to community care. The degree of validity of the adjusted figures can be considered high in view of the facts that data were of hospital provenance, and that communicable diseases, the main subset of group I, contributed 60% of total disease burden in Africa.¹²

Unlike other age groups, group I mortality rates in the 'adult' and 30 - 49-year categories doubled between 1989 - 1993 and 1994 - 1998, after which they dropped to the initial level, although the number of inpatients remained high. This had been observed in a Kenyan national referral hospital¹⁴ and a rural South African hospital.¹⁵ The drop after the second period was more dramatic among males than females. One could speculate that this unexpected trend was related to health care beneficiaries and/or health care providers. It is probable that from 1989 - 1993 to 1994 - 1998 the population had not fully appreciated the impact of HIV/AIDS on their health, and therefore still had confidence in the efficacy of the health services. Consequently, they continued to seek health services and therefore more AIDS patients died in the hospital as the incidence of AIDS rose. However, from 1994 - 1998 to 1999 - 2003, information about AIDS was spreading and diagnoses were being made. Patients and relatives were realising that AIDS was a terminal illness, and they only sought admission for acute conditions and thereafter requested discharge.

Another reason could have been prohibitive cost of a protracted stay in hospital for the majority of patients and their relatives. In addition, social reasons such as stigma associated with AIDS, and intractable and embarrassing conditions such as chronic diarrhoea, could have lowered the threshold for eschewing hospital care. On the other hand, health care provider-related factors could have provided an alternative explanation. The health care providers may have encouraged patients to be cared for at home for two reasons. Firstly, this would have decongested the wards and allowed more patients suffering from other conditions to be admitted. If this were the case, it would have signified a health delivery system that was being overwhelmed by chronic end-stage disease. The risk of collapse of the hospital services had been predicted in the

early stages of the HIV epidemic.¹⁶ This school of thought, however, still lacks empirical corroboration. For instance, a baseline assessment for health sector reform in Lesotho reported a bed occupancy rate of 58%.¹⁷ Besides availability of beds, limitation of other resources could have encumbered hospital services, but a study carried out in a Nairobi hospital in Kenya nullified the hypothesis that hospital services were likely to collapse under the burden of HIV/AIDS.¹⁴ Secondly, the health care providers could have encouraged utilisation of community- and home-based care health services. Whatever the reason, it was clear that many patients were probably dying at home, thus shifting the burden to the nascent community and home-based care.

The death rate of males (in the 'adult' and 30 - 49-year age categories) fell dramatically from 1994 - 1998 to 1999 - 2003, while the decrease for females was not as dramatic. Common factors must have been driving the mortality rate for both males and females; however, it is probable that the maternal conditions were confounding the trend of the female curves. A study found that the maternal death rate variable was proportional to the HIV prevalence variable.¹⁸ Moreover, the 1999 confidential enquiry into maternal deaths of the South African Department of Health stated that AIDS was clearly demonstrated to have a heavy impact on maternal death, reporting that of the 35.5% of maternal deaths with HIV sero-status, 68% were HIV- positive.¹⁹ It is probable that the difference between male and female mortality rates from 1994 to 1998 can be attributed to the impact of AIDS on maternal mortality.

Although group II had only 13% of inpatients, it contributed 17% of the total deaths. The number of inpatients and death rates in group II increased over the 15-year period covered. The death rate increased at the same rate as that of group I, suggesting progress into a double burden scenario of pre-transitional and non-communicable conditions. This is consistent with the WHO observation that, in Africa, the burden of non-communicable diseases continued to increase in tandem with communicable diseases.¹² However, the rate of progress into the double-burden scenario may differ from one country to the other. For instance, in 2003 group II was responsible for 15% of deaths, which was lower than the 37% reported in South Africa in 2000.²⁰ This is probably because Lesotho had a shorter life expectancy at birth (35.7 years, 2002) than South Africa (50.7 years, 2002),¹² and therefore fewer people reached old age to succumb to chronic non-communicable diseases. Secondly, Lesotho could have been lagging behind South Africa in epidemiological transition.

Group III had 30% of inpatients but contributed the lowest portion of deaths (10%). The number of inpatients declined slightly between 1989 - 1993 and 1999 - 2003, while the

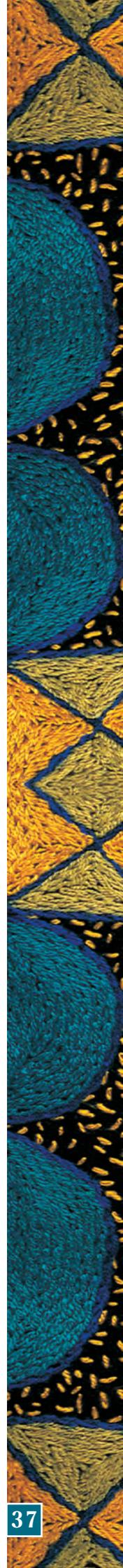
death rate rose marginally. Males accounted for 61% of injuries, indicating that they shoulder a heavier burden of injuries, as has been reported in South Africa (males 74%)²⁰ and estimated by the World Health Organisation (WHO) (males 70%).¹² The higher burden of injuries among males in Lesotho could probably be ascribed to their higher risk for, *inter alia*, road traffic accidents and interpersonal violence. Despite this stability, the WHO fears an exponential rise in road traffic-related injuries in developing countries and warns against complacency.¹²

CONCLUSION

The HIV/AIDS pandemic has had a huge impact on the inpatient mortality in Lesotho, and it has modified the trend in a similar way as reported in Zimbabwe and South Africa and as predicted by the ASSA 2000 prediction model. The ASSA 2000 model was used to make similar predictions in Lesotho. It appears that the AIDS burden is shifting from the hospitals to the homes and communities, which in turn may require additional resources to cope with the increasing demand. AIDS may be accelerating maternal mortality, but this requires further investigation. In addition, the pandemic in Lesotho is progressing into a double-burden scenario of pre-transitional and non-communicable conditions. The injuries-related burden has remained stable, although this cannot justify complacency.

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IMPLICATIONS OF FORMULA FEEDING TO REDUCE HIV TRANSMISSION

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Background. The risk of vertical transmission of HIV during breast-feeding has prompted renewed interest in the role of supplementary feeding during childhood. However, it is also known that supplementary feeding is an important vector of disease transmission. The aim of this study was to investigate the level of microbial contamination present in bottle feeds given to infants living in Mangaung, South Africa.

Methods. The study followed a cross-sectional design. Two hundred randomly selected households were visited and caregivers of bottle-feeding infants in the selected area were requested to provide a sample of the infants' bottle feed. Nutritional and microbial content of each bottle feed were measured. Bottle feeds were classified as unfit for human consumption if they had a standard plate count greater than 50 000 organisms per millilitre feed, or a total coliform count greater than 10 coliform organisms per millilitre.

Findings. A total of 84.5% of all the bottle feeds were classified as unfit for human consumption. There was no major difference in nutritional quality of the fit and unfit feeds. The infants receiving unfit bottle feeds were younger than those receiving fit bottle feeds (11.1 ± 6.9 months compared with 14.0 ± 7.6 months, respectively; $p = 0.010$) and also weighed less.

Interpretation. This finding underlines the need to address the content of feeding literacy programmes. Bottle-feeding in Mangaung is currently not a safe alternative to breast-feeding and should therefore not be promoted.

The global HIV epidemic has a major impact on the health and survival of infants in sub-Saharan Africa.¹ Recent advances in reducing HIV transmission from mother to child during the intrapartum period have been made by studies such as the 076 Study, the Thai Study, Petra, and the HIVNET012 Study. However, the postpartum risk of HIV transmission through breast-feeding remains a challenge in resource-constrained settings. Breast-feeding is believed to bring multiple benefits to infants and to improve the health of mothers.² (Coutsoudis *et al.*, 2001). The most serious threat to breast-feeding in modern times has been promotion of the use of artificial milks, particularly, but not only, in developing countries. More recently realisation that breast-feeding can transmit HIV-1 to the infant has resulted in HIV-infected women in the industrialised world choosing to avoid this feeding method.² It is believed that the rate of HIV transmission via breast-milk ranges from 12% to 26%.^{1,3}

The risk of transmission of HIV to the infant associated with exclusive bottle-feeding is, in theory, negligible. However, bottle-feeding and weaning have been associated with

increased infant and child mortality and morbidity even in the absence of HIV.⁴⁻⁷ Furthermore, mortality among children who are not breast-fed or are weaned because of preceding morbidity in mother or infant is higher than mortality among children who are not breast-fed or are weaned as a result of maternal choice.¹

The most prevalent infections among children are respiratory and diarrhoeal infections, and children become most susceptible to them when weaning foods or liquids complement or replace breast-milk. Diarrhoea is believed to be the most common cause of child morbidity and mortality in developing countries. It is estimated that across the world, excluding China, 1 400 million episodes of diarrhoea occur annually in children under the age of 5 years. In 1990 over 3 million children died worldwide as a result of diarrhoea. It is also suspected that almost 70% of these diarrhoeal episodes could be caused by pathogens transmitted through food.

The total number of deaths in South Africa's Free State province for 1999 was approximately 6 870. Deaths of infants in the age group 0 - 5 years comprise 15.6% of this

total. The contribution of food-borne pathogens to this figure is unknown.

The aim of this study was to investigate the level of microbial contamination present in a representative sample of bottle feeds given to infants in the Mangaung region of Bloemfontein. Social, environmental and economic factors believed to affect the preparation of bottle feeds were also examined. Information from this study will assist in planning intervention methods to improve the standard of health education among caregivers, and ultimately contribute to a decrease in mortality and morbidity associated with poorly prepared bottle feeds.

MATERIALS AND METHODS

STUDY DESIGN

A cross-sectional design was used. The Ethics Committee of the University of the Free State approved the study. A representative sample of 200 randomly selected households in Mangaung, a traditionally black township in Bloemfontein, was visited and caregivers of bottle-fed infants in the selected area were recruited for the study. The caregivers were defined as those individuals responsible for preparing the bottle feeds of each infant for at least 5 days per week. Only caregivers who gave informed consent were included in the study.

POPULATION AND SAMPLE SIZE

The study population included four neighbourhoods in Mangaung region, the number of households for each neighbourhood being proportional to its population size. The Department of Biostatistics, Free State University, determined the method of sampling. Ineligible households, i.e. not including a bottle-fed infant, were substituted by the second household to the left of the original household, or following that with the second household to the right of the original household. All black infants aged under 24 months and receiving bottle feeds were included in the study.

SAMPLE COLLECTION AND PREPARATION

In each household, the caregiver was requested to provide a 50 ml sample of a bottle feed given to the infants at the time of the visit or stored to be given during the next feeding session. Caregivers were unaware of the study before the visit.

Samples were collected in standard sterilised 50 ml sampling bottles and immediately placed in a dark container filled with ice and transported to the laboratories of the Technikon Free State. The samples were processed into aliquots. One aliquot was immediately sent to the Laboratories of Dairy Belle, Bloemfontein, for analyses of

protein, fat and carbohydrate content. A commercially available milk sample was used as external control sample. The manufacturers of the various diagnostic kits used throughout the study supplied internal control samples. A water sample from the household was collected at the same time as the bottle feed sample in order to assess background contamination levels. Every participating caregiver was asked to complete a questionnaire after giving informed consent. Information regarding previous breast-feeding and bottle-feeding practices, whether the infant currently had diarrhoea and a total clinical history, including the infant's weight and height, were obtained. The information also included household socio-economic status, educational level, parity and other relevant particulars.

BIOCHEMICAL MEASUREMENTS

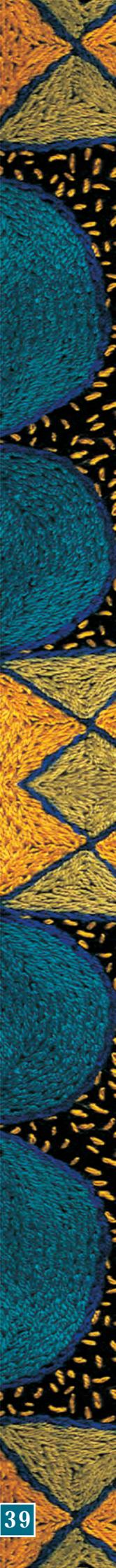
Carbohydrate, protein, and fat content

These analyses were performed in the laboratory of Dairy Belle, Bloemfontein. Samples were analysed on an ultraviolet Milk-O-Scan 104 Type 19900 automatic analyser. The coefficient of variation, expressed as the standard deviation as a percentage of the mean value of a set of control examples, for protein was 0.71, for lipids 0.32 and for lactose 1.17%.

MICROBIAL ANALYSES OF BOTTLE FEEDS

Analyses were performed according to the procedures as described in Annex A of Regulation 1555 of 1997 of the Foodstuffs, Cosmetics and Disinfectants Act (Act 54 of 1972). Counts recorded were minimum counts as no provision was made for fastidious bacteria. Procedures rely only on indicator organisms to indicate specific problem areas. The microbial analyses performed on the bottle feeds included the standard plate count, total *Escherichia coli* count and total coliform count. Standards for milk as described in the Foodstuffs, Cosmetics and Disinfectants Act (1972) were used. Total counts were determined using Petrifilm Total Aerobic Count supplied by 3M (St Paul, Minn., USA). The total *E. coli* counts were also determined using Petrifilm. The total coliform count was determined using Chromocult Coliform Agar supplied by Merck (cat. no. KgaA 64271, Darmstadt, Germany). *E. coli* detection was confirmed by coating the dark blue to violet colonies with a drop of Kovacs' Indole Reagent (Saarchem Pty Ltd).

Bottle feeds were classified as unfit for human consumption using a standard plate count greater than 50 000 organisms per millilitre, or a total coliform count greater than 10 coliform organisms per millilitre feed (as suggested by the Foodstuffs, Cosmetics and Disinfectants Act 54, 1972).



SOURCE OF FUNDING

This study was funded by the National Research Foundation (NRF), South Africa. The NRF did not play any significant role in the study after approval of the proposal. There was no conflict of interest between the funding agency and the authors.

RESULTS

A total of 200 households participated. A total of 84.5% of all the collected feeds had total plate counts greater than 50 000 organisms per millilitre feed, or total coliform counts greater than 10 coliform organisms per millilitre (Table I). These feeds were classified as unfit for human consumption. No significant differences in nutritional quality between the feeds classified as fit and unfit for human consumption were apparent, except for a higher fat content in the unfit group of feeds (1.89 ± 1.10 g/100 ml compared with 1.30 ± 0.93 g/100 ml, respectively; $p = 0.005$).

Caregivers responsible for preparation of the bottle feeds that were unfit for human consumption tended to be older

than those who prepared the acceptable feeds, but this difference was not significant (Table I). However, the average level of education of the caregivers responsible for preparing the unfit bottle feeds was significantly lower than that of the caregivers who prepared the fit bottle feeds (3.38 ± 3.72 and 4.93 ± 2.61 years of schooling, respectively; $p = 0.005$).

Infants who received bottle feeds with high levels of contamination were significantly younger than those receiving bottle feeds with acceptable levels of contamination (11.1 ± 6.9 months in the unfit group compared with 14.0 ± 7.6 months in the fit group; $p = 0.010$).

Caregivers responsible for preparing unfit bottle feeds reported a lower monthly income than the other group (Table I). This difference was not significant. However, the proportion of households in the group that prepared the unfit bottle feeds with direct access to electricity was significantly higher than that for the group that prepared fit bottle feeds (41% v. 23%; $p = 0.040$, $\chi^2 = 3.702$). Furthermore, a significantly higher proportion of households in the unfit group had access to an electric stove for cooking purposes (32% v. 21% within each

TABLE I. RESULTS FOR FIT AND UNFIT BOTTLE FEEDS

	Bottles fit for human consumption (N = 31)		Bottles unfit for human consumption* (N = 169)		p-value
	Mean	SD	Mean	SD	
Coliforms organisms/ml	1.97	3.22	399.85	465.32	0.000 [†]
Total counts/ml	9 782	10 987	4 114 732	4 488 321	0.000 [†]
Demographics					
Age of caregiver	29.7	8.9	30.9	10.7	NS [†]
Educational level of caregiver/years schooling	4.93	3.72	3.38	2.61	0.005 [†]
Infant background					
Age of infant (mo.)	14.0	7.6	11.1	6.9	0.010 [†]
Gender					
Males	20		84		NS
Females	11		85		NS
Birth weight of infant (g)	2 993	553	2 894	521	NS [†]
Current weight of infant (g)	9 562	2 784	8 717	3 365	NS [†]
Age at weaning (mo.)	13.9	1.4	6.3	0.8	0.000 [†]
Age at introducing solids (wks)	15.0	7.8	11.8	8.8	0.045 [†]
Household information					
Household income (R)	1 290	739	1 252	804	NS [†]
Electricity (%)	23		41		0.040
Open fire (%)	10		9		NS
Water in house (%)	8.5		9.0		NS
Stove (%)	21		32		0.016
Primus (%)	55		58		NS
Knowledge on preparing a bottle					
From label (%)	25.8		4.2		NS
From family (%)	61.3		37.2		0.022
Clinic (%)	12.9		56.2		NS
Work (%)	-		1.2		NS
Guessed (%)	-		1.2		NS
Nutrient contents					
Fat (g/100 ml)	1.30	0.93	1.89	1.10	0.005 [†]
Protein (g/100 ml)	0.98	0.90	1.36	1.00	0.052 [†]
Carbohydrates (g/100 ml)	4.91	1.70	5.18	2.56	0.571 [†]
Solids	7.65	2.90	8.94	3.78	0.072 [†]

*Bottles were classified as unfit for human consumption using the following criteria: standard plate counts > 50 000 organisms/ml, and total coliform counts > 10 coliform organisms/ml, as suggested by the Foodstuffs, Cosmetics and Disinfectants Act 54, 1972.
[†]Independent sample t-tests; categorical variables were tested using the χ^2 -test.

respective group; $p = 0.016$, $\chi^2 = 8.254$). There was no significant difference in access to water supply between the two groups.

Antenatal clinics (56.2%) or family members (37.2%; $p = 0.022$, $\chi^2 = 3.888$) were reported to be the main source of knowledge on how to prepare infant formulas by caregivers responsible for the preparation of unfit bottle feeds. The caregivers who prepared the fit bottle feeds reported either a family member (61.3%) or formula feed container label (25.8%) as their main source of knowledge.

DISCUSSION

The results of this study show that while the nutritional content of bottle feeds was adequate, levels of bacterial contamination were unacceptable. Contaminated complementary foods account for a substantial proportion of cases of diarrhoea among infants and young children, especially in developing countries.⁸ Factors such as unhygienic living conditions, an unsafe water supply, inadequate refuse removal and disposal of excreta, contamination of food and kitchen utensils and the decline in the prevalence of breast-feeding are believed to be directly associated with high levels of bacterial contamination of food sources, yet the importance of food safety in the prevention of diarrhoeal disease is often overlooked or neglected. It is estimated that up to 70% of diarrhoeal episodes could be due to pathogens transmitted through food.⁸ Contaminated bottles, teats and bottle feeds are associated with high bacterial counts that can increase the risk of diarrhoeal events.⁹

Frequent diarrhoeal episodes, in turn, suppress infant growth, leading to wasting and malnutrition. Diarrhoeal infections are second only to respiratory infections in negative impact on the growth of infants and young children.⁸ The relationship between diarrhoea and malnutrition is well established. Diarrhoea has a direct effect on the nutritional status of the infant that not only prolongs the individual diarrhoeal episodes, but also increases the risk of mortality.¹⁰ Yet health professionals tend to regard energy-poor weaning foods and liquids as the major cause of malnutrition in infants receiving complementary feeds.¹¹ In this study the nutritional content of bottle feeds was acceptable and there was no major difference in nutritional quality between the feeds classified as fit and unfit for human consumption. At the same time, the current weight of the infants tended to be lower in the group receiving contaminated bottle feeds.

The majority of caregivers responsible for preparation of the bottle feeds that were fit for human consumption were

trained by a family member, while the majority of those who prepared the unfit feeds were trained by personnel of the local clinic. This finding is of great concern and underlines the need to address the content of bottle feeding literacy programmes according to current needs. A successful literacy programme should also address other determinants of infant health, such as the age of weaning, which was shown in this study to contribute significantly towards the risk of receiving contaminated bottle feeds.

CONCLUSION

This study supplies valuable information that could be used to educate caregivers in the Mangaung district of Bloemfontein. The main shortcoming of the study is its inability to isolate a single source of contamination. However, it does show that the level of contamination is multi-factorial and depends on a combination of demographic, socio-economic and environmental factors. Literacy programmes should be based on these findings. Only then should mothers infected with HIV be encouraged to use bottle-feeding as a safe alternative to breast-feeding.

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CASE STUDY

PERSISTENT PLEURAL EFFUSION IN AN HIV PATIENT TREATED FOR TUBERCULOSIS

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HISTORY ON FIRST PRESENTATION

A 31-year-old woman presented to the oncology clinic at Tygerberg Hospital in November 2003 with grade 3 dyspnoea and a dry cough for 2 weeks. She was known to be HIV-positive and had received 8 months' treatment at a primary health care facility for pulmonary tuberculosis. There was no other history of note.

On physical examination she had a performance status of 2, generalised lymphadenopathy, six small, raised Kaposi's sarcoma (KS) lesions on the right temporal area of the face, and a large perpendicular KS mass extending from the right tonsil and falling into the valleculae on breathing, causing obstruction of the airway (Fig. 1). Auscultation revealed diminished breath sounds and a large right-sided pleural effusion.

Laboratory studies revealed the following: haemoglobin 10.5 g/dl, white blood count $4.1 \times 10^9/l$, neutrophil count $2.0 \times 10^9/l$, lymphocyte count $1.62 \times 10^9/l$, and platelet count $208 \times 10^9/l$. The results of liver function tests and the serum creatinine, electrolyte, protein and uric acid levels were all within normal limits. The lactate dehydrogenase (LDH) level was 184 U/l (within the normal range). A CD4+ count at the onset of treatment was 324 cells/ μ l. A chest radiograph confirmed a large right-sided pleural effusion (Fig. 2).

Investigations on the pleural effusion revealed:

1. Chemistry: total protein 70 g/l, LDH 304 U/l (normal > 200 U/l) and adenosine desamidase (ADA) 82.7 U/l (> 30 U/l is suggestive of tuberculosis or malignancy).
2. Microscopy, culture and sensitivity tests were negative for tuberculosis.
3. Cytological examination confirmed a picture compatible with a non-Hodgkin's lymphoma (NHL) with the presence of CD30+ and CD45+ cells.

This picture was compatible with the diagnosis of a primary pleural effusion lymphoma (PEL).



Fig. 1, a and b. Kaposi's sarcoma lesion of the right tonsil and field marker for external beam radiation.

Staging for lymphoma was completed with the following examinations:

An abdominal ultrasound scan revealed bilateral inguinal lymph nodes. Histological examination of a lymph node

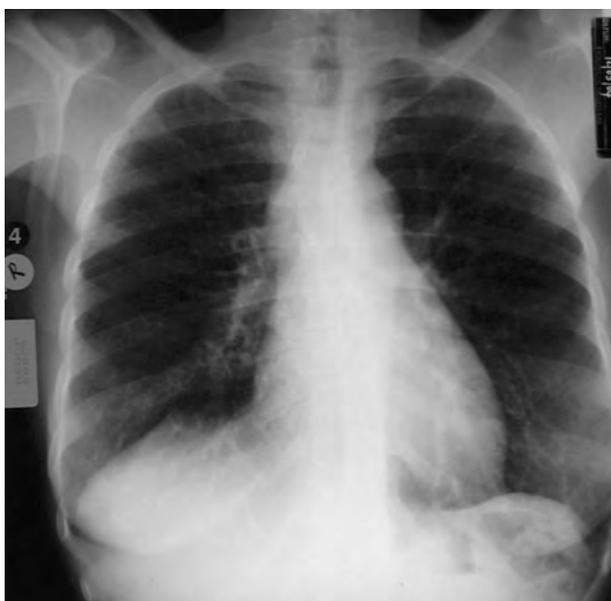
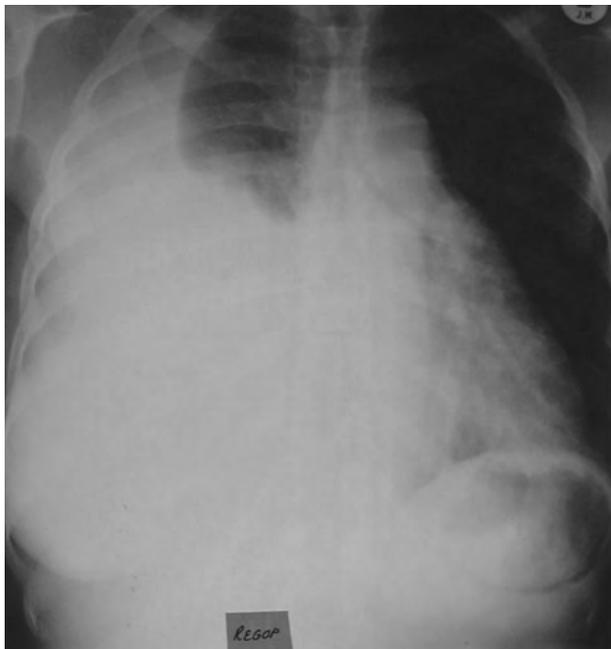


Fig. 2, a and b. Consecutive chest radiographs of pleural effusion lymphoma after 4 cycles of CHOP, showing a complete response.

confirmed the diagnosis of KS (immunochemistry HHV-8 positive). Bone marrow aspiration and biopsy demonstrated no abnormalities. This case was considered to be a stage IaE (pleural effusion) NHL and KS T1, I0, S1 (poor risk) in a patient with WHO stage IV HIV disease.

TREATMENT AND RESPONSE

External beam irradiation (EBRT) with 60-cobalt, consisting of 4 Gray (Gy) × 5 fractions, was given to the oropharyngeal KS lesion to relieve the obstructive symptoms. The patient was then treated with the standard CHOP chemotherapeutic regimen consisting of cyclophosphamide 750 mg/m² on day 1, doxorubicin 50 mg/m² on day 1, vincristine 1.4 mg/m² on day 1, and

prednisone 60 mg/day on days 1 - 5. Between January 2004 and April 2004, 6 courses of CHOP were given without significant toxicity apart from alopecia. The patient's general condition improved after the first course of chemotherapy for the NHL and EBRT to the KS, and sequential follow-up chest radiographs showed clearance of the pleural effusion after four courses of treatment. The first re-evaluation with chest radiograph was performed after the second course of chemotherapy. At the time, the pleural effusion was greatly reduced in size. The CD4+ count had decreased to 172 cells/μl by the end of treatment.

The patient thus presented with KS and PEL simultaneously, as late manifestations of her HIV disease. Chemotherapy for the lymphoma was well tolerated, probably because of the degree of immunosuppression (CD4+ count 162 cells/μl) at the commencement of therapy.

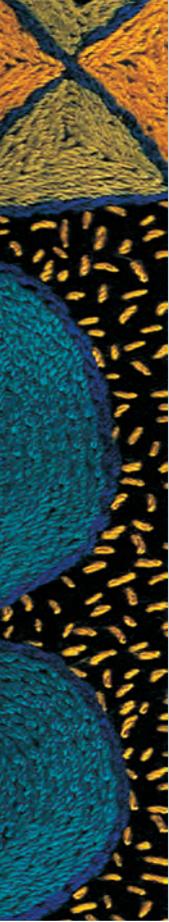
DISCUSSION

A rare type of NHL called primary lymphomatous effusion has been recognised as a separate entity based on distinctive biological features and the concomitant infection with the human herpesvirus 8 (HHV-8)/Kaposi's herpesvirus (KSHV). Because of the tropism of this entity for serous cavities it has been designated as a body cavity-based lymphoma (BCBL). In the USA, BCBL is also known as PEL.¹⁻³

The majority of cases arise in the setting of HIV infection and most patients have been young to middle-aged men who have sex with men. Among patients with HIV the incidence of lymphoma is estimated to be between 1.6% and 8% per year.³ In a recent publication by Simonelli *et al.*⁴ only 4% of 277 AIDS/NHL patients were diagnosed with NHL. PEL also occurs in the absence of HIV infection, especially in areas with a high prevalence of HHV-8/KSHV infections. The HHV-8/KSHV is present within tumour cells, which often harbour the Epstein-Barr virus.^{2,3}

The differential diagnosis of a pleural effusion in a HIV/AIDS patient should exclude tuberculosis, lymphoma, KS, hypoproteinaemia and bacterial and fungal infections.

Clinically PEL/BCBL gives rise to effusions without mass formation, although such masses have been reported. The most common sites of involvement are the pleural, pericardial and peritoneal cavities. Typically only one body cavity is involved. Other sites of involvement include the gastro-intestinal tract and extranodal tissues. Some patients have a pre-existing KS.^{2,5} In most series the clinical outlook remains extremely unfavourable, with or without therapy, and a median survival of less than 6 months is reported.¹⁻⁵



Our patient represents a typical case of PEL/BCBL with pleural effusion. The patient also had an associated KS. She responded well to EBRT for the oropharyngeal KS lesion, followed by CHOP chemotherapy for the PEL. Her facial KS lesions and lymphadenopathy also responded to the doxorubicin/vinca-alkaloid-containing CHOP regimen. She remains in complete remission for PEL after 4 months of follow-up.

At present, no recommendations can be made for treatment strategies for PEL/BCBL that differ from other AIDS/NHL treatments. However, a lesson from this case

study is to be aware of other causes for a persistent pleural effusion in an HIV-positive patient.

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CASE STUDY

CANCRUM ORIS (NOMA) IN A MALNOURISHED HIV-POSITIVE CHILD FROM RURAL KWAZULU-NATAL

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Cancrum oris (noma – derived from the Greek *nomein*, 'to devour') is an infectious disease with a fulminating course that destroys the oro-facial tissues and other neighbouring structures.¹ Although cancrum oris can occur at any age, it is most commonly in malnourished children between the ages of 1 and 5 years whose general health has been further weakened by some infectious disease, usually measles but also tuberculosis, gastro-enteritis, typhoid, whooping cough, or malignant disease such as leukaemia. The possible relevance to HIV has not been fully investigated. This report details a case presenting to East Griqualand and Usher Memorial Hospital, Kokstad, KwaZulu-Natal.

CASE REPORT

A female toddler aged 2 years and 5 months from a poor rural area in the Eastern Cape, presented at East Griqualand and Usher Memorial Hospital in June 2002 for treatment of a lesion on the lower lip affecting the mandibular gingivae and bone associated with the lower incisors (Fig. 1). The mother gave a history of a small ulcer which began on the interdental papilla of the lower incisors and in the course of 6 weeks had spread causing huge tissue destruction.

The child had been born at term following a normal pregnancy and apart from a single admission for 1 week had been relatively well. Physical examination confirmed features of typical cancrum oris with severe destruction of superficial and deep tissues and accompanying disfigurement of the face. The attending physician prescribed augmentin, gentamycin, metronidazole and folate.



Fig. 1. Typical cancrum oris with severe destruction of superficial and deep tissues and accompanying disfigurement.

The dentist and oral hygienist gave oral hygiene instruction, provided a mouth care pack and irrigated the area using hydrogen peroxide 20 volume 5 ml in 250 ml warm water. The child was able to eat and drink well and appeared to be in very little pain. She was transferred to the regional referral centre for further management.

On admission the patient was afebrile and had generalised pallor, hypotonia and wasting. Her weight was 7.9 kg, 60% of her expected weight for age. The left half of the lower lip was absent and the gum covered by slough. Her skin was clear, she had no lymphadenopathy or hepatosplenomegaly, and the remaining systems were all normal.

Apart from a normochromic, normocytic anaemia the full blood count and urea and electrolyte levels were normal.

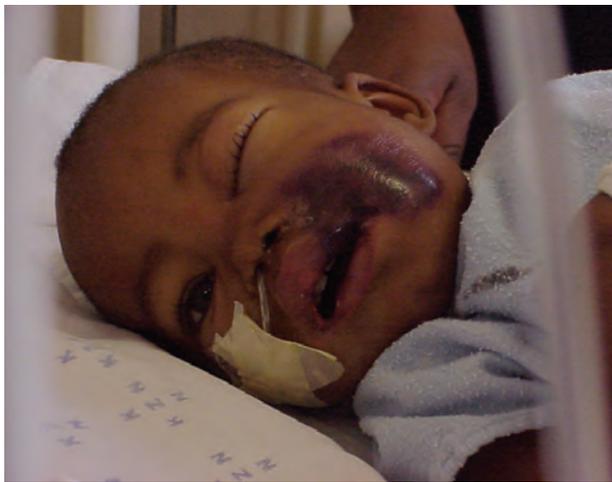


Fig. 2. The second case of noma, showing typical severe necrosis, rapid dissemination and tissue infiltration.

The serum total protein level was 75 g/l and the albumin level 26 g/l. Enzyme-linked immunosorbent assay (ELISA) for HIV was positive.

Nutritional support was started, treatment with augmentin, metronidazole and oral toilet continued, and fluconazole, topical anaesthetic and acyclovir added.

Despite an improvement in the patient's nutritional status and general wellbeing over the next month, during which her weight increased to 9.7 kg, the local lesion deteriorated with further involvement of the mandible leading to a fracture of the left ramus.

DISCUSSION

The early detection of this infection is of paramount importance. If the lesion is detected at the gingival stage, local disinfection, appropriate antibiotics and nutritional rehabilitation can prevent progression. Clinical diagnosis is imperative as laboratory analysis is inconclusive and early treatment and support is the only option for reducing mortality and morbidity rates.

The link with HIV needs to be explored.

The incorporation of oral examination and mouth care needs to be urgently revisited by the medical profession as multiple intra-oral lesions have a particular association with HIV and can be highly diagnostic. In their early stages they can be relatively easily managed.

Noma is a public health scourge of economically disadvantaged children particularly in sub-Saharan Africa.² The World Health Organisation (WHO) estimates that an annual total of 500 000 cases of noma occur worldwide, most in a belt from Senegal to Ethiopia, where the mortality rate associated with the condition is close to 90%.

Poverty is the most important risk factor for noma, with chronic malnutrition, very poor environmental sanitation, poor oral health, unsafe water supply, close residential proximity to livestock and increased exposure to viral and bacterial infections the major predisposing factors.

Recently a few atypical cases have been reported in adults, in whom the primary risk factor appears to have been immune deficiency.³ This raises concern over a possible causal relationship between HIV infection and noma, as in the case reported above.

The global distribution pattern of noma cases shows a striking similarity to the worldwide distribution of malnutrition, particularly the vitamin A deficiency in children under 5 years of age, as compiled by the WHO Programme on Nutrition.² Perhaps of relevance is the reported observation that malnourished children with compromised vitamin A status are prone to develop deep erosive ulcers of the oral mucosa and eyes following measles. Emslie⁴ has proposed the possibility that primary herpes simplex infection may be an initiating factor in noma and acute necrotising ulcerative gingivitis (ANUG). ANUG is generally considered a risk factor for noma.⁵ Published reports indicate an escalation in the incidence of ANUG in poor African countries and this is independent of the current AIDS pandemic on the continent.

Since preparing this article a second case of noma has been identified at St Apollinaris Hospital, Centocow (Fig. 2). The child was transferred to the regional referral centre, but lived for only a few days.

In conclusion, these cases must alert us to the possibility of an increase in noma, for which we all need to be prepared.

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FUNERAL AND ESTATE PLANNING FOR PEOPLE LIVING WITH HIV/AIDS

Some preliminary points

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The issue of funeral and estate planning should form part of HIV counselling, but this presupposes knowledge on the part of the counsellors/social workers/health care providers of basic legal principles underpinning the field of funeral and estate planning. Moreover, funeral and estate planning is often grounded in culture and religion, and perceptions of death, after-life, care of those left behind ('legacy', 'inheritance', etc.), burial and burial ceremonies, etc. This also relates to family relationships and family organisational structures and goes beyond the particular patient or client who visits a health establishment, voluntary counselling and testing (VCT) service or counselling service.

There may be a need for a patient/client brochure on this, possibly translated into all the official languages.

ESTATE PLANNING AND APPLICABLE LEGISLATION

People should know the difference between dying testate (with a will) and intestate (without a will) and the implications thereof. This also ties in with marital property and the recognition of the rights of people in polygamous unions.

The Wills Act of 1953 governs wills, and is important as it sets certain prerequisites for wills to be valid, including who may draft a will, who may witness it, and who may act as executor. It also deals with the effect of divorce and annulments on wills. The Intestate Succession Act of 1987 deals with persons who die without a will and basically provides 'rules' as to what will happen with a person's property in certain circumstances (e.g. whether person is survived by a spouse and/or parents and/or children, etc.). The Administration of Estates Act of 1965 provides for a number of issues that may also involve family members of a person planning his or her estate, such as reporting the death to the Master of the High Court. People should also be aware that certain financial institutions may undertake 'estate planning' and may draft wills of a general nature to their clients, of which the client may sometimes not even have a copy.

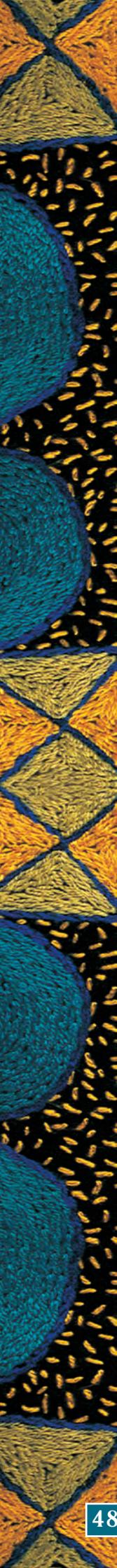
Two other factors complicate the above system, i.e. (i) inheritance in terms of traditional indigenous/cultural/religious systems and (ii) marriage and life partnerships. The Matrimonial Property Act of 1984, most importantly the accrual system in terms of which after divorce or death 'of one or both of the spouses, the spouse whose estate shows no accrual or a smaller accrual than the estate of the other spouse, or his estate if he is deceased, acquires a claim against the other spouse or his estate for an amount equal to half of the difference between the accrual of the respective estates of the spouses'. People should be able to establish whether they are married in or out of community of property. People who have registered their 'marriages' in terms of the Recognition of Customary Marriages Act of 1998 have to take specific heed of the property consequences regulated by Section 7 of this Act. Women who are or were joined to a customary union as the second or further wife should be aware that the property consequences of their marriage will be or are governed by a contract set after application to a court of law.

Cohabitation is not governed by any South African law specifically as yet (the Law Commission is currently working on this), but people should be advised to 'formalise' their life/domestic partnerships by means of wills, the appointment of a partner and/or children as beneficiaries on their pension funds, life insurance policies, and setting agreements to deal with issues such as care of children after death, etc.

The Maintenance of Surviving Spouses Act of 1990 has as its objective to provide the surviving spouse in certain circumstances with a claim for maintenance against the estate of the deceased spouse, and from it some cases have been decided by our courts on who would qualify as a 'spouse'.

PENSION FUNDS AND EMPLOYEE BENEFITS

Certain pension or provident funds make provision for funeral and/or surviving spouses/partner benefits. Patients/clients should be encouraged to find out what the



benefits and exclusions are in terms of HIV/AIDS and in terms of disability, funerals, etc. This could be done via trade union representatives, who often sit as trustees of pension/provident funds. The Promotion of Equality Act (mentioned below) may also be applicable in cases of alleged unfairness in terms of HIV-related benefits.

Specific laws, such as those applicable to the police services and the military, provide for (limited and restricted) funeral assistance.

LONG-TERM INSURANCE AND FUNERAL POLICIES

The following is an extract from the SAMA HIV Human Rights and Ethics Guidelines.

Medical practitioners are often approached to fill out forms relating to a patient's HIV status or whether he or she underwent an HIV test. The same ethical principle applies, i.e. patient information is confidential. Life insurance, burial policies, etc. often become problematic when a person who has been living with HIV dies or when the company suspects that the insured person may be HIV-positive. The primary contract is between the policyholder and the insurance company. The medical practitioner may only make medical details known if the insurance company can provide the medical practitioner with a copy of a document in which the patient has provided informed consent that his/her medical details may be released to the insurer. Failing that, the medical practitioner should only write 'confidential information' in the spaces provided and/or use the example above in relation to third-party requests as a response to the requesting company. If the insured person has died, the next of kin may consent to the disclosure of the medical information. Where the policyholder and the insured person are not the same, the insured person should provide informed consent before medical details are disclosed.

The medical practitioner should not take the responsibility for disclosing medical information where an insurance company has not provided sufficient safeguards to protect its own financial viability based on actuarial reasons. These safeguards should take the form of contracts with (prospective) policyholders. Case law has affirmed the duty placed on an insured person to disclose 'material facts', based on Section 59 of the Long-term Insurance Act of 1998. The question is whether the (mis)representation would have materially affected the assessment of risk at the time of issue of the policy, objectively spoken (Joubert v. ABSA Life, 2001).

Many insurance companies do not provide cover if a person tests positive. Insurance companies should adhere to all the principles of HIV testing, i.e. pre-test counselling, informed

consent, post-test counselling and confidentiality. This becomes the duty of the medical practitioners involved in testing for insurance purposes. SAMA believes that blanket consent provided for insurance purposes does not conform to the principles of informed consent.

The Promotion of Equality and Prevention of Unfair Discrimination Act of 2000 contains, *inter alia*, in the illustrative list of unfair. Included is the insurance sector 'unfairly disadvantaging a person or persons, including unfairly and unreasonably refusing to grant services to persons solely on the basis of HIV/AIDS status'. Patients may approach any Magistrate's Court with complaints against insurers if they suspect unfair treatment based on their HIV status.

DEATH NOTIFICATIONS

The following is an extract from the SAMA HIV Human Rights and Ethics Guidelines.

New regulations on death notifications were passed in 1998. The new death certificate has two pages, which are detachable. It is for authorisation of burial by the Department of Home Affairs. It is used to issue the death certificate. On this page the cause of death can only be indicated as 'natural' or 'unnatural' and no underlying causes are indicated. This is the page the family sees. This page has to be detached from the second. The second page should be placed in a sealed envelope which is then stapled to the first page before handing it to the undertaker and/or family. Undertakers are empowered by law to handle these documents and bound by the same confidentiality as medical practitioners. The second page is confidential and is used by the state (Department of Home Affairs) to collect data. On this the medical cause of death, which may include reference to HIV status, must be indicated. Insurance companies have no right to demand these two pages or copies thereof. If they need a medical report, irrespective of whether it relates to a natural or an unnatural cause of death, it should be requested from the relevant doctors with the necessary supporting documents of consent.

Important contact numbers:

- | | |
|--|---|
| • Short-term Insurance Ombudsperson | Long-term Insurance Ombudsperson |
| PO Box 30619 | PO Box 45007 |
| Braamfontein, 2017 | Claremont, 7735 |
| Tel.: (011) 726-8900 | Tel.: (021) 674-0330 |
| Fax (011) 726-5501 | Fax (021) 674-0951 |

CPD QUESTIONS

Journal 16

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

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

NAME	QUALIFICATION
ADDRESS	
.....	
.....	POSTAL CODE
HPCSA NO	
TELEPHONE	FAX
CELL NO	E-MAIL

PLEASE INDICATE WHICH OF THE FOLLOWING STATEMENTS ARE TRUE:

- Approximately 2 million South Africans are co-infected with tuberculosis and HIV.
 - Approximately 1.9 million South Africans are co-infected with tuberculosis and HIV.
 - Approximately 2.5 million South Africans are co-infected with tuberculosis and HIV.
- The new World Health Organisation (WHO) guidelines for the prevention of MTCT recommend the following regimens for HIV-infected pregnant women who do not have indications for ARV treatment, or do not have access to treatment:
 - Zidovudine (AZT) from 24 weeks of pregnancy plus single-dose nevirapine (NVP) during labour and single-dose NVP and 1-week AZT for the mother and infant. This regimen is highly efficacious, as is initiating AZT later in pregnancy.
 - Alternative regimens based on AZT alone, short-course AZT + lamivudine (3TC) or single-dose NVP (sdNVP) alone are also recommended.
 - The new WHO guidelines for the prevention of MTCT recommend the following regimens for HIV-infected pregnant women who do not have indications for ARV treatment, or do not have access to treatment:
 - Zidovudine (AZT) from 28 weeks of pregnancy plus single-dose nevirapine (NVP) during labour and single-dose NVP and 4 days of AZT for the infant. This regimen is highly efficacious, as is initiating AZT later in pregnancy.
 - Alternative regimens based on AZT alone, short-course AZT + lamivudine (3TC) or single-dose NVP (sdNVP) alone are not recommended.
 - The new WHO guidelines for the prevention of MTCT recommend the following regimens for HIV-infected pregnant women who do not have indications for ARV treatment, or do not have access to treatment:
 - Zidovudine (AZT) from 28 weeks of pregnancy plus single-dose nevirapine (NVP) during labour and single-dose NVP and 1 week of AZT for the infant. This regimen is highly efficacious, as is initiating AZT later in pregnancy.
 - Alternative regimens based on AZT alone, short-course AZT + lamivudine (3TC) or single-dose NVP (sdNVP) alone are also recommended.
- At the recent Bangkok Conference South Africa's National Roll-out Guideline's first-line therapy (d4T/3TC and efavirenz) received the accolade of 'second best on test'.
 - At the recent Bangkok Conference South Africa's National Roll-out Guideline's first-line therapy (d4T/3TC and efavirenz) was not well received.
 - At the recent Bangkok Conference South Africa's National Roll-out Guideline's first-line therapy (d4T/3TC and efavirenz) received the accolade of 'best on test'.
- The South African public sector PMTCT regimen remains nevirapine until further notice.
 - The South African PMTCT regimen has been amended to include AZT.
 - The South African PMTCT regimen has been amended to include AZT plus 3TC for 4 days post partum.
- Cancrum oris (Noma) is derived from the Greek *nomein*, 'to devour' and is non-infectious.
 - Cancrum oris (Noma) is derived from the Greek *nomein*, 'to devour' and is infectious.
 - Cancrum oris (Noma) is derived from the Latin *nomein*, 'to devour' and is non-infectious.
- Rapid testing for the diagnosis of HIV is not suitable for use in the antenatal clinic setting.
 - Rapid testing for the diagnosis of HIV in the antenatal clinic setting is gaining acceptability, confirming the powerful effect of an immediate HIV result on uptake.
 - Rapid testing for the diagnosis of HIV adversely affects the uptake of VCT (voluntary counselling and testing).