

# HATIP

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## A more unified South African AIDS conference

By Theo Smart

For the most part, there seemed to be a rather harmonious tone set between the South African Government, civil society, scientists and health professionals at the Fourth South African AIDS Conference held in Durban earlier this month. This in itself is remarkable. A barometer for whatever is going on in the fight against HIV in the country, the conference has always been marked by controversy.

But there has been a change in the country's administration since the last national conference in 2007, with a new Minister of Health, Barbara Hogan, who is known for her strong managerial skills, warm relations with civil society, and a respect for the skills and know-how of the dedicated researchers and healthcare providers working at the coalface of the struggle against HIV/AIDS. The messages coming from the Government have clearly shifted. Even so, with a national election only weeks away, it is unclear whether she will be in the next administration.

Whoever is in charge, the challenges facing the healthcare system in South Africa are unparalleled and enormous.

Despite an ambitious national strategic plan to combat HIV and the rollout of antiretroviral therapy (ART), hundreds of thousands die from the disease each year. Most South Africans remain unaware of their current HIV status, and efforts to get people to test regularly have had, at best, only patchy success. A steady influx of new infections is refuelling the epidemic among adults and even infants, despite the scale-up of the prevention of mother-to-child transmission (PMTCT) programme. And HIV has been a major driver in the region's resurgent epidemic of tuberculosis (TB) including increasingly drug-resistant TB.

Although South Africa is better resourced to meet these challenges than most other African nations, and now has the largest free ART programme in the world (with around 700,000 people placed on ART), there have been some serious hiccups in implementation and the delivery of services. For instance, in the Free State Province, the ART programme grew so fast that it outstripped its allocated budget and the enrolment of new patients into treatment ground to a halt.

Elsewhere in the country, there are reports of stock-outs of drugs and medical supplies, and it is not clear yet how the global recession will impact on the country, or affect the ability of the health services to grow to meet the need for HIV services.

The one major demonstration at the meeting, organised by the Treatment Action Campaign (TAC) and others was mostly in response to these issues. There are indeed worrying signs that as the number of patients grow, costs could limit efforts to improve the quality of services delivered, and that, in some areas, the programme might be pressured to 'cut corners'.

Despite this, the general sense at the conference was one of hope borne out of the feeling that (for now at least) the government and society may finally be working towards a common purpose.

### The history of the conference

Durban has been associated with AIDS conferences ever since the XIII World AIDS Conference, held in 2000, focused attention on the disparities between the industrialised world, where ART was making HIV a chronic manageable disease and Africa "where \$1000 a month determined whether you lived or died," as Dr Gustaaf

Wolvaardt of the Foundation for Professional Development noted at a pre-meeting press conference.

Since the Durban World AIDS Conference, there has been a paradigm shift in the world's response towards HIV in resource-limited settings – partly made possible by a dramatic fall in the price of antiretroviral drugs driven by activism – resulting in large-scale public-health ART programmes.

But one of the most memorable things that happened at the 2000 World AIDS Conference was the confrontation between a young boy with HIV, eleven-year-old Nkosi Johnson, and the former President of South Africa, Thabo Mbeki. Nkosi gave an address at the opening ceremony, challenging his president for treatment, and better PMTCT services (Nkosi died later that same year). But his president went on to shock conference goers by questioning the link between HIV and AIDS – something he persisted in doing publicly despite (or perhaps partly because of) the backlash.

"We've had a difficult period over the past few years, with a situation almost unique for a modern democracy: to have the challenges between science, on the one hand, and the state on the other," said Professor Hoosen 'Jerry' Coovadia, of the Nelson Mandela School of Medicine, University of KwaZulu-Natal, at the pre-meeting press conference. "This conference has been the crucible of major disputes between the state and society."

ANC party leadership eventually persuaded the administration to cut back, at least somewhat, on the denialist rhetoric. Three years after the World AIDS Conference, the first national South African Conference was held, and at the close of the meeting, the MEC for Health announced plans to launch a national ARV programme.

But mixed messages from the government persisted, with some officials seeming to obstruct advancement at every available opportunity. Then, during a period in which the former Minister of Health, Dr Manto Tshabalala-Msimang had to step down for health reasons, the Deputy Health Minister Nozizwe Madlala-Routledge worked to create a new partnership with civil society and medical experts that led to the development of a progressive National Strategic Plan on HIV/AIDS 2007-2011 (NSP).

Accordingly, the organisers of the Thirrd South African AIDS Conference gave Ms Routledge a position of honour to speak at the opening plenary. But with Minister Tshabalala-Msimang having resumed her post, this was quashed by the Ministry of Health. Not long afterwards, President Mbeki fired Ms Routledge from her post, allegedly for attending an HIV vaccine conference against his will.

Last year, President Mbeki was himself forced out of government by his own political party, and Minister Tshabalala-Msimang then given a promotion to a much less visible post in the cabinet. An indication of how much times seem to have changed? In Durban this year, South African journalists Kerry Cullinan and Anso Thom of the Health-e news service released a new book, *The Virus, Vitamins and Vegetables: The South African HIV/AIDS Mystery*, which chronicles the often bizarre goings-on when AIDS denialism held sway in the government of South Africa. Addressing the crowd at the book's launch, Ms Routledge, now the Deputy Speaker of the South African National Assembly, suggested that it was time for the country to have "a truth and reconciliation commission on HIV/AIDS".

Minister Hogan could not open the conference as originally planned, because she was attending a high-level meeting in Beijing on drug-resistant TB. In her stead was Ms Baleka Mbete, the Deputy President of South Africa, who was quite forthright about some of the challenges the country faces:

"Approximately 250,000 people die annually from a variety of AIDS-related illnesses and nearly double that number become newly

infected," she said. "Women and girls are still raped almost everywhere, which makes it necessary for our health system to address the health needs of rape survivors. The NSP has set clear targets for access to health services by rape survivors and SANAC must ensure that this target is reached."

She even mentioned groups many politicians continue to marginalise:

"Despite our constitutional provisions, discrimination based on sexual orientation persists, resulting in rapes of gays and lesbians. The NSP requires that we develop 'a supportive legal environment for the provision of HIV and AIDS services to marginalised people'. In this regard, I want to congratulate the Western Cape Health Department, the Paediatric HIV Research Unit and PEPFAR for opening the Ivan Toms Men's Health Clinic at Woodstock Hospital in Cape Town, which provides health services to gays. It will hopefully be a model for other regions planning the same facility."

When Minister Hogan didn't appear at the opening plenary as stated in the programme, there were concerns that she was being censored by the government for her comments criticising the decision to refuse to issue the Dalai Lama a visa to visit South Africa (and this may indeed have repercussions down the road). However, conference-goers were clearly relieved when she made it back from the TB meeting for the closing of the conference.

Giving a thank you to all "the healthcare and community workers, activists, scientists, academics, researchers, volunteers and clinicians for spending enormous amounts of energy to respond to the AIDS epidemic in our country in the last decade." And then she added "If not for you, where would we be now?"

Indeed, the activists and healthcare workers had to lead the way, with the government often working at cross-purposes.

#### **The salt of the earth**

This may be particularly true of the activists and people with HIV, who, through Professor Linda-Gail Bekker's efforts, were at the conference in greater force than usual, with the community accorded their own track of conference sessions.

But an AIDS conference isn't complete without at least one march or group act of civil disobedience. The protest, called 'HIV is not in recession!', focused on financial resourcing in the scaling up of healthcare service delivery.

The protest was quickly shut down in a heavy-handed way by security, and the protesters threatened with eviction. This was probably more of a reflection on the security team than on the conference organisers or chair, who had made an effort to involve more people with HIV. Even so, if it is indeed a new era of co-operation between civil society, government and the medical establishment, the people working or involved in these events need to be more sensitised to the fact that, were it not for the actions of AIDS activists, there would be no ART programme and little reason to host such a conference. Their engagement should be encouraged, if not celebrated.

The activist's message was an important one.

"Wealthy countries are spending multiple trillions of dollars on bailouts, but only a fraction of this could have provided access to comprehensive healthcare for millions of poor people in the world," said TAC's spokesperson Victor Lakay. And yet, he pointed out, the Global Fund for AIDS, TB and Malaria is having difficulty securing funding, and resources that are available are being shifted away from HIV programmes to primary healthcare (even though HIV treatment should be an essential part of primary healthcare.)

Meanwhile, within South Africa, the activists noted that the budget allocations for antiretroviral drugs in the provinces are short of what was initially budgeted; but the moratorium on putting new

patients on ART in the Free State, and similar shortages in drugs and medical supplies that are occurring in provinces across the country – including in Gauteng, the wealthiest province – have mostly been ignored.

Minister Hogan acknowledged the issue in her speech: "With the coming financial year, I hope that we will be able to address many of these issues, but there are no quick fixes... As a community of health promoters, we must ensure that health services are not cut, but sustained. For every job that is cut, for every sector that buckles, for every health cent cut, there will be consequences for public health... We must be aware that we are, for the first time, experiencing real resource constraints."

Indeed, it is hard to see how the programme will continue to expand, begin to treat people with higher CD4 cell counts (rather than waiting for people's CD4s to fall below 200), or improve the quality of care. For instance, many clinicians and activists at the conference called for the programme to switch from d4T-containing ART regimens, as d4T is associated with most of the toxicity on treatment in South Africa, to the much safer tenofovir. But, as one DoH official pointed out, tenofovir costs about 10 times more.

The South African government suggests it will be taking a more aggressive role.

"At the current medicine price regime and escalating private health costs, the provision of antiretroviral therapy will not be affordable," said Deputy President Mbete. "As government, we will exploit various options to make medicine affordable, including through the amendment of the Patents Act and regulating the private health sector."

In another talk, Dr Susan Cleary, a health economist at the University of Cape Town addressed these issues in considerable detail. She concluded that the scale-up could continue – but it will take careful planning.

Minister Hogan also noted this "The issue for all of us is how to spend the resources we do have with efficiency and increase the pot; with maximum public health benefit... so that the NSP and the TB Strategic Plan targets are met."

This will require exceptional management skills – yet another reason to keep Minister Hogan in her post.

#### **Moving forward with hope**

It would be a shame if the financial crisis holds back the progress that South Africa has been making. The general mood of the conference was pride in the scale-up and relief that state and society were now working together without reservations.

Perhaps more than anyone, the conference chair Professor Linda-Gail Bekker, of the Desmond Tutu HIV Foundation, voiced this optimism: "We have a national strategic plan that is both ambitious and comprehensive, we already have the biggest treatment programme in the world, which urgently needs extension and to be sustained. We have proven tools, interventions and strategies today that can make a dent in the joint HIV and TB epidemics in this region... We just need to roll up our sleeves collectively, turn on the scale-up and start to roll the numbers back."

Noting that the conference is increasingly becoming regional (about a quarter of the delegates came from other countries), she said she hoped this progress would sweep from South Africa north up through the Southern African region. "It is high time to start pushing back the 'red zone' covering southern Africa on maps that indicate the high prevalence and incidence of AIDS and TB. Can we do it? Yes, we can."

But the high point once again may have been the speech given by a young man with HIV, 16-year-old Luyanda Ngcobo, who gave the Nkosi Johnson Memorial Lecture – and provided a testimony of the

difference that ART makes. Luyanda was born with HIV, but in stark contrast to Nkosi nine years ago, Luyanda is now healthy on ART. Well-spoken and witty, he enjoys playing video games with his friends, and says he just wants to be seen as a normal teen. His plans for the future? He wants to be an archaeologist.

## TB/HIV

### Infection control programme has reduced TB incidence in Tugela Ferry hospital at centre of XDR-TB outbreak

By Lesley Odendal

The prevalence of culture-positive tuberculosis, and multidrug-resistant and extensively drug-resistant tuberculosis (MDR-TB and XDR-TB respectively) has decreased significantly between 2005 and 2008 at the Church of Scotland Hospital (COSH) in Tugela Ferry in KwaZulu-Natal, due to an improved infection control programme.

A point prevalence survey of the inpatient TB wards for one single day in both 2005 and 2008 showed that for the patients screened (n=25 and 35 respectively), the proportion of patients with culture-positive TB has decreased from 88% to 25.7%. The proportion with drug-resistant (DR) TB has also dropped dramatically from 64% in 2005 to only 8.6% in 2008.

These declines indicate that fewer patients are able to transmit TB to others in the facility.

The Infection Control Manager of the facility, Kathryn Catterick, presented the findings and methods of the Church of Scotland Hospital (COSH) at the Fourth South African AIDS Conference in South Africa. Simple and feasible measures that are already outlined in national policy were used and practices were monitored on an ongoing basis.

Church of Scotland Hospital was the first site to identify the presence of XDR-TB in HIV-positive patients, when, in 2005 it detected an alarmingly high death rate among patients previously doing well on antiretroviral therapy.

Investigation [subsequently detected 53 cases at the hospital during the first year, growing to 266 by mid-2007.](#)

COSH is a rural 40 to 50-bed district hospital with congregate wards serving a population of around 172,000 patients. The annual TB incidence is 1054 per 100,000 and the annual incidence for MDR-TB is 141 per 100,000. Since 2005, 820 confirmed drug-resistant TB cases have been seen at the facility, 43% of which were MDR-TB and 57% XDR-TB.

Nosocomial transmission of TB (that which takes place in a healthcare setting and is secondary to the condition originally being treated) is a documented problem in this facility. In COSH in 2005, it was found that, of the 53 cases of XDR-TB, 85% of the isolates had similar genetic fingerprint by spoligotype, 55% had not previously received TB treatment and 67% had been hospitalised in the last two years.. These findings indicate that most patients acquired XDR-TB from others in the hospital.

Since 2005, 13 healthcare workers have been diagnosed with drug-resistant TB and nine have since died. Nosocomial transmission due to poor infection control practices in South Africa is also evidenced in the fact that for 2006, 2442 more cases in absolute numbers of all MDR-TB patients occurred in people diagnosed with TB for the first time and not in re-treatment cases. A synergistic and multifaceted approach was used in the infection control programme including the appointment of an infection control

officer and cough officers. Cough officers screened every patient entering ambulatory care on five days of the week.

In the outpatient clinic it was found that 10.8% of those screened were AFB smear-positive. In the Gateway clinic, 6.5% were smear-positive and 9% in the ARV clinic. However, culture testing showed that 20% of patients screened in the ARV clinic were culture-positive, including DR-TB cases, indicating a high prevalence of smear-negative TB.

Attempts to reduce patients' length of stay were also made. However it was found that, although the number of admissions was decreasing, the length of stay was not significantly different. Natural ventilation is emphasised in COSH. In 2006 extractor fans were installed and an open-window policy was instituted.

Unannounced audits were conducted to monitor the opening of windows. In the male ward, this improved from 78% of the time to 93%. In the female ward, improvements was observed from 68% to 82%. To reduce risk of transmission, the DOT office and the ARV clinic were moved to the periphery of the hospital.

In 2007, a staff survey regarding understanding and knowledge of mask and respirator use was conducted, followed by mask education on the use of N95 respirators. Fit testing and fit checks were regularly conducted. In unannounced audits, it was found that respirator use amongst staff was consistently as high as 95%. Staff are also screened for TB regularly and voluntary testing and counselling and testing for HIV are promoted. Staff are discreetly moved to lower risk areas if they are HIV-positive.

The proportionate decrease in the number of TB cases being diagnosed in COSH is assumed to be due to the improved infection control programme. The approach must be multifaceted and continuously monitored. Through utilising existing resources, strategies that are feasible, practical and measurable can be implemented in rural facilities to prevent nosocomial TB transmission. However, Kathryn Catterick emphasised that infection control measures in communities are being neglected.

#### Reference

Catterick K et al. *Feasible and effective infection control programme to limit nosocomial transmission of drug-resistant TB in Tugela Ferry.* Fourth South African AIDS Conference, Durban, abstract 455, 2009.

### Integrated screening tool improves TB screening rate in HIV patients in Eastern Cape

By Lesley Odendal

Integrating a TB screening tool into the adult clinical record (ACR) in HIV treatment facilities in South Africa's Eastern Cape has resulted in a significant increase in the number of HIV-positive people diagnosed with TB, say researchers from the International Centre for AIDS Care and Treatment Programs (ICAP).

Screening for TB is critical in HIV-positive people, given the increased risk of infection and differences in clinical presentation. Researchers Sabine Verkuijl and Jeanette Wessels from ICAP piloted the integration of TB screening into the adult clinical record in public health facilities in three subdistricts in the Eastern Cape. The first step in completing the adult clinical record involves assessing if the patient enrolled into HIV or ARV care is symptomatic for TB, using a screening questionnaire.

Those patients who screen positive, meaning that they have one or more of six listed symptoms or signs, are then further investigated to confirm active TB. This includes investigations for pulmonary TB (sputum smears and/or culture, chest X-ray) and for extra-pulmonary TB (lymph-node aspirates, pleural taps, abdominal

ultrasound and other measures). If active TB is confirmed, TB treatment is started and these patients also receive cotrimoxazole prophylactic treatment.

Overall, the percentage of ARV patients who were screened for TB increased from 73.2% to 95% between 2007 and 2008.

Of those screened, the percentage of patients with a positive symptom screen remained approximately the same: around 49% in both 2007 and 2008.

Out of those with a positive screen, the percentage of patients diagnosed with TB dropped from 40.6% to 23.8%.

The data collected from the ACR allows for comparison of TB screening practices across regions and between facilities. In the ICAP-supported districts, clear differences can be seen in the extent to which TB screening is routinely done. In Nelson Mandela Bay almost all patients are routinely screened at enrolment into HIV care. In Buffalo City LSA (East London), only 35% of patients are screened, and less than 60% of those with a positive screen are investigated for TB.

The availability of these data allows for increased monitoring of the extent of TB screening for people in HIV care.

The proportion of HIV-positive people being screened for TB in South Africa is exceptionally low, with an average of only 40% in 2007. For the Eastern Cape Department of Health, this is significantly lower at 27% in 2007.

The main advantages of the integrated screening tool in the clinical record are the quality and continuity of care it allows. It reminds clinicians to screen for active TB at each and every visit for patients enrolled in HIV care and on antiretroviral treatment (ART).

It also prevents unmasking of TB through immune reconstitution inflammatory syndrome (IRIS) in patients with lower CD4 counts.

The ruling out of TB through the ACR is also crucial for the correct implementation of isoniazid preventive therapy (IPT).

The ACR also allows the clinician to monitor TB investigation results, TB treatment progress and TB treatment outcome. Essentially, the ACR improves practical integration between the HIV and TB programme.

In order to get feedback from users in the facilities, an eight-question questionnaire was administered in facilities in the Nelson Mandela Bay Municipality. Respondents were asked to indicate on a scale from 1 to 5 whether or not they agreed with different statements regarding the ease of use of the ACR and the perceived impact on the quality of care. Feedback was generally very positive, with scores between 4.6 and 5.

The operating characteristics of the TB screening questionnaire, including the sensitivity and specificity of the symptoms and signs included, will be evaluated in a public health evaluation in two ICAP-supported facilities.

#### Reference

Wessels J et al. *Integration of a TB screening tool into a comprehensive HIV adult clinical record in the Eastern Cape, South Africa*. Fourth South African AIDS Conference, Durban, abstract 485, 2009.

### Smear-negative TB: C-reactive protein may provide useful screening method

By Lesley Odendal

Screening HIV-positive people with smear-negative pulmonary TB for high levels of C-reactive protein (CRP) can detect the presence of active TB with a fairly high degree of accuracy, suggesting that C-reactive protein could provide the basis for a point-of-care test to detect active TB in smear-negative cases in high-burden settings,

according to findings from a study presented at the Fourth South African AIDS Conference in Durban in early April.

Smear microscopy is the first line of diagnosis in people with suspected TB. Sputum is added to a slide, stained with a dye that shows up TB bacilli and then viewed under a microscope to determine if TB bacilli are present.

However, in people with HIV, pulmonary infection with TB is more likely to produce a smear-negative result, resulting in delayed treatment while further diagnostic tests are carried out, or – in some cases – a complete failure to treat active TB. Both lead to increased mortality in HIV-positive people.

A simple point-of-care diagnostic test to overcome these problems is urgently needed.

C-reactive protein, a marker of inflammation that is easily measured in a blood sample, is elevated in untreated smear-negative pulmonary TB.

Previous studies in HIV-negative patients suggest that C-reactive protein is more likely to be elevated where more serious tissue damage has occurred in the lungs as a result of TB.

In order to investigate the relationship between CRP levels and the presence of active TB in smear-negative individuals with suspected pulmonary tuberculosis, Douglas Wilson from the University of KwaZulu-Natal and colleagues conducted a sub-group analysis on a prospective cohort of people with suspected smear-negative tuberculosis, recruited from primary health care clinics in the Edendale Hospital catchment area between 2005 and 2007.

For each patient recruited into the study, mycobacterial culture was performed on induced sputum and other clinically relevant material. The two groups were divided into those with confirmed pulmonary TB and those who had pulmonary TB excluded.

Inclusion criteria for both groups were that individuals had to be HIV-positive or have clinical evidence of HIV infection, have been coughing for more than two weeks and have two AFB-negative sputum smears, as well as having been evaluated by a primary health care clinician, including with a chest X-ray.

For the confirmed pulmonary TB group, laboratory evidence of TB through culture testing was necessary and patients would be initiated on TB treatment. For the pulmonary TB-excluded group, all laboratory evidence would have to confirm the exclusion of pulmonary TB.

Of the 504 people with suspected TB who were screened, 421 were enrolled into the cohort. Of these:

- 105 patients (24.9%) were confirmed with smear-negative pulmonary TB
- 102 patients were confirmed culture-positive
- two patients tested AFB smear-positive
- one patient was lymph-node histology positive for TB
- 46 patients (10.9%) were diagnosed with smear-negative pulmonary TB
- 67 patients (63.8%) received an oral antibiotic.

At baseline, 88% of the pulmonary TB cases were experiencing night sweats and 89% experienced severe weight loss, compared to 61% experiencing night sweats and 76% severe weight loss in the pulmonary-TB-excluded group.

The median C-reactive protein level in the confirmed pulmonary TB group was significantly higher than in the pulmonary-TB-excluded group (86.5 mg/L (95% CI 47.7 to 126) in the PTB group versus 5.5

(95%: CI 2.9 to 31.1) in the excluded group). Elevated C-reactive protein was found to have 79% sensitivity and 85% specificity for detecting pulmonary TB, indicating that the test would miss active TB in around one in five people and wrongly diagnose a person as having active TB in about one in seven cases.

While the findings have positive implications for the diagnosis of pulmonary TB in HIV-positive populations, as this study is a sub-analysis which needs validation, more research into the topic is necessary. Further research also needs to be conducted on diagnosing extrapulmonary TB in HIV-positive people.

#### Reference

Wilson D *Performance of C-reactive protein (CRP) as a screening tool for smear-negative pulmonary TB in HIV-positive adults*. Fourth South African AIDS Conference, Durban, South Africa, abstract 413, 2009

### Children in rural South Africa may be at increased risk of acquiring MDR-TB in hospitals

*By Hayden Eastwood* Children may be at risk of acquiring multidrug-resistant TB (MDR-TB) in hospitals in South Africa and more resources should be directed at preventing and controlling infection spread in hospitals, according to research published at the Fourth South African AIDS Conference in Durban.

TB is the leading cause of death in HIV sufferers in South Africa. Of the nine million reported global cases, almost 10% occur in children.

Attempts to treat TB in recent years have resulted in some strains becoming multidrug-resistant.

A variety of studies have been conducted on the transmission of TB multidrug resistance in adults; however, comparatively few studies have been conducted on multidrug resistance in children who, for many biological and behavioural reasons, frequently have different demographics, clinical characteristics and outcomes to adults.

A Yale research group conducted a study to increase the understanding of multidrug resistance in children by investigating three HIV-infected children who were admitted to a paediatric hospital in rural South Africa.

Each of the children studied was malnourished at the time of hospital admission and two of them, both diagnosed with TB, were also found to be suffering from kwashiorkor. Anti-TB treatment was given to both children but only one responded, leaving researchers to conclude it was a case of multidrug-resistant TB. The third child was found to be free of TB.

Within eleven months both the child free of TB and the child infected with drug-susceptible TB acquired multidrug-resistant strains. Scrutiny of hospital records revealed that the children had all overlapped in the ward by four months. At the time of diagnosis, two of the three had been receiving antiretroviral therapy.

The period of hospital overlap suggested strongly that multidrug-resistant TB had passed in a chain-like manner between each child.

Following the diagnosis, each youngster was subjected to individual drug-susceptibility testing followed by an aggressive, tailor-made antibiotic treatment regimen. In each case the children responded well to antibiotics and recovered.

The researchers caution that the sample size examined was not statistically significant and call for more extensive research into the problem.

The preliminary findings suggest, however, that children may be at risk of infection by multidrug-resistant TB in a hospital setting, particularly if they remain in close proximity to one another for many

months. Performing drug-susceptibility tests on a case-by-case basis may help to treat children when drug resistance has developed. The researchers conclude that more time and money should be invested into understanding, preventing and treating the spread of multidrug-resistant TB in South African paediatric hospitals.

#### Reference

Thomas T et al. *Successful treatment of extensively drug-resistant tuberculosis in children with HIV from rural South Africa*. Fourth South African AIDS conference, Durban, South Africa, abstract 360, 2009.

## Antiretroviral therapy

### Higher rates of breast enlargement in men in South Africa on ART

*By Theo Smart*

"Gynaecomastia [breast enlargement] is a frequent side-effect of antiretroviral therapy (ART) and is seen earlier and more frequently in our patient population than in European cohorts," said Dr Tom Heller, the HIV and TB Co-ordinator in the Hlabisa district in the Northern KwaZulu-Natal at the Fourth South African AIDS Conference earlier this month.

Dr Heller was reporting on a study he and his colleagues conducted at Hlabisa Hospital, which found that 14% of the men developed breast enlargement. However, it is not clear whether the side-effect is due to d4T (stavudine) or possibly efavirenz.

#### Background

In South Africa, first-line HIV treatment in the public sector consists of d4T/3TC plus either efavirenz or nevirapine. But with prolonged treatment, increasing numbers of patients are experiencing metabolic complications and lipodystrophy (or fat redistribution) on the regimen.

Some forms of fat redistribution have been reported more commonly than others. For instance, a lot of patients experience facial lipoatrophy (fat loss) and central lipohypertrophy (abdominal fat accumulation), most of it caused by d4T. Lipohypertrophy can also be localised around the patient's neck forming a 'buffalo hump' and sometimes in the breast area (sometimes on one side only).

"A lot of females complain about growing breasts [on ART], but it's particularly a nuisance in male patients," said Dr Henner. But it is unclear whether this is true gynaecomastia (with glandular enlargement possibly related to a hormone imbalance) or actually represents a fat redistribution.

A few studies (mostly European) have reported on the condition. A French study in 180 men reported that after about 39 months on ART, 2.8% developed breast enlargement on d4T and protease inhibitor-containing regimens (Piroth). A Spanish study reported that 2.3% of 1304 men with HIV had breast enlargement after about 49 months on treatment, which it associated with ddI and efavirenz (Mira). A study in Germany reported 5.1% of 490 men developed breast enlargement after 52 months of therapy containing ddI or d4T (Paech).

A couple of the studies looked at hormone changes but were not very conclusive. [For instance, a Spanish study noted that testosterone levels in most of the men with enlarged breasts were somewhat lower compared to controls.](#)

The only study in a resource-limited setting, conducted at the HIV Clinic at Johannesburg Hospital, reported a somewhat higher rate of breast enlargement: it was observed in 27 out of 305 patients (8.5%) (Wong). This study, though, included both men and women.

However, during a plenary talk at the conference Dr Francois Venter, who works at that clinic, spoke about how fear of this side-effect has had a tremendous impact in South Africa.

"A front page article in *The Sowetan* – a very popular daily newspaper from Johannesburg – showed a graphic picture of a man who developed a severe gynaecomastia, breast enlargement, while on ARVs," he said. "I can't tell you how much damage this particular article did and how much fear it spread within the HIV community. Can you imagine being a patient and being exposed to all the 'politically correct government programmes' about accessing care and how you'll feel better, and then you see a front page article like this! It has done a huge amount of harm to the programme and legitimately causes a great deal of fear."

#### The Hlabisa Study

News of breast enlargement spread through the country. In fact, after hearing the news, the counsellors at Hlabisa were worried about what to tell their clients. So they decided to conduct a survey to measure the proportion of male patients on ART presenting with breast enlargement in their rural setting, describe their demographic factors and characterise the hormonal profile of the patients affected by breast enlargement.

Hlabisa hospital and its clinics serve a population of 220,000, mainly Zulu-speaking, people. The HIV prevalence in general is high (19% of people older than 15 years), according to a local population-based study conducted by the Africa Centre over the past five years. Currently 6647 patients in the area are receiving treatment at 16 peripheral clinics. Approximately one-third of the ART patients are male. In the KwaMsane clinic – the largest of the clinics in a more urban setting – more than 1300 patients are treated and around 60 patients per month are initiated on ART. For two months the HIV counsellors asked all male patients who came for follow-up visits to the KwaMsane Clinic if they had experienced any breast enlargement. If they reported they had, the patient was referred to a physician for history and examination with further investigations and blood was drawn to measure cholesterol, triglycerides and hormone levels.

#### Results

Sixteen out of the 113 men on ART surveyed (14%; 95% CI: 7 to 21%) reported breast enlargement. In four, gynaecomastia resolved spontaneously after a period of one to two months. In nine, breast enlargement was unilateral. The median age of the men with breast enlargement was 45 years (range: 30 to 48). The median duration on treatment at onset of breast changes was only 16.5 months (range: 5 to 32), a much faster onset than in the European studies. The median CD4 cell count of men beginning ART was 123 (range: 43 to 187). By the onset of breast enlargement, CD4 cell counts were around 265 (range: 90 to 775).

"So, it's safe to conclude the men were on effective treatment," said Dr Henner.

The clinical team investigated a number of hormones, including follicle-stimulating hormone (FSH), luteinising hormone (LH), oestradiol, testosterone and prolactin, as well as cholesterol and triglycerides. All were within normal range except for two patients who presented mildly elevated oestradiol (235 and 256 pmol/l – normal: 191 pmol/l) only but no other hormonal changes. One patient had mildly elevated triglycerides (2.8 mmol/l, normal: >2.3 mmol/l) which was not clinically relevant. Only one patient had concomitant diseases (hepatitis B and MDR-TB, on treatment), which could possibly contribute to breast development.

"It is definitely difficult to distinguish clinically between true breast development (gynaecomastia) and focal lipodystrophy syndrome (lipomastia) – there are studies reporting that you can distinguish

by high-resolution ultrasound and MRI but obviously these are not available in our setting," said Dr Henner. "The underlying pathophysiology also remains unclear. Hormonal changes have been described by different authors (elevated oestrogen, reduced testosterone); however, we could not really find that in our few patients. Hormone and lipid studies don't seem to be warranted routinely as they showed only minimal abnormalities in very few cases."

#### Management

"The 'culprit drug' is difficult to identify as patients are usually on multiple drugs," he said (though in this cohort, it would have to be associated with d4T or efavirenz). But he felt that "treatment changes may be difficult. First of all because we don't know which one to change, and then secondly due to the limited number of ARVs available."

Treatment options are also limited. One study looked at the local application of androgen (dihydrotestosterone gel) but that is not available in this setting (Benveniste). Surgical mastectomy is a possibility but Henner said that this was "a drastic measure that is rarely indicated. We have to remember that in a number of cases, the gynaecomastia disappears spontaneously."

Men with breast changes in this cohort were counselled and all of them continued ART on the same regimen – all but one with undetectable viral load.

"With counselling, and reassurance of the patient about the nature of the changes – because there is often fear when you have a breast growth that does not belong there – I think sufficient adherence can be achieved to continue ART successfully," he said. Other clinicians think that d4T (or other d-drugs) are the most likely culprit, however, and that countries need to start coming up with alternatives.

"I think for most clinicians, d4T is really one of the 'bad guys' on the block," Dr Venter said during his plenary. "D4T toxicity drives most of the treatment changes. But it's still used by the vast majority of people in the world – and certainly within the developing countries and in southern Africa."

"Does everyone eventually get d4T toxicity? I think we don't know that answer yet but if it is the case, we may have to start thinking about what substitution treatment we could use."

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## ART for children feasible in small rural clinics, South African study shows

By Carole Leach-Lemens

Paediatric antiretroviral therapy is feasible in decentralised, nurse- and counsellor-led programmes in public health clinics in rural areas in South Africa, according to research presented at the Fourth South African AIDS Conference in Durban earlier this month. Mortality rates in children receiving ART at public health clinics in Hlabisa, a sub-district in rural northern KwaZulu-Natal, were no different from rates seen in other African cohorts. The health infrastructure of the sub-district of Hlabisa, which has a population of 220,000, is typical of most rural health districts in South Africa and has 16 primary health care clinics, two mobile clinics and one 300-bed district-level hospital.

The ART programme, a partnership between the Department of Health (DOH) and the Africa Centre for Health and Population Studies, follows DOH national guidelines. Physicians visit the 16 clinics to initiate ART. Services are decentralised and patients are able to access free care at their nearest primary health care clinic which is managed by nurses and counsellors.

Children are less likely to receive treatment than adults, in part because HIV diagnosis is more complex in children under the age of 18 months due to the carriage of maternal antibodies that may result in a false-positive diagnosis. But children may also fail to receive treatment due to a lack of awareness of the presentation of HIV-related symptoms in children, especially infants.

In order to review how well the programme was meeting the needs of children with HIV, a retrospective study was undertaken of the clinical records of all children (477) on ART in the districts from January 2004 until June 2008.

At baseline, recorded values included a mean age of 76 months and 5% of the sample were under 12 months of age. Nearly a quarter were receiving TB treatment and over 75% were classified as having WHO Stage 3 or 4 HIV disease (symptomatic illness). CD4 count and CD4 percentage, viral load, haemoglobin (anaemia) and albumin (malnutrition) levels were recorded. Most of the children were malnourished and anaemic.

Close to 90% of children who began first-line treatment over the four-year period were still alive as of July 2008. Thirty-two (6.7%) had died, 12 (2.5%) had transferred out of the programme and 18 (3.8%) were lost to follow-up. Most deaths occurred within the first 90 days across all age groups and were associated with a lower weight-for-age ratio, being anaemic, being classified as WHO Stage 3 or 4 and having a lower CD4 percentage at the start of treatment. Unlike the deaths, loss to follow-up occurred both before and after the first 90 days of treatment and was associated with a lower CD4 percentage and stage 3 or 4 disease at the start of treatment. After six to twelve months on treatment, 75% of children had viral load suppressed below 25 copies/ml (the limit of detection), a median increase in CD4 cell counts from 432 to 519 and in CD4 percentage from 17% to 22%.

At the conclusion of their analysis in June 2008 the researchers, concerned with the low number of children under the age of one receiving treatment, set up new procedures to ensure that HIV-positive children were not being missed.

Treatment for children at disease stage 3 or 4 was often delayed since doctor referral and subsequent ART initiation was dependent upon viral load or CD4 results.

Clinic nurses were notified that all sick HIV-exposed children, as well as those who were malnourished, could see a doctor regardless of HIV status. Nurses and counsellors received enhanced paediatric HIV training. Importance was placed on recognising TB as a WHO stage 3 condition and the eligibility of all children with HIV who had a history of TB for antiretroviral therapy.

From 1 July 2008 to 31 December 2008 a 42% increase in children receiving ART across all age groups was recorded, with an increase of almost 50% in children under one year of age.

The authors conclude: "We believe we've shown that paediatric ART is feasible in a devolved programme in a rural area. However there are still too few children under one year (of age) on treatment, and there is an urgent need to identify HIV-exposed children."

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## Monitoring

### Study shows potential for using dried blood spots for HIV viral load testing

By Theo Smart

Dried blood spots can be used to measure HIV viral load, using the Abbott RealTime HIV-1 assay, although they tend to produce somewhat higher values than viral load tests in plasma, and the method may fail to quantify the virus in some specimens from subjects with low plasma viral loads, according to South African and international studies described at the Fourth South African AIDS Conference in Durban.

In a study with 497 samples, the method would detect 94% of viral loads below 10,000 copies/ml, according to Professor Lesley Scott of the Department of Molecular Medicine and Haematology at the University of the Witwatersrand.

While still not perfect, these results suggest that the method does have potential to be used to confirm antiretroviral treatment failure virologically in situations with limited access to plasma viral load measurement because of technical or logistical constraints.

### Scaling up laboratory monitoring for people on antiretroviral therapy (ART) in resource-limited settings

In the South African national programme, about 560,000 people with HIV on ART currently require viral load testing at least twice a year. The test is no longer used for staging disease in people not yet on ART. Rather, it is used to monitor whether patients have failed on first-line treatment (defined as a viral load over 5000 copies/ml) and need to be switched to a second-line drug regimen.

Laboratory testing in the public sector is currently performed by the National Health Laboratory Service (NHLS) using nucleic acid testing. Out of 265 laboratories in South Africa, only 17 perform viral load testing.

There are a number of challenges in rolling out viral load testing in South Africa, including: the high sample volumes, that will only increase as the programme grows; the logistics of transporting specimens from remote sites; costs (of the equipment, maintenance, supplies, labour); phlebotomy, which is particularly difficult in children; a shortage of qualified technicians; and the limited sample throughput (number of tests that can be performed at once) using the different technology platforms.

The South African National Health Laboratory Services have responded by trying to increase throughput, develop more automated and central laboratories, and improve sample collection, transport and storage techniques. They have also evaluated alternative viral load testing technologies – an example of which is using flow cytometry as a screening technology to reduce testing volumes for viral load.

“And of course – the ‘Holy Grail’ is that we would all like to have point of care [POC] testing of viral loads in the clinics,” said Prof. Scott.

#### **Dried blood spots**

Viral load testing of dried blood spots (DBS) could help address some of the problems with sample collection, transport and storage. DBS are increasingly being used for the diagnosis of HIV in infants because they can easily be collected from infants, packaged and sent to a centralised lab for testing. But all that is required for diagnosis is to detect HIV in the specimen – which is much easier than reliably measuring how much virus there is.

“The big research question is: can DBS [be used to] measure at least 5000 copies/ml for monitoring?” said Prof. Scott.

#### **Methods**

To find out, Professor Scott looked at the Realtime HIV-1 assay, a commercial platform that has recently been introduced for plasma viral load testing in South Africa. [This section describes the methods for a laboratory audience.]

The platform has an extraction stage, which is automated, and a real-time detection (m2000rt) system that is based on fluorescence. In contrast to other viral load tests, an advantage of this system is that it can be performed in a single room. On plasma specimens, the assay has a very broad linear range: from 40 copies to 10 million copies/ml with a fairly high throughput of 93 samples per day per run, more with overnight testing.

To use DBS, 50 µl per spot from treated blood were collected on Whatman Protein Saver 903 cards within 24 hours post-venesection. These were manually punched into 50 ml Nunc tubes to prevent any further handling. The DBS was stored in the desiccant for two weeks at room temperature before being tested and the results compared to those with 1 ml of plasma. Two spots (100 µl) were used in the extraction.

Professor Scott and colleagues performed a pilot study to determine the correct extraction requirement and found an hour’s incubation in 1.7 ml lysis buffer was adequate.

#### **Studies**

Testing 21 samples (previously stored at -20°C), and comparing them with viral load measurements of plasma samples obtained from the same patients, they found that, in the majority of the samples, DBS viral loads actually yielded a higher value, which was surprising because the amount of blood sampled was very low. This would normally be expected to result in a less sensitive reading. However, the mean difference was 0.2 log, with a lower standard deviation.

But most remote sites can’t refrigerate their specimens. So a bigger study was performed with 98 DBS samples stored at room temperature, again compared with plasma samples drawn from the same patients.

Viral load measurements could be obtained on 85 of these, with values ranging from 1.6 to 6.82 log copies/ml. In these specimens, DBS still gave viral load values higher than in plasma, though again the mean difference was within an acceptable range. However, some of the specimens were outliers: 20 (23%) had values that were over 0.5 log higher, and six (7.1%) had values that were more

than 1 log higher than in plasma. But of the latter six, all had absolute values of less than 4 log copies/ml with DBS viral load. “It’s interesting to note that this assay can actually generate results down to the lower level and actually yield a higher value,” said Professor Scott.

Viral load was undetectable in 13 of the samples, five of which were also undetectable on plasma viral load. The eight remaining had values ranging from 40 copies/ml to 546 copies/ml with plasma viral load. Thus, anything lower than 500 should be considered undetectable with this method.

Prof. Scott was also involved in an international study of 497 samples that were tested at eight other international sites. Again, there were outliers, again in the lower range, and DBS generally produced a higher viral load measure than plasma but with mean acceptable differences, according to Professor Scott.

“If you had to ask what are the sensitivities of the DBS to provide viral load results, in the range between 400 to 1,000 copies/ml, at least 70% of the DBS values could generate those results. This extended to at least 94% of viral load results given in plasma values that had less than 10,000 copies/ml,” she said.

#### **Implications**

A little more experience may have to be gained with this methodology to figure out what to make of the higher values among the outliers – particularly when those differences might determine whether a person is switched to second-line therapy or not. Under the South African guidelines, a half log higher value could make a difference if the person has a viral load close to 5000 copies/ml already – many other settings, however, use a 10,000 copies/ml cut-off.

Professor Scott is investigating whether the higher values might be due to the test picking up proviral HIV DNA which comes from the whole blood on the DBS.

But, with a little more refinement, DBS viral loads (using this platform at least) may offer a way to perform viral loads for patients at remote clinics that cannot access a laboratory. Furthermore, it may be possible to outfit more of the laboratories in South Africa with these machines and increase monitoring capacity.

At present, the SA NHLS must perform at least 1.2 million viral load tests per annum for the current number of individuals on treatment, and the demands for viral load scale-up will keep growing. Later in the conference, Dr Terry Marshall of the NHLS gave an upbeat forecast of the programme’s ability to keep scaling up – the service has indeed grown at an astounding pace.

But in a press conference afterwards, Dr Marshall said that while they were hopeful about DBS viral loads, specimen collection is trickier than when DBS are collected for infant diagnosis.

“The problem with quantitating from a dried blood spot is that you need exactly the right amount of blood to be placed on the spot at the time of collection. With the DBS in infants, we have a lot of ‘fun’ already. We get all sorts of variability occurring [in the size of the sample] already, sometimes just a tiny smear on the paper, which you cannot analyse. So it’s something that is very very doable, but it does involve very very careful specimen collection and I anticipate that we will have our greatest challenge in getting the clinics consistently trained up to the point where we will always get good quality specimens,” she said.

#### **Reference**

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## Mothers and children

### Maternal HIV-positive status shown to be linked to poor vaccination coverage in children

By Lesley Odendal

Children born to HIV-positive mothers were 25 to 40% less likely to be vaccinated for childhood diseases, according to findings from a study based on data from rural KwaZulu-Natal, presented at the Fourth South African AIDS Conference in Durban in early April. The distance to mobile clinics was also a significant determinant of vaccination. Wealth index was a significant determinant for vaccinations given once, but for those vaccinations that required three visits to healthcare facilities, coverage was mediated by other factors, such as distance to the nearest road, since mothers have to overcome transport challenges more than once to complete the course of vaccinations.

Globally, vaccinations have led to reduced morbidity and mortality in children, with an estimated 2.9 million potential deaths prevented by vaccinations between 2000 and 2007, according to the World Health Organization.

However a cross-sectional study conducted among pregnant women in Rakai, Uganda, showed that children born to HIV-infected mothers were significantly less likely to be vaccinated (OR=2.21, 95% CI; 1.14 to 4.29).

To investigate the relationship between immunisation status of children and maternal HIV status, 2431 children in the Hlabisa district were included in a regression analysis by James Ndirangu from the Africa Centre for Health and Population Studies, at the University of KwaZulu-Natal.

The sample included all children born between January 2004 and December 2005 and resident in the area covered by the Africa Centre's demographic survey, an ongoing research project in a rural district in northern KwaZulu-Natal.

Maternal HIV status was found to be positive for 890 (36.6%) and negative for 275 (11.5%) of the mothers. More than half of the mothers (52.1%) did not know their HIV-status.

Data were collected from each child's Road to Health (RTH) card and mothers were also requested to recall the vaccinations of their children.

After adjusting for maternal age, maternal education, household wealth and distance to the nearest road, mobile clinic or fixed clinic, it was found that children born to HIV-positive mothers were 40% less likely to have received a BCG vaccination than those born to HIV-negative mothers.

For the polio, DTP and hepatitis B vaccinations, which must be administered three times, it was found that children born to HIV-positive mothers were 36% less likely to have received the vaccinations than those born to HIV-negative mothers ( $p = 0.05$ ). Possible reasons for HIV-positive mothers to be less likely to vaccinate their children may be due to maternal HIV-related diseases and weakness. Another factor that may be contributing to the lower rate of immunisation is the time and resources mothers have to devote to accessing antiretroviral treatment, especially in this rural setting. Fear of stigmatisation is also a suggested factor, with mothers not wanting to attend facilities where their status may be known.

Distance to mobile clinic was also a significant determinant of vaccination. Sixty-five per cent of mothers in the study area walk for one hour or more to the nearest clinic.

The median distance to the nearest road was 2.01 km, while the median distance to the nearest mobile clinic was as much as 5.77km and to the nearest fixed clinic was 3.11km. The relative distance to mobile clinics as opposed to fixed clinics is also a contributing factor, as fixed clinics provide comprehensive primary care while mobile clinics are specifically for vaccination, family planning and antenatal care.

Future interventions to improve vaccination coverage should take into account the relationship between maternal HIV status and vaccination coverage. Specific vaccination campaigns which target HIV-positive mothers should be carried out at community and individual level to improve coverage. This is especially important given that the children of many of the HIV-positive mothers may be HIV-positive themselves and hence more likely to fall ill with the diseases they need to be vaccinated against.

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### Home stimulation programme shows positive impacts on the neurodevelopmental status of children infected with HIV

By Lesley Odendal

Participation in a basic home stimulation programme can lead to improvements in both motor and cognitive development in HIV-positive children under 30 months, according to findings from a study presented at the Fourth South African AIDS Conference in Durban in early April.

The results of this study also support the inclusion of developmental screening and long-term management of all children who are infected with HIV, especially those in developing countries who do not have easy access to antiretroviral therapy.

Dr Joanne Potterton of the University of the Witwatersrand and colleagues conducted a randomised controlled trial to measure the impact of the home stimulation programme on the neurodevelopment status of HIV-positive children.

HIV is neurotropic (i.e. a virus capable of affecting nerve cells) and hence can have a negative effect on the development of the central nervous system. Many questions remain regarding the natural progression and pathogenic mechanisms of HIV-related central nervous system disease in children.

Affected children initially present with developmental delay, failure to achieve development milestones and deterioration of intellectual abilities. Although HIV affects all facets of neural development, children may present with spastic quadriparesis (a spastic rigidity of the limbs often accompanied by difficulty in swallowing and seizures), dystonic posturing (abnormal or 'locked in' movements) and regression in motor milestones as the disease progresses.

Understanding the impact of HIV on development is critical given that the rehabilitation needs of HIV-positive children on antiretroviral therapy (ART) will increase as the chronic manifestations of HIV infection become more apparent.

For this study, 122 HIV-positive children were recruited from a paediatric HIV clinic at Chris Hani Baragwanath hospital in Soweto, South Africa.

After randomisation, children in the control group continued to receive all the standard services at the clinic while children in the experimental group received a home stimulation programme in addition to the standard services.

The aim of the home programme was to optimise the child's functional potential and to encourage age-appropriate activities and normal movement patterns. All children were seen at their routine clinic visits every three months. Baseline demographic information was collected and children's heights, weights and head circumferences were measured at each visit. The home programme was updated at each visit.

Developmental status of the children was assessed using the Bayley Scales of Infant Development II, by a blinded assessor at baseline, six and twelve months. This included measuring change in cognitive (MDI) and motor (PDI) developmental status over time.

For MDI, the amount of change that occurred over time was significantly greater in the experimental group compared to the control group ( $p=0.01$ ). Although improvements occurred in both groups over time, the amount of improvement in the experimental group was significantly greater than that in the control group ( $p=0.02$ ).

Children who were older, in the experimental group and from a household with a higher income were more likely to show an improvement in MDI over a one-year period. Improvements in PDI over one year were more likely in children who were older, in the experimental group and on ART.

The results of the study suggest that ART may have a positive impact on motor development.

The baseline developmental scores were extremely low for both MDI and PDI. Poverty, malnutrition and lack of access to antiretroviral therapy may all contribute to these very low scores. Although the children in the experimental group did improve through the use of the basic home programme, they remained delayed and need further long-term follow-up, according to the study.

While the findings from this study have positive implications for the neurodevelopment of HIV-positive children, the study also illustrates that South African children who are infected with HIV are at risk of severe cognitive and motor delay. While the participation in a basic home stimulation programme led to improvements in both motor and cognitive development, the results of this study also support the inclusion of developmental screening and long-term management of all children who are infected with HIV, especially those in developing countries who do not have easy access to antiretroviral therapy.

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## Clinical management

### Fracture patients infected with HIV infection may not warrant extra precautions against opportunistic infection

By Hayden Eastwood

Doctors treating open fractures in patients infected with HIV do not need to be more cautious about opportunistic infections compared with HIV-negative patients. The finding, presented by James Aird of Ngwelezane Hospital at the Fourth South African AIDS

conference in Durban this month, follows research conducted in KwaZulu-Natal, South Africa.

Many surgeons who treat open fractures (those which result in skin breakages) are concerned that HIV-infected patients may be at higher risk of developing opportunistic infections. Furthermore, this risk of infection may depend on whether the fracture is fixed internally (by mending the fracture with artificial pins and plates) or externally (by repairing the fracture with external splints, pins or supporting structures).

There are few published articles that describe the effects of HIV on fracture healing; those that do often involve small numbers of patients and are frequently statistically insignificant. However, management of bone fractures in HIV-positive individuals is a significant clinical concern in settings where between one in five and one in three adults is infected with HIV.

A previous study suggested that a four-fold increase in infection rate arises when HIV patients have internally fixed fractures. The researchers in this study attempted to reproduce and extend this finding by comparing fractures repaired with internal and external fixation in both HIV-positive and HIV-negative patients. The study involved co-operation from 93 patients with open fractures, who were examined in a dedicated clinic with a follow-up period of between one and five months. The socio-economic backgrounds of the individuals were recorded in order to determine possible external risk factors of infection and each patient was offered an HIV test.

Of the fracture patients, 25 were treated with external fixation and 68 with internal fixation. Twenty-four per cent of the patients tested were found to be HIV-positive, while 15% refused to be tested. Within the HIV-positive group, CD4 counts ranged between 131 and 862 (with a mean of 366). Eleven per cent of the wounds suffered a superficial infection, with a relative risk for HIV of 0.66 (0.15 to 2.9). For external fixators, 44% of the pin sites developed superficial infection that required antibiotics with a relative risk for HIV-positive patients of 1.21 (0.5 to 2.98).

These findings suggest that the risk of serious infection in HIV patients with open fractures (fixed with either internal or external fixation) may not be as high as some previous studies have suggested and, by extension, imply that HIV status does not necessarily need to affect the management of fracture patients, particularly those with higher CD4 counts.

The researchers suggest that a larger and more statistically representative study be conducted.

#### Reference

Aird J et al. *Study into wound infection rates in open fractures treated with internal fixation, in relation to HIV co-infection* Fourth South African Conference on AIDS, Durban, South Africa, abstract 473, April 2009

### Incidence of Kaposi's sarcoma rising among black South Africans

By Hayden Eastwood

The incidence of Kaposi's sarcoma is increasing amongst Black South Africans and is a growing health problem that requires urgent attention, according to work published by the University of KwaZulu-Natal at the Fourth South African AIDS Conference in Durban.

Kaposi's sarcoma (KS) is a rare cancer that is much more common in people with immunosuppression, such as those with advanced HIV infection. The condition, which is characterized in its early stages by dark skin lesions and subsequently by lesions in the

mucous membranes, the lungs, the gut and the lymph nodes, is caused by infection with human herpes virus 8 (HHV-8). Despite the association between HIV infection and KS, there is still no well established incidence estimate for AIDS-associated KS in South Africa.

The current study, which attempted to estimate this incidence, made use of anonymous administrative records for patients receiving care for KS in KwaZulu-Natal between 1983 and 2006 in public-sector oncology clinics. Age-standardised incidence rates were calculated using provincial census data for the local population in the years of 1985, 1996, 2001 and 2005.

Age-specific rates, which were subject to different data constraints, were assessed for the years 1983 to 1989 (the baseline) and for 2006 (the generalised HIV epidemic).

The researchers report that age-standardised incidence rates (per 100,000 people) increased from 1.04 to 19.7 between 1983 and 2007. This compares with a standardised incidence ratio in a Ugandan HIV-positive population of 6.7 when compared to the general population.

More worryingly, the incidence rate for women during the same period increased fifty-fold, from 0.21 to 11.51. Gender-averaged figures pointed towards an incidence increase from 0.52 to 14.76. Furthermore, the age of peak incidence (the age group in which KS is most likely to occur) was shown to shift from a 55 to 60-year age bracket to a 40 to 50-year age bracket for both men and women. This was expected because HIV is more prevalent in young people than old people.

The authors stress that only public-sector patients were considered in the study. Many cases of early and late stage KS may very well have been treated by private doctors or left untreated and, if this was a common occurrence, may very well have contributed to a serious underestimation of KS incidence.

The study illustrates the alarming growth of KS as a health problem in rural South Africa. The researchers call for more resources to be directed at quantifying the problem and for better medical resources to be made available for KS sufferers.

Our newsletter *HIV & AIDS Treatment in Practice* published a [clinical review of Kaposi's sarcoma management](#) in resource-limited settings in February 2008.

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## Anaemia is a risk factor for mortality in patients with AIDS

By Hayden Eastwood

HIV patients suffering simultaneously from anaemia and WHO stage 4 HIV disease have a 59% (or greater) chance of dying, even when opportunistic diseases like TB are being treated with antibiotics. The findings, presented at the Fourth South African AIDS Conference in Durban, suggest that anaemia is an independent risk factor that needs to be managed separately from other HIV-associated ailments.

Previous studies have shown that patients suffering from advanced AIDS can have their lives prolonged by treating opportunistic infections with aggressive antibiotic or antifungal treatment and

antiretroviral therapy. Co-infected HIV-TB patients who are treated with anti-TB drugs, for example, have a much lower chance of dying (40% death rate) compared to those who don't take treatment (60% death rate).

Anaemia is a set of symptoms, including fatigue, headaches and shortness of breath, which result from blood haemoglobin levels becoming abnormally low. People with advanced HIV often suffer from anaemia because their bodies can no longer (for a variety of reasons) produce the hormones required to stimulate red blood cell production.

Previous published work from a number of cohorts in resource-limited settings has suggested that anaemia, which is not responsive to antibiotics, is a major risk factor for death in people with advanced HIV disease.

The South African research team, working at Settlers Hospital in KwaZulu-Natal, evaluated the impact of anaemia on survival in a South African cohort by collecting data about blood transfusions, haematinics (substances necessary to make red blood cells, such as iron and folic acid) and anti-HIV treatment history from people admitted to the palliative care ward.

The team found that AIDS patients with anaemia suffered a death rate of 59%. This was high compared to patients who died of causes like TB (26% death rate), sepsis (22%), HIVAN, a kidney disease developing with HIV (12%), Kaposi's sarcoma (10%), cancer (7%), dementia (7%) and other diseases (16%).

Furthermore, the average CD4 counts in anaemic patients who died were often similar to non-anaemic patients who lived, leaving doctors to suspect that anaemia, and not opportunistic infection arising from poor immunity, was a major cause of death.

In most cases, blood transfusions and intravenous *Venofer* (a source of iron) did not seem to reverse the anaemia. Furthermore, the levels of blood ferritin (a protein required to store iron and prevent anaemia) remained unresponsive to treatment, leaving most patients trapped in a high-risk anaemic state.

The findings provide further evidence that anaemia is an independent death-risk factor for patients suffering from advanced AIDS.

The researchers call for more money and resources to be spent on treating anaemia in people with advanced AIDS.

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## Rheumatologic symptoms after ART may be due to immune reconstitution inflammatory syndrome (IRIS)

By Hayden Eastwood

New or worsening rheumatologic symptoms that follow antiretroviral therapy may be due to immune reconstitution inflammatory syndrome (IRIS), according to findings reported at the Fourth South African AIDS Conference in Durban.

IRIS is a collection of symptoms that frequently emerge soon after antiretroviral therapy is started in HIV-positive people. IRIS is believed to result from a rejuvenated immune system mounting an inflammatory response.

Despite a well-defined case definition, there is debate within the medical community about which symptoms should fall under an IRIS classification.

British and South African researchers attempted to determine whether joint pain should be regarded as an IRIS symptom by

closely monitoring the onset of joint symptoms in patients undergoing antiretroviral treatment.

The study, which was conducted in Durban, South Africa, involved 498 adult HIV-infected patients who were due to begin antiretroviral treatment at two clinics during 2006 and 2007. Participants were subjected to normal clinical health checks before treatment started and also at two, four, eight, twelve, 16, 20 and 24 weeks following the start of treatment.

Patients who reported joint symptoms were assessed clinically and alternative diagnoses of their joint pains explored. In each patient, baseline and CD4 cell counts were tracked alongside C-reactive protein (CRP), which is present in blood during inflammatory responses and which, accordingly, allows doctors to measure the extent of inflammation.

Laboratory analysis of the patients' blood revealed a median CD4 cell count of 106 (interquartile range of 53 to 165) and a baseline viral load of 5 log (interquartile range of 4.4 to 5.6 log).

Seventy-seven (15%) of the patients reported joint symptoms before or during the study period. Of these, some were excluded as IRIS cases because alternative explanations existed for their joint symptoms. Eleven patients, for example, were found to have mechanical causes of joint pain and six were found to be suffering from the side-effects of other drug treatments. After correcting for alternative diagnoses, 23 cases (30%) remained, presumably an inflammatory side-effect of antiretroviral therapy.

The median onset period for joint symptoms occurred at eleven weeks (range one week to 22 weeks) after anti-HIV treatment started, within the normal IRIS onset period. Only one patient had elevated levels of rheumatoid factor.

The researchers highlight that joint pain is common in many HIV-TB co-infected patients during the first six months of antiretroviral treatment. In the absence of other diagnoses, these symptoms may be part of the IRIS spectrum.

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## Prevention

### Beliefs about gender equality predict multiple concurrent sexual partnerships

*By Hayden Eastwood* Beliefs about gender equality are strongly predictive of multiple concurrent partnerships and HIV risk behaviours in South Africa, suggesting that better prevention of HIV could be achieved with education campaigns that promote ideas of gender equality to men, and more frequent condom use to women, according to findings presented at the Fourth South African AIDS conference in Durban.

Multiple partnering, often described as concurrency, is a strong risk factor for HIV and is believed by some scientists to be the key factor in explaining why HIV prevalence in southern Africa is so high compared to other regions of the continent. However, despite some evidence of the dangers of the practice, little is known about it, particularly with regards to its interplay with condom use.

In order to better understand the role of concurrent partners and HIV risk, scientists at the Aurum Institute For Health Research

examined the 2001 census and randomly sampled 16 of 154 areas in Rustenburg, South Africa. Fieldworkers then superimposed the population distribution onto a satellite map and performed interviews with people from 512 randomly chosen houses. Residents in each dwelling were numbered and one of them randomly subjected to an interview geared towards obtaining demographic information, beliefs about HIV vulnerability, condom use and perceptions of gender equality. The survey captured sexual acts that occurred three months previous to the interview. Multivariate logistic models were then used to statistically analyse the data.

Of the 351 people sampled, 59.8% were female and 84.9% black. Seventy three percent were sexually active and, of these, 9.7% admitted to having more than one sexual partner. Furthermore, only 56.1% of those surveyed reported using condoms (the definition of condom use included all those who had used a condom once or more during the three months).

Men believing in greater gender equality were more likely [OR 95%, CI: 0.30 (0.13 to 0.68)] to be monogamous while, paradoxically, women of the same belief were more likely to have multiple concurrent partners. [OR 95%, CI: 0.30 (0.13 to 0.68)].

The results suggest that beliefs about gender relations play a strong role in determining multiple concurrent partnering and HIV risk. Men are protected by believing in equality but women are at heightened risk.

The researchers call for more resources to be directed at gender equality campaigns and for women to be more actively encouraged to use condoms.

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### Estimates of HIV incidence may be unreliable: techniques need refinement

*By Hayden Eastwood* The BED method for estimating HIV incidence should be standardised so that it can be reliably used in an African setting, and the technique needs to be improved to avoid counting people with longstanding HIV infection as recent infections, according to two South African research groups. Their findings were presented at the South African AIDS Conference in Durban earlier this month.

The BED assay is an enzyme-based method that allows the time of HIV infection to be estimated for research purposes. It is not routinely used for diagnosis of HIV infection in the clinic. The procedure is based on measuring the proportion of anti-HIV antibody immunoglobulin G (IgG), and comparing it to the total blood IgG using an ELISA method that permits the concentration of blood IgG to be measured. The time of HIV infection can then be estimated because, in principle, the ratio of IgG (normal vs HIV) varies in accordance with disease progression.

The BED technique is often used in conjunction with mathematical techniques to estimate the incidence of HIV and has been widely used in South Africa, Uganda and the USA. However, despite its popularity, there have been complaints that the method can be inaccurate.

Thomas McWalter, of the University of the Witswatersrand in Johannesburg, South Africa, hoped to shed light on the accuracy of

the BED assay by testing whether it had been uniformly applied in a cross-section of published BED incidence estimates.

His research team searched journal databases and discovered a total of 1136 publications that included review articles, full texts and abstracts. Of this article group, a total of 27 studies were included in a final review that took location, period, population, reported HIV incidence, the incidence estimation formula, and adjustment for false-recent results into account.

McWalter's team discovered substantial divergence in methods in the studies. Differences were found in laboratory parameters, optical density cut-offs (the measure of the ratio of HIV-IgG to total-IgG seen as sufficient for people to be considered seroconverted), window periods, incidence estimate methods and sensitivity analysis methods (mathematical methods for testing the consistency of results).

McWalter's team then applied a universal, standardised set of procedures and parameters (such as optical density cut-offs and incidence estimate formulae) to each of the published data sets. This resulted in dramatic changes to many of the calculated incidence values.

The research indicates that using different methods gives rise to different incidence values and so clear and standardised procedures are needed if incidence values are to be comparable. Further research presented at the conference by Professor John Hargrove of the South African Centre for Epidemiological Modeling and Analysis (SACEMA) highlighted additional problems with the technique.

It is well known that a subset of HIV-positive people tested with the BED assay always appear to have been recently infected even when they have been infected for many months or years. The reason for this slow (or non-existent) progression to a full antibody response is not well understood, although its occurrence is well documented. To complicate matters, another subset of people who initially seroconvert later revert to a non-seroconverted state according to the BED assay, an event, which if frequent enough, also produces incidence inaccuracies. (It should be noted that this phenomenon does not apply to standard HIV testing using the ELISA-based test.) The Hargrove research team tested the extent to which these inaccuracies existed within a Zimbabwean dataset of 14,000 mothers, each of whom had been followed after giving birth. Of those who were HIV-positive, 5.2% were found to have BED absorbances less than 0.8 after their twelve-month retest and had, therefore, been falsely identified in the initial study as recent seroconverters. Consequently, the estimated BED annual incidence at twelve months for this group (7.6%) was 2.2 times higher than it should have been.

The Hargrove team stress that, unless the proportion of long-term false-recent cases is adjusted for, the BED method cannot be reliably used, even when estimating relative changes in HIV incidence. He further emphasised that the proportion of people who test false-recent may be location-specific and that estimates of the proportion of people in this group should be obtained in any incident estimate study.

Both bodies of research indicate that the BED technique needs to be improved and standardised before reliable HIV incidences can be estimated from cross-sectional studies. These findings have strong implications for public policy because, without an accurate estimate of HIV incidence, it is impossible to measure whether or not prevention and treatment programmes are having an effect on HIV incidence.

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## Policy

### Task-shifting key to achieving South Africa's treatment goal

By Carole Leach-Lemens

Task-shifting is the key to helping to reach South Africa's goal of treating at least 80% of those in need of antiretroviral therapy (ART) by 2011, according to a joint statement by Médecins sans Frontières (MSF), Reproductive Health and Research Unit (RHUR) of University of the Witwatersrand, the Southern African HIV Clinicians Society, and Treatment Action Campaign (TAC), released at the Fourth South African AIDS Conference in Durban earlier this month. The group called on the South African government to issue, without delay, clear directives for nurse-initiated and managed ART together with expanded roles for pharmacy assistants and lay counsellors in the comprehensive delivery of HIV/AIDS services.

Task-shifting is the reallocation of tasks among available staff. For example, doctors focus on providing care at hospitals for inpatients and complicated cases rather than handling all clinical management of patients, while nurses assess patients to diagnose and treat opportunistic infections and start and monitor ART rather than solely supporting doctors.

ART services have been primarily hospital-based and doctor-led. The rapid roll-out of ART has resulted in overburdened ART clinics, revealed considerable gaps in access and left many without the appropriate follow-up that ART management requires.

Currently 200,000 people start treatment each year in South Africa. This number needs to double, to 420,000 each year, if the goal of 80% coverage is to be reached by 2011. In 2007, 34% of those in need were on treatment. An estimated 1000 deaths due to HIV/AIDS-related complications are recorded daily. More than five million people in South Africa are living with HIV.

To date, an estimated 700,000 have started ART and it is anticipated that an additional 1.2 million will need ART by 2011. Legislation already supports the following the HIV/AIDS National Strategic Plan recommendations:

- A decentralisation of comprehensive HIV/AIDS services to the primary health level
- Professional nurses to initiate and manage ART for adults and children (at present only doctors do)
- Trained lay counsellors to administer HIV rapid tests (at present only nurses do); and
- Supervised pharmacy assistants to dispense ARVs (at present only allowed by pharmacists).

Task-shifting can provide more points of care, improving access to treatment, increasing adherence and allowing better management of those currently on ART. Evidence from MSF programmes in Khayelitsha and in rural Lusikisiki supports the effectiveness of

task-shifting. MSF built on these experiences in Lesotho where, as in Malawi and Mozambique, regulatory guidelines have already changed, enabling nurses to initiate and manage ART and allowing all levels of nurses broad clinical and prescribing powers.

Uptake of voluntary testing and counseling would be improved if trained lay counsellors were able to administer HIV rapid tests and free up nurses to see more patients.

"The 2008 National PMTCT Guideline recommends dual therapy to prevent mother-to-child transmission of HIV and triple therapy for pregnant women that are in clinical need, but midwives and nurses working in ANC services need the training and authorisation [to initiate and manage antiretroviral therapy]," said Dr Eric Goemaere, Medical Co-ordinator for MSF in South Africa and Lesotho.

"Pharmacy assistants must be able to dispense ARVs, with distance supervision from pharmacists."

Incomprehension as to why these apparent regulatory blockages persist in South Africa was expressed by Francois Venter, President of the Southern African HIV Clinicians Society. "The evidence supports that quality is maintained, so what are we waiting for? The current inflexibility shown by the professional councils and trade unions is illogical at best and damaging for patient care at worst. Only leadership from the National Department of Health (NDOH) will be able to cut through the stalemate," he said.

The group called for:

- The National Department of Health (NDOH) to issue a directive clarifying that trained professional nurses can initiate and manage ART for adults and children, and to issue guidelines to allow trained lay counsellors to administer HIV rapid tests, and supervised pharmacy assistants to dispense ARVs
- Provincial Departments of Health and district managers to issue a clarifying directive allowing trained professional nurses to initiate and manage ART
- The South Africa National AIDS Council (SANAC) to hold a mid-term review of the NSP, highlighting the issue of task-shifting as no progress has been made
- The South Africa Nursing Council (SANC) to expedite legislation pertaining to scope of practice for professional nurses to initiate and manage ART and the South African Pharmacy Council to revise scope of practice for pharmacy assistants to dispense ARVs
- Professional associations, including the Democratic Nursing Organisation of South Africa (DENOSA), the South African Medical Association (SAMA), and the Pharmaceutical Society of South Africa (PSSA), to support task-shifting, as described above.

Anecdotal reports at the conference suggested that, in the meantime, these barriers might be overcome by approaching the respective provincial Departments of Health and submitting a proposal outlining a pilot nurse-initiated and managed ART project for approval.

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Lesotho: 2006-2008 programme report available at [www.msf.org.za](http://www.msf.org.za)

## South Africa faces treatment funding shortfall

South Africa will face tough choices in the years ahead as its government strives to extend treatment to all who need it through the public health system, a leading health economist told the Fourth South African AIDS Conference earlier this month.

Dr Susan Cleary, the director of the Health Economics Unit at the University of Cape Town's School of Public Health and Family Medicine, outlined the financial dilemma that South Africa will face in the coming decade as the number on HIV treatment grows.

The long-term sustainability of South Africa's antiretroviral treatment programme is a major concern, given the fact that 17% of people living with HIV worldwide are estimated to reside in South Africa, and an estimated half million individuals need to start treatment each year.

How will this volume of treatment remain sustainable, and how can equity of access be ensured in a country with one of the highest levels of income inequality in the world?

One of the starkest indicators of inequity in South Africa is the level of health spending. Overall South Africa spends more on health than almost any other developing country (7.7% of GDP in 2005), and its expenditure is comparable to many rich nations.

However there is a huge gap in resourcing. Fifteen per cent of the population receive health care through the private system, where per capita spending is approximately R9,500 a year.

The remainder of the population receive health care through the public system, where per capita spending is no more than R1500 a year.

That translates into one general practitioner to every 590 patients in the private sector, compared to 4,200 patients to each general practitioner in the public sector.

Specialist physicians are even thinner on the ground in the public sector: one per 11,000 patients in the public sector compared to one per 500 patients in the private sector.

Given the huge reliance on the public health sector for health care, it's inevitable that South Africa will have to simultaneously build the capacity of the public health system while tailoring its treatment programme to fit the very constrained resources available.

South Africa is doing well at meeting the targets set out in the National Strategic Plan for numbers on treatment, although many argue that the national targets could be more ambitious.

But over the next 15 years treatment and prevention costs are projected to grow tenfold from R2.4 billion in 2008 to R25 billion in 2022, potentially consuming more than half of the public health budget at 2008 expenditures.

How will South Africa cope? Using the cut-off of one-third of health expenditure devoted to HIV care delivered through the current model, Susan Cleary projects that in ten years time it would be possible to achieve 62% antiretroviral coverage. Task-shifting and reducing unit costs of care would increase coverage by 10% - another 400,000 people treated.

Restricting treatment to the provision of first-line therapy only would increase coverage by 16% - an additional 700,000 people treated.

If the resources of the private sector could be engaged, Cleary suggests that treatment could be delivered to all who need it, taking up 21% of the country's total health budget. In these circumstances

earlier treatment and better tolerated first-line drugs could be offered to all.

However, Cleary says that in reality, treatment in South Africa is already rationed, and will continue to be rationed in the future. The challenge facing the country, she said, will be in deciding how to use scarce resources in the future. In particular, South African society will have to decide whether it is better to reach fewer people with a higher standard of care, or whether less effective but more cost-effective treatment should be provided to a wider population?

But Mark Heywood of the AIDS Law Project highlighted the finance gap already facing South Africa. "If we take the existing numbers of patients who are on treatment, which is estimated to be just over 600,000 people, and if you add to that another 200,000 who will require to be initiated onto treatment this year, then the shortfall between what has been budgeted for and what it would actually cost just to meet the treatment needs is over one billion rand [110 million dollars]."

"The NSP is budgeted to cost R48 billion over the five year period. In the next three years up until 2011, the total HIV/AIDS allocation is only 11.4 billion," said Nonkosi Khumalo, Chairperson of the Treatment Action Campaign. "How are we to reach the NSP targets if we do not have the budget for it? We have seen moratoriums in some provinces this year, but that is just the tip of the iceberg."

The worst example of the effects of the funding shortfall have been seen in the Free State, where the provincial government suspended the enrollment of new patients on antiretroviral treatment in November 2008 due to over-spending. The AIDS Law Project has estimated that 15,000 people need to start treatment, and drug supplies have been interrupted for many patients on treatment.

Advocates have criticised bad planning and poor budgetary controls for the shortfall in funding.

"It's not that South Africa does not have enough funds, but about where the funds are allocated," said Mark Heywood.

"We need to recognise the importance of health in this country, and ensure that adequate finances are available to scale up healthcare, in accordance to the Constitution," said Mark Heywood. "A major problem is that health budgeting is not needs-based. We are given a figure and then we determine how many people we can reach, instead of assessing how much it would cost to meet the health and treatment needs. We call on government to provide budget allocations based on need and that all funds are spent effectively and efficiently to save as many lives of people waiting for treatment as possible."

## New column: HIV and TB in Practice

By Theo Smart

*With this issue, we are launching a monthly column focused on advancing the integration of HIV and TB services, exploring the challenges and practical solutions to the implementation of TB/HIV collaborative activities, and the improving the diagnosis and treatment of the more difficult to manage forms of TB that are*

*common in people with HIV, including smear negative, extrapulmonary and drug resistant TB.*

The focus of this issue of HATIP, and of the column this month is South Africa with recent news from the South African AIDS Conference. Several TB news stories from the conference are included below.

In addition, there were a number of interesting posters and other TB highlights at the meeting:

### Improving the diagnosis of smear-negative TB

One of our stories addresses the work of HATIP advisory panellist, Dr Doug Wilson of Edendale Hospital who has found that screening for high levels of C-reactive protein (CRP) can help identify active TB cases in smear-negative individuals with suspected pulmonary tuberculosis.

At present, smear microscopy fails to detect TB in a large proportion of people with HIV. Although the WHO has published [an algorithm to speed the diagnosis of smear negative TB](#), potentially effective TB treatment is still delayed for three to five days, at least while clinicians wait to see whether the TB suspect responds to a trial course of antibiotics. In practice, this sometimes takes longer, because the antibiotics can improve the health of someone with TB, but only transiently. As Dr Wilson pointed out in his talk, a low cost point of care diagnostic that quickly recognises active TB would greatly improve the confidence to simply treat for TB.

A poster presentation from Gous et al suggested another possible option — sputum PCR. Last year, several countries announced the intention to roll out the use of PCR for drug sensitivity testing — as drug resistant PCR needs to be diagnosed as quickly as possible. South Africa is scaling up capacity to perform these tests countrywide — and the goal is to have every TB patient quickly screened for drug resistance. However, the tests have not really been optimised for smear-negative specimens.

However, the researchers from Johannesburg found that the PCR tests performed virtually as well as culture — in much less time. Three different TB PCR formats were evaluated, and their results compared to that of culture, microscopy and clinical case definitions. The Roche Lightcycler Mycobacterium Detection Kit detected 16 out of 17 culture positive specimens (6 were smear negative), and correctly diagnosed 17 other specimens as negative (94% sensitivity and 100% specificity). Two other assays, the Hain GenoType MDRplus and MTB ACE Detection assays were in complete agreement with culture — plus they detected two cases of drug-resistant TB.

"Preliminary findings show sputum PCR may facilitate the diagnosis of smear-negative TB in HIV-positive patients and can be readily implemented in routine diagnostic workflow," wrote Gous et al.

That is, if health officials can get healthcare workers to send in specimens to the laboratory, and then improve management of results delivery. But another poster from Lancaster et al, on diagnosis of TB in HIV-infected patients, provided another clear reason to make sure that the drug sensitivity assays are rolled out and utilised — HIV-infected people were more likely to have drug resistant TB.

The study evaluated baseline indicators for HIV infection is specimens collected during South Africa's last drug-resistant TB survey in 2001 to 2002. A number of the indicators, such as the higher risk of being smear-negative, or having a "scanty" culture result, come as no surprise. But people with HIV showed a trend toward a higher risk of rifampicin resistance (odds ratio 1.33, 95% confidence interval (CI) 0.97-1.82,  $p = 0.076$ ) and a significantly

higher risk of ethambutol resistance (odds ratio 2.16 (95% CI 1.13-4.103,  $p=0.020$ ).

“Drug resistance testing against all first-line drugs for HIV-positive cases at baseline will have benefit,” wrote the poster’s authors.

### Improving the diagnosis of extrapulmonary TB

WHO’s diagnostic guidelines also contain criteria for the diagnosis of some forms of extrapulmonary TB. However, they say little about abdominal TB, which is common in people with HIV. Dr Tom Heller and other colleagues at Hlabisa District Hospital and the Africa Centre for Health and Population studies presented two posters assessing whether ultrasound, which they said would be the most commonly available imaging modality in rural district hospital settings. Diagnostic criteria included: abdominal lymph node enlargement ( $>1.5$ ) and visceral involvement in the form of focal splenic lesions. Ascites were also noted, but were not considered diagnostic if found on their own (as they may be related to cirrhosis or congestive heart failure, etc).

180 consecutive patients were screened by ultrasound — and 30 showed signs of abdominal TB. The most common sonographic finding was enlarged lymph nodes were, seen in 97% of the subjects. 73% had ascites and 50% had focal splenic lesions. Clinical symptoms included weight loss in 87%, abdominal pain in 73%, diarrhoea in 60% and abdominal distension in 33%. The patients had very advanced HIV disease, with a median CD4 count of 78 and either underweight or severely underweight. The authors noted that the weight loss decreased the likelihood of fat and air interfering with the ultrasound. Also worth noting — 23 of these 30 also had chest x-ray evidence compatible with TB, 21% with a miliary pattern.

Follow-up was available for 25 of the patients after a mean of 17 weeks on TB treatment. Six had died within the first two weeks of initiating treatment, but the remainder continued on treatment with clinical improvements. All but one had also initiated antiretroviral therapy.

Dr Heller’s second poster stressed that while ultrasound showed utility, “trained ultrasonographers are scarce in the rural environment.” So they developed a short training course ‘Focused assessment with sonography for HIV/TB’ (FASH), and trained 4 clinicians without prior experience in ultrasonography or radiology (one who had very limited access to the scanner dropped out). After gaining some experience, most of the clinicians eventually achieved a high level of confidence using the technique. In an assessment of 62 patients, use of sonography added a diagnosis in 28, and excluded a diagnosis that was previously expected in 30. In 32 therapy was changed on the basis of the sonographic results.

### Challenges and solutions to TB/HIV service integration

Dr Heller’s colleagues also presented their experience at integrating TB and HIV services in these same rural settings. One key element, they found was optimising the physical proximity of the services. They actually placed the TB and ART teams directly next to each other in a shared park home at one peripheral clinic. They also set up a streamlined referral system to a central ‘cough’ clinic” to expedite TB diagnosis. Also, “training activities for the nurses and counsellors in both programmes as well as strategies to monitor and feed back the performance are important to ensure sustained commitment of the staff,” Wallrauch et al wrote. Although HIV testing in South Africa is voluntary, the Hlabisa district achieved 88% uptake of testing in its 16 clinics— and had CD4 cell count measurements available for 81% of those testing positive.

The difficulty getting this sort of uptake of collaborative services countrywide was the subject of a health system survey by researchers at the University of the Western Cape and the TB/HIV Care Association (Uwimana). One of the chief problems cited by the survey was the lack of a coordinating body above the TB and HIV programmes. Generally, the HIV/AIDS, Sexually transmitted infections and TB (HAST) unit is perceived of as the framework for the coordination of collaborative activities, but the HAST manager has the same rank as the TB and HIV/AIDS programme managers, which leads to power and role conflicts.

Another problem noted was that programme managers lack an understanding of what “integration” means, which leads to uncooperative attitudes. (This survey and similar presentations will be addressed in greater detail in a future issue)

Addressing issues such as poor understanding of the concept of integration and collaborative services will take better communication and education efforts targeting programme managers, clinicians, nurses and other healthcare professionals. Conferences offer one venue where these messages can be delivered, but the competition for conference-goer’s attention can be fierce.

The Aurum Institute may have found a way around this, when it held a symposium on the Three I’s (isoniazid preventive therapy, TB infection control, and intensified case finding). The room was packed — they had to turn about 250 people away. They held small money lotteries, distributed ice cream and even had entertainment. It seems they are putting the lessons learned from providing incentives that CREATE studies have been using to enrol and engage clinical trial participants to getting the doctors and nurses in at these conferences as well.

### Improving the management of drug-resistant TB

There were several presentations that could help address some of the therapeutic nihilism surrounding the treatment of drug resistant (DR) TB, especially extensively drug resistant TB (XDR-TB). In one poster, researchers from the MRC presented findings suggesting that replacing ethambutol with terizidone (similar to cycloserine but much less toxic) could result in a faster culture conversion rate in HIV-positive MDR-TB cases (Odendaal).

Previous research had noted better clinical responses among MDR-TB patients who are resistant to ethambutol than those who were susceptible to the drug. The chief difference between these patients was that rather than being put on an ethambutol-containing regimen, those with ethambutol resistance had been put on regimens containing either cycloserine or the closely related (but much less toxic) terizidone. So they performed an analysis of 1189 subjects on regimens containing the three different drugs (note only 89 were on terizidone). The hazard ratio for time to culture conversion was 1.80 (90% CI 1.06-3.05,  $p=0.067$ ) in people with HIV and MDR-TB. Oddly, culture conversion took longer in the HIV-negative subjects.

And a late breaker presentation from Dr Karen Shean and colleagues at the University of Cape Town reported better than expected survival in people with HIV and XDR-TB. The researchers reviewed case record for 224 patients with XDR-TB on treatment in the Western Cape, Eastern Cape and Gauteng Provinces. 43% were HIV infected and 83.3% were smear negative at diagnosis. The 12-month survival in HIV-positive and HIV-negative subjects was 52% and 75% respectively. Survival time and time to conversion did not differ by HIV status (log rank test  $p=0.08$  and 0.55 respectively). These findings up the ante on the early detection of XDR-TB, because early treatment can save lives.

But the best news came at the very end of the conference, when the South African Minister of Health, Barbara Hogan, just back from a high-level meeting in Beijing on drug resistant TB was clearly quite energised about tackling TB/HIV and drug resistant TB issues. There were a number of high points in her speech include her mention of the need to address the cross-border dumping of patients with drug-resistant TB and her goal for South Africa to lead the way to developing more effective regional responses to TB/HIV. She also opened the door to moving more towards the community-based care of drug-resistant TB."

"At the ministerial MDR-TB meeting, I requested the agencies there to offer technical assistance in determining how best to ensure that hospital based treatment and isolation are not a permanent means of treating DR TB," she said. "It is arguably unaffordable and it presents a whole range of other ethical and human rights issues that require further thought. The encouraging outcomes of the two pilot community based DR-TB programmes in the Western Cape and KZN tell us that we need to ask how and to what extent we can replicate them in a manner that protects the human rights of the patient, healthcare worker and the community.... I am hopeful that a policy recommendation will be consolidated within the next 4-6 weeks by officials in the National Department of Health for consideration."

As votes are being counted in the South African election, it is our sincere hope is that Minister Hogan will remain in her position in the next administration to fulfil these promises, or that at the very least, her successor will carry this vision forward.

#### **TB/HIV Research meeting in Cape Town, South Africa, July 18-19**

The TB/HIV Working group of the Stop TB Partnership and WHO, in conjunction with other partners such as the International AIDS Society and CREATE, will host an international meeting in order to enhance networking and scientific interest for priority HIV/TB research issues.

The meeting will bring notable researchers and leaders in the areas of TB prevention, childhood TB/HIV, TB treatment and diagnosis, and the interaction between HIV and drug resistant TB.

It is also intended to create a forum to exchange ongoing research activities, including data among researchers. The meeting will also inform the revision of the WHO HIV/TB research priorities.

The meeting will be held in the Desmond Tutu HIV Centre, University of Cape Town on July 18- 19, 2009, prior to the opening of the 5<sup>th</sup> International Conference on HIV Pathogenesis, Treatment and Prevention Conference.

Deadline for registration: Registration should be submitted no later than June 15, 2009 by emailing Ms Rosalie Edma at edmar@who.int ; mention "HIV/TB research meeting" in the subject line.

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## about HATiP

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