CONFERENCE REPORT

THE 3I's SATELLITE SYMPOSIUM: REDUCING THE RISK OF TUBERCULOSIS IN HIV-INFECTED INDIVIDUALS

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'I have twelve minutes to give this talk, but I can make my point in twelve seconds: There's a lot of TB in our HIV services and we need to do something about it!' said Dr Steve Lawn of the Desmond Tutu HIV Centre at the University of Cape Town at the start of the '3I's Satellite Symposium' held on 31 March 2009, just before the 4th South African AIDS Conference (SAAC).

HIV-infected individuals, especially those requiring antiretroviral therapy (ART), are at a greatly increased risk of developing active tuberculosis - and one consequence of this has been the resurgent TB epidemic in sub-Saharan Africa and other settings with a high burden of HIV.

People working in HIV/ART services can reduce the risk of TB in people with HIV by performing three activities that the World Health Organization (WHO) has promoted as the '3I's' strategy: *infection control* (measures to reduce the spread of TB, especially in health facilities); *intensified case finding* to proactively identify TB in people with HIV; and *isoniazid preventive therapy* to prevent active TB.

South Africa and other countries have endorsed the 3I's strategy as policy, but implementation has been slow and somewhat limited. For this purpose, the 3I's symposium, sponsored by the Aurum Institute, Thibela, and the Consortium to Respond Effectively to the AIDS TB Epidemic (CREATE), was held to increase awareness of these measures to reduce HIV-associated TB and to encourage the implementation of existing guidelines.

'*Just do it* should be the mantra of this symposium,' Professor Gavin Churchyard of the Aurum Institute told the standing-room-only audience. But to show just *how* to do it, more than a dozen experts at the meeting spoke about the gaps between policy and present practice, identified the barriers to implementation and offered possible solutions. Several recently completed or ongoing research studies were described that could help guide future policy and implementation. Speakers shared their hands-on experience about on how to put the 3I's into practice.

OVERVIEW OF TB/HIV IN SOUTH AFRICA IN THE HIV AND TB CLINICS

There has been a threefold jump in mortality in South Africa over the past several years, and although there is often an underlying disease, such as HIV, 'TB has been the most commonly reported cause of death on the death certificate', according to Professor Anton Stoltz of the Foundation for Professional Development, 'and it is killing people in the prime of their lives.'

Globally South Africa ranks fifth in the absolute number of people with new smear-positive TB, but the countries with heavier burdens (such as China, India and Indonesia) are far more populous. Swaziland and South Africa have the highest incidence rates per capita in the world (with close to 1 000 cases per 100 000 people), according to 2006 data from the WHO.

At the same time, the type of TB being diagnosed in South Africa has changed over the past decade with a dramatic increase in smear-negative TB, extrapulmonary TB, retreatment TB and now increasingly drug-resistant TB.

Professor Stoltz listed multiple factors that could contribute to the TB epidemic, starting with overpopulation, climate change and malnutrition, as well as conflict and turmoil leading to displacement and migration. Lack of strong political will to provide adequate support of the health system has resulted in low cure rates, high default rates and inadequate follow-up of patients, ultimately spawning an epidemic of drug-resistant TB. Poor infection control practice in health facilities has led to the spread of TB (drug-susceptible and drug-resistant) to other patients and to health care workers. Economic hardship and poor living conditions lead to spread of TB in communities as well.

'Poor people living in shacks with little air circulation are at high risk of infecting each other,' said Professor Stoltz. 'But by far the biggest driver of TB is HIV.'

Nowhere is this more evident than in the Western Cape of South Africa, where Dr Lawn said that 'three oceans have come together, the Atlantic Ocean on the West and Indian Ocean on the East; and in between the two there is a vast ocean of TB and HIV'. In fact, in one of the peri-urban communities where Dr Lawn works, TB notifications exceed 2 000 per 100 000 - rates unprecedented in the era of modern multidrug chemotherapy - despite a model local TB programme. Everyone living in this resource-strapped community is at substantial risk of TB, but the risk is greatest in people with HIV, even when they are on ART.

'The burden of TB among people with HIV before, during and *after* ART initiation is huge,' according to Dr Lawn. In one analysis of the cumulative burden of TB in people arriving into an ART clinic in Gugulethu, 'more than half have had one or more episodes of TB before they even set foot in the door. Another quarter of the patients either have active TB on treatment or previously undiagnosed TB. So, at baseline, two thirds of the people either have had or have TB currently,' said Dr Lawn. Most of the previous TB cases occurred within the 2 - 3 years before initiating ART.

In another study of 235 patients enrolling into the ART programme, Dr Lawn and colleagues actively screened for TB using culture instead of induced sputum. They found that 25% (*N*=58) had culture-positive TB and the risk was even greater (at 38%) in those with CD4 counts below 100.[1] But in the absence of culture it would have been difficult to identify everyone with TB - 22% of those with culture-positive TB had no TB symptoms (cough, fever, night sweats or weight loss), 30% had no sign of TB on chest radiograph, and fluorescent smear microscopy was positive in only 14%. Culture, while sensitive, took over 3 weeks to produce a diagnosis, and drug sensitivity testing (via Lowenstein-Jensen medium) took 3 months.

Once on ART, the risk of TB is extremely high during the first 3 months, probably due to unmasking of TB missed by baseline screening.[2] During the first year on ART in the Gugulethu study, about 11% developed incident TB after which the risk plateaued at around 4 - 5% per year. Even after 3 years on ART, the TB incidence remained four or five times higher than the background rate in the HIV-negative p opulation.

The key determinant of TB risk is a person's CD4 cell count, and those with poor immune recovery on ART are at even higher risk. In the Gugulethu cohort, for every rise of 100 cells/µl, there was a 25% reduction in risk of TB. Even with optimal CD4 cell count recovery (over 500 cells/µl), the incidence of TB remains about twice the background rate in the HIV-negative population.

Conversely, many people are only diagnosed with HIV after they have been placed on treatment for active TB. Globally, about 1.4 million TB cases are co-infected with HIV - leading to about 0.5 million deaths each year - while in South Africa there are about 350 000 co-infected cases of TB (for an HIV infection rate of about 70% among TB patients).

Since there are drug interactions and overlapping toxicities between ART and TB treatment, 'one of the most critical questions in this population has been when the optimal time is to initiate antiretrovirals in people on TB treatment', said Dr Kogie Naidoo of the Centre for the AIDS Programme of Research in South Africa (CAPRISA). To answer this question, Dr Naidoo and colleagues conducted a randomised trial of 642 patients with HIV and CD4 cell counts below 500 cells/µl who were on standard TB treatment. Patients began ART in one of three time periods:

- During the first 2 months of intensive TB treatment (early integrated treatment)
- After the 2-month intensive phase of TB treatment was completed (later integrated treatment), or
- After the entire 6 - 8-month course of TB treatment is completed (sequential treatment).

An interim Safety Monitoring Committee review of the data found that patients in the two integrated treatment arms had a 56% lower death rate than those in the sequential treatment arm. The sequential treatment arm was subsequently terminated, though the two integrated treatment arms of the study are ongoing.

Of note, 'TB outcomes were similar in both arms - mortality in the sequential treatment arm occurred late in TB treatment and after TB treatment was completed, hence the TB programme may not be aware of the higher mortality,' said Dr Naidoo. The programmatic implications include offering every TB patient HIV testing and counselling, and those with TB-HIV (and CD4 <500) should be started on ART while they are still taking TB treatment. Dr Francois Venter of Johannesburg Hospital said this would probably mean that TB nurses should be initiating patients on ART. If South Africa were to do this widely, Dr Naidoo estimated that 150 000 more TB patients would be placed on ART and about 10 000 deaths prevented annually.

But even though concurrent ART improves TB outcomes, the management of active TB is still quite complicated in people with HIV. TB remains the leading key cause of death in ART services - probably more than we know, since much TB goes undiagnosed.[3] Despite ART, people with prevalent or incident TB and HIV are two

or three times more likely to die than their HIV-negative counterparts. In addition, people with HIV and TB contribute to onward transmission in the community and the clinic. Although many cases of TB in people with HIV are sputum smear-negative, Dr Lawn noted that 'smear-negative does not mean non-infective ... Smear-negative TB cases may be contributing substantially to TB transmission within the clinic, [especially] because patients with HIV are exquisitely susceptible to infection.'

'We need adjunctive strategies to prevent TB - upstream of ART services,' he said. That is, strategies such as the 3I's - the first and perhaps most fundamental of which is infection control.

TB INFECTION CONTROL (IC)

'TB infection control is the strongest preventive tool we have; it is crucial that we get this basic step right in the first place,' said Lesley Odendal, an IC co-ordinator for Médecins Sans Frontières (MSF) in Khayelitsha, and one of three speakers on the subject at the symposium.

IC measures are essential to prevent the spread of *Mycobacterium tuberculosis* to vulnerable patients, health care workers, the community and those living in congregate settings. The concept of IC has been around ever since Florence Nightingale wrote that hospitals 'should do the sick no harm'. For years, TB IC measures were standard policy in health care settings until they fell out of practice with the advent of TB chemotherapy. Since the outbreak of extensively drug-resistant TB (XDR-TB) - where there were clear indications of transmission at the Church of Scotland Hospital in Tugela Ferry in KwaZulu-Natal - TB IC has once again become a public health priority.[4]

'High rates of TB infection and disease in health care workers have been demonstrated in a number of studies, implicating nosocomial transmission,' said Dr Lilanganee Telisinghe of the Aurum Institute. These include a recent literature review by Menzies *et al.* that 'found that latent TB infection was consistently associated with ... occupational exposure,' she said.[5] Those who worked longer in some areas had consistently higher rates of TB than that of the general population, plainly making TB IC an occupational safety issue - 'and a human rights issue,' Ms Odendal pointed out.

There is an established hierarchy of controls to reduce the risk of TB transmission, beginning with *administrative and workplace measures* to reduce the generation of infectious TB particles in the facility and prevent the spread of the disease by quickly identifying, separating and investigating suspects and treating the TB cases; *environmental control measures* to reduce the concentration of infectious TB particles in a facility by ventilation or air cleaning; and *personal respiratory protection* to decrease or prevent inhalation of infectious TB particles by staff and clients.

Administrative and workplace control measures include a written infection prevention and control plan for each facility. Procedures in the plan need administrative support, including quality assurance, as well as training and supervision of staff. Patients and the community need to be made aware of how TB is transmitted (and taught cough etiquette). Finally, every facility needs to communicate and work closely with the TB programme to co-ordinate these efforts.

Although Menzies *et al.* reported that administrative controls may be less effective in lower middle-income countries than in high-income settings (where training and resources may improve implementation), Dr Sidney Parsons, an engineer specialising in IC at the Council for Scientific and Industrial Research (CSIR), said that administrative measures remain the very foundation of IC.

'Fundamentally, everything starts and ends with the infection control plan,' he said, noting that generic IC plans or templates alone are inadequate. 'We've got to develop a specific plan for every facility because every facility is unique, and we need to make certain that the plan is in writing, easy to understand, and accessible. The plan must be practical, affordable, comprehensive and creative but in line with the accepted hierarchy of controls.'

Speakers alluded to a document released by the WHO last year to help countries and programmes prioritise TB IC interventions: 'Essential actions for effective TB infection control: Safety without stigma' (http://www.stoptb.org/wg/tb_hiv/assets/documents/10%20Essential%20Actions%20for%20Effective%20TB%20Infection%20Control.pdf). These steps highlight community engagement, developing a facility IC plan, safe sputum collection, promoting cough etiquette, triaging TB suspects, rapid diagnosis and treatment, improved room ventilation, protecting health care workers, capacity building and monitoring IC practices.

'With the exception of improving room ventilation, these are all administrative policy measures,' Dr Parsons reiterated.

Environmental TB IC measures may include engineering solutions, such as mechanical ventilation or air filtration systems, which are expensive to install and costly to maintain. Dr Telisinghe described experiments by Dr Rod Escombe and colleagues showing that low-cost measures, such as natural ventilation and ultraviolet germicidal irradiation (UGI), could help reduce the risk of TB infection in facilities in resource-limited settings. A Peruvian study found that simply opening the win-

dows could work better than mechanical ventilation.[6] More recently, using guinea pig studies and mathematical models, Escombe *et al.* concluded that the use of UV lights could significantly reduce TB infection and disease - provided there is adequate mixing of room air (to enhance air movement, and hence the transportation of droplet nuclei, through the upper-room UV disinfecting zone).[7]

Once environmental and administrative controls are in place, personal respiratory protection - wearing an N95 or FFP2 respirator mask to prevent inhalation of infectious TB particles - may offer additional benefit.

'The evidence for using N95 masks comes from mathematical modelling, laboratory testing ... and expert opinion,' said Dr Telisinghe. There is little epidemiological evidence demonstrating effectiveness in the field. Still, the case is strong enough for health care workers to wear them in high-risk settings.

However, masks are often not available or used in health facilities, Ms Odendal noted. 'You need all three components - and all require education for patients and training for health care workers.' She added that TB treatment, isoniazid preventive therapy and ART are all part of TB IC.

A mathematical model for XDR-TB transmission in rural South Africa published in *The Lancet* estimated that the combination of IC measures with TB treatment could avert 48% of facility-based XDR-TB cases (range 34 - 50%) by the end of 2012.[8] The combined measures included early discharge of patients from hospitals, enforced respirator and mask use, improved natural ventilation, isolation of patients into 5-bed units, rapid drug sensitivity testing (and appropriate treatment), hospital-based HIV testing and counselling, and ART use. Of note, although respirators would only prevent 2% of the total cases, consistent use would prevent about two-thirds of the cases among health care workers.

MSF and the Western Cape Department of Health are working on improving TB IC at all nine of the clinics providing TB services in Khayelitsha. Dr Telisinghe described site assessments of the risk of TB infection in different clinic areas that found that while some TB IC was in place, there was room for improvement. Ms Odendal described the steps subsequently taken, including the establishment of IC committees at each facility, training and provision of information materials, implementing triage and intensified case-finding, and the provision of respirator masks for staff, and paper masks for cough hygiene to all clients in waiting areas. They have improved natural ventilation by installing wind-driven air extractors (whirly-birds) on existing buildings, and established outdoor waiting rooms that have roofs but are otherwise open - though they have heaters and blankets to make patients more comfortable. Finally, sputum collection booths have been moved outside.

Unfortunately, many designs for new health facilities lack natural ventilation and rely on forced ventilation systems, according to Dr Parsons. 'Is this the way to go in resource-limited settings with unreliable electricity?' he asked. 'On the other hand, are we going to try to use "simple" solutions that we know won't work? We need to design appropriately.' He cautioned the audience against assuming that 'simple' measures are always adequate.

'I was in Peru with Rod Escombe for some of his tests', he said, 'and the rooms he investigated had five metre high ceilings and [high] windows-to-floor ratios ... do you find that in all the facilities in our hospitals? No you don't. It's not that I don't agree with the open window policy, in fact, I really support opening windows, but I think we need to put it in the appropriate context.'

'We need to act in a multidisciplinary group to resolve these issues,' he said, adding that engineers and architects need to be engaged, and often have better access to the national legal and regulatory framework that should guide TB IC in facilities. For example, the National Infection Prevention and Control Policy and Strategy (April 2007) makes reference to a long list of regulations in South Africa, including the Occupational Health and Safety Act 85 of 1993, which mandates that hazards in the workplace be analysed and responded to appropriately, with the regulations regarding hazardous biological agents addressed in notice R1390.

'Anybody who runs or manages a health facility and does not adhere to the regulations embedded in the Occupational Safety Health Act is actually culpable,' he said. Dr Parsons also referred to new proposed building codes of which many health care workers may not be aware (see Appendix 1). These codes need to be enforced at every type of health facility, he stressed, 'not just at the multidrug resistant TB facilities', because people with TB could be encountered anywhere within the health system. But the provincial departments of health have to be held accountable to upgrade health facilities.

'Four hundred million rand has been made available per year for 3 - 4 years to the provinces to address infection control in facilities. We can only account for something like 110 million,' he said, and urged the audience to find out what was going on in their province.

TB IC also needs to be addressed within the home and community, according to Ms Odendal.

'The hype around drug-resistant TB is actually driving the TB epidemic underground because people don't

want to go for diagnosis if there is a chance they have drug-resistant TB and will be isolated,' she said. Community-based treatment of drug-resistant TB would offer one solution, 'but the lack of guidance regarding TB IC in homes and communities has been a big barrier.'

MSF is pioneering community-based drug-resistant TB treatment in Khayelitsha. To reduce the risk of transmission in the home between starting treatment and sputum culture conversion, the following measures have been adopted in households. First, there is an initial assessment of crowding and ventilation in the home, and the vulnerability of household members. Then a risk reduction plan is developed, involving education about TB transmission and cough hygiene, and separate sleeping arrangements when necessary. Patients and other household members are given at least two IC education sessions and follow-up, and patients are given paper masks to be worn in overcrowded and closed conditions.

Most households have been able to minimise contact between the patient and vulnerable household members, by arranging separate sleeping for patients and improving natural ventilation, according to Ms Odendal. 'Once they have been provided with information and support, people are more than willing to make necessary changes and able to reduce the risk of TB transmission. If a safe environment could not be brought about, patients are hospitalised until culture conversion,' she said.

In the meantime, they are trying to address TB IC in the community through treatment literacy campaigns to encourage community acceptance and support for ambulatory treatment. They are also engaging taxi associations and drivers in the taxi ranks with the goal of increasing ventilation on public transport, and promotion of cough hygiene. They hope to expand these efforts to other overcrowded settings such as prisons, mines, schools and detention centres.

INTENSIFIED CASE-FINDING (ICF)

Another measure that could help with TB IC efforts in the community is ICF - since more aggressive and earlier case detection could reduce the period of time during which people are unwittingly spreading TB in the community. Dr Celine Gounder of Johns Hopkins University described study after study demonstrating that case detection rates are too low in many settings where TB is common.

For example, Professor Robin Wood and colleagues in the Western Cape found that the prevalence of pulmonary TB among people with HIV was 7.6% - but passive case-finding (waiting for people to come in to have their illness investigated) only resulted in a third of the smear-positive TB diagnoses.[9] Dr Liz Corbett reported that ICF detected a prevalence of 3.8% of previously undiagnosed pulmonary TB among HIV-positive goldminers.[10] Other ICF studies have found high rates among HIV-positive pregnant women, and contacts of other smear-positive cases. Studies where people attending ART clinics are routinely screened for TB have found even higher rates of case detection.

ICF in communities in Zambia and South Africa also detects large numbers of previously undiagnosed TB cases, according to Musonda Simwinga, manager of the Zambian AIDS-related TB (ZAMSTAR) study. The trial involves randomly allocating 24 whole communities across Zambia and South Africa to receive one of two public health interventions: community-enhanced case-finding (increasing access to diagnostic services within the community), or targeting households of TB patients and counselling the whole household to make better use of diagnostic services within the existing health system.

According to Simwinga, prevalence studies for the trial demonstrated a huge burden of tuberculosis, with a culture-positive prevalence of 960/100 000 in two Zambian sites and 2 200/100 000 in two South African sites (14 894 adults).

'Many adults with a chronic cough have never sought care in their local health centre, and even when they have, they have often not been offered available diagnostic tests,' he said. Or they may present quite late for diagnosis and care.

'Patients who are identified through passive case-finding are picked up much later in the course of their disease,' Dr Gounder said, 'and as a result, their illness is often more severe.' For instance, a study in the Western Cape found higher frequencies of major symptoms such as weight loss among cases detected through passive case-finding.[11] Late recognition also leads to poorer outcomes: Professor Churchyard found a higher case fatality rate after initiating treatment among goldminers whose TB was detected by passive case-finding rather than ICF.[12]

'Intensified case finding should also have an impact on disease duration and thereby transmission of disease,' said Dr Gounder, noting that in another study by Professor Wood '87% of the total person years of untreated sputum smear-positive TB is among people with HIV - so people with HIV are a very significant source of disease transmission within the community.'

The WHO recommends that people living with HIV, their household contacts, groups at high risk for HIV and those in congregate settings should be regularly

screened for TB whenever they come into contact with the health services. But even though 109 countries have adopted ICF as part of their national TB/HIV policy, implementation has been limited.

'Are our HIV care services, our ART services, our VCT service points aware of intensified case finding or that they should implement it? Probably not; if they are, they are not convinced that it is their responsibility. They say it is for somebody working within the TB clinic,' said Dr Kgomotso Vilakazi-Nhlapo of the National Department of Health, who added that 'the communities aren't demanding it yet. And there is also a lack of training on screening for TB in HIV-positives.'

But one of the key barriers is the lack of agreed-upon tools that can be used by trained counsellors and health care workers to screen for TB in people with HIV.

'The difficulties screening for TB in HIV-infected patients are well known', said Dr Salome Charalambous of the Aurum Institute, 'and include the lack of typical symptoms, an increase in smear-negative TB, atypical chest X-ray changes, a large incidence of extrapulmonary disseminated TB and also the presence of other pulmonary disease [such as *Pneumocystis jirovecii* pneumonia]. So for symptom screening, we don't really know which symptoms are the best to use. Sputum microcopy is rapid and cheap, but patients are smear-negative ... and we must be careful not to overstretch our laboratories. With chest X-rays, there are issues with access and interpretation.'

Dr Charalambous described several studies exploring optimal screening methods. She noted conflicting data on usefulness of chest X-rays. In Botswana's IPT programme, a pilot study suggested that X-rays didn't add much to screening, but more recent experience has suggested that X-rays do indeed detect some cases of TB in asymptomatic patients. In one study in South African goldminers, adding a chest X-ray to a symptom screening tool (night sweats, cough and weight loss) improved sensitivity from around 60% to 90%.[13]

In another study, 381 patients at Tshepong Wellness Clinic in North West Province were screened for active TB before starting ART. TB was diagnosed in 31.6%.

'Using a symptom screen alone would miss one quarter of the TB cases, while chest radiography improved sensitivity substantially,' said Dr Charalambous. 'One thing I'd like to emphasise, is that [in this study] 62.5% of patients had TB symptoms, so even if we are just screening with symptoms, we would still have to further screen these patients with sputum microscopy and culture, which would lead to overstretching our laboratory facilities. That's a problem that we're going to have to deal with.'

South Africa's National Guidelines state that TB screening should take place before initiating ART and that TB should be suspected if any two symptoms are observed (including weight loss of 1.5 kg or more, cough >2 weeks, night sweats over 2 weeks or fever >2 weeks). The diagnosis should then be confirmed by smear microscopy or culture. Before initiating IPT, sputum should be sent for microscopy and culture if there are one or more symptoms.

In practice this does not seem to happen, according to an analysis Dr Charalambous conducted in Aurum's clinics. Even when clinic visit forms (with a checklist of symptoms) have been filled out and show that patients had two or more symptoms of TB, sputum was very rarely sent in for microscopy or culture.

'Only about 1.8% was screened correctly according to South African national guidelines,' she said. As a result, they are recommending changes to the screening form. 'Clinical data systems we use should facilitate care by prompting care providers to screen for TB.'

A range of screening tools are needed at the different points where people with HIV enter into care, according to Dr Vilakazi.

'One size does not fit all - different settings have particular needs. You can't have the same tools for prevention of mother-to-child transmission (PMTCT) as you have for prisons, community screening, household contacts,' she said. But if ICF is to be rolled out at VCT clinics, effective referral mechanisms need to be established to make certain that someone who is screened by a counsellor as a TB suspect makes it to a TB clinic for diagnosis.

'Referral systems between HIV [services] and TB diagnostic and treatment centres are mostly only verbal. Patients are referred, but not properly "encouraged" to reach services. How do we follow up? How do we ensure the patient has been screened?' She noted that patients often don't follow through on the referral because they are too sick or busy. 'So we need to promote the use of HIV resources to strengthen TB diagnostics capacity at all levels. We need to address long laboratory turn-around times and promote TB diagnostic capacity in all of our ART clinics.'

'We need to develop practical guidelines at national level to operationalise ICF,' she said. 'National Policy should emphasise ICF as the gatekeeper for IPT and IC. To implement IC, you need to know how to exclude TB so that you can triage the patients. And you cannot say a person should start IPT without first excluding TB.'

ISONIAZID PREVENTIVE THERAPY (IPT)

Access to isoniazid to prevent TB is even more limited, even though a Cochrane meta-analysis of seven major studies conclusively showed that its use would reduce active TB by about one-third in people with HIV.[14]

'In the global TB report that came out last year from the WHO, it was reported that only 29 000 people were started on IPT globally. That's less than 0.1% of the estimated 33 million people estimated to be infected with HIV globally compared with 3 million people on ART globally and 2.1 million on ART in sub-Saharan Africa,' said Professor Harry Hausler of the TB/HIV Care Association. 'If you think about ART versus IPT, 10 - 20% of people who are HIV positive are eligible for antiretroviral therapy, but close to 40% of people who are HIV positive are eligible for IPT. So we should be looking at *6 million* people on IPT globally rather than 29 000.'

In South Africa, only 6 818 out of the 455 150 people who tested positive last year (1.5%) were put on IPT.

The current Department of Health IPT guidelines may partly be to blame for the low uptake, as people on ART are not eligible while a positive tuberculin skin test (TST) is required to qualify for IPT.

'TST is in fact an obstacle to IPT,' said another speaker, Dr Kerrigan McCarthy of the Reproductive Health and HIV Research Unit (RHRU). 'Firstly there's the hassle of the supply chain management of TST (for tuberculin syringes, PPD RT23/cold chain management).' An appreciable percentage of clients don't return to have their TST interpreted. In addition, Dr McCarthy said that Johannesburg clinics reported wide variations in the promotion of TSTs interpreted as positive, indicating lack of consistency in performing and interpreting the test. 'Quality control of TST is impossible; if the quality of a test cannot be controlled, that test should not be used.'

Even when patients who are eligible under the current guidelines are identified, many health care providers are reluctant to administer IPT, because they fear it may cause drug resistance or severe toxicity, or they believe it is not needed in someone on ART.

At present there is very little evidence to suggest that IPT promotes drug-resistant disease, according to Professor Harry Hausler of the TB/HIV Care Association, who chaired the session on IPT at the symposium.

'When active TB occurs among those given IPT, standard four-drug first-line therapy works,' he added, citing evidence from one 2006 meta-analysis that included over 18 000 people on IPT showing a slight increase in INH resistance but a fairly low relative risk (1.45, 95% confidence interval (CI) 0.85 - 2.47).[15,16] However, the authors recommend ongoing surveillance to exclude an increase in INH resistance with the roll-out of large-scale IPT programmes. If INH is used appropriately - not given to people with active liver disease or to those who abuse alcohol, with monthly monitoring and vitamin B_6 - severe toxicity is rare. Finally, at least one open-label study suggests that ART and IPT synergistically decrease TB when given together.[17]

Preliminary data from the first 6 months of the Botswana IPT study seem to support that IPT can be safely and effectively administered even to rather ill patients, according to Dr Tefera Agizew, Senior Medical Research Officer, TB/HIV Research, BOTUSA.

During the first 6 months of the study, all eligible participants received open-label INH with vitamin B_6 (after which point they were randomised to continue with 30 months of placebo or INH). Of 1 995 subjects enrolled in the trial, only 7 (0.35%) were diagnosed with active TB (3 of whom were culture positive). There was no evidence of INH resistance. Adherence was also good by pill count: 91% took more than 80% of the pills.

Severe adverse events were seen in 28 (1.4%) of participants: 19 were due to hepatitis (for a rate of 0.95% compared with an expected range of 0.5 - 5.3%), 5 were rashes, and 4 were other events. There was 1 death, due to hepatic encephalopathy. Most of the hepatitis was asymptomatic. However, a couple of factors, such as having a CD4 cell count below 200 cells/µl, and a problem with alcohol, were significant risk factors for severe hepatitis.

'Alcohol dependence screening is recommended to reduce the risk of hepatitis,' said Dr Agizew.

However, in the much larger Thibela TB study in South African goldmines, comparing the effectiveness of community-wide IPT in addition to standard TB control, hepatitis has been quite rare in preliminary findings, according to Professor Churchyard.

'Isoniazid is safe,' he said. 'And this is a group of men that are elderly and drink - I wouldn't say excessively, but they drink and have a high rate of hepatitis B and use traditional medicine. And yet despite all this, in an analysis of almost 13 500 individuals, we only had 3 cases of hepatitis - only one of which was severe -and the patient fully recovered.' (Other events included hypersensitivity, which was seen in 55 participants, and peripheral neuropathy in 41 of the first 13 425 patients.)[18]

Initially, adherence wasn't quite as good in this study, with only about 40 - 50% adherence by 6 months, but this has now been improved to about 80%.

Professor Churchyard also presented some of the first resistance data from the study so far (Table I).

'We would expect to see a higher proportion of INH resistance in people taking IPT, as INH won't work against INH-resistant TB,' said Professor Churchyard. 'And although it is slightly higher in terms of INH resistance, it is not significantly higher.'

Similarly, Dr Neil Martinson of the Perinatal HIV Research Unit reported that IPT did not drive resistance in a study he conducted comparing different TB preventive therapy regimens, including IPT for 6 months, and continuous IPT. There was no resistance in 14 out of 19 TB cases out of 328 patients who received 6 months of isoniazid (specimens were not available for 5), and only 1 case of MDR TB in the 7 breakthroughs out of 164 people on the continuous IPT arm.

That being said, Dr Martinson stressed that it was very important to exclude active disease - but he wasn't certain that chest X-rays would really be appropriate in the field.

'I would recommend not doing a chest X-ray. I think it's really an excuse just to keep people away from receiving isoniazid preventive treatment, especially when we consider that IPT is meant for well people,' he said. 'Clearly asymptomatic TB in HIV-infected individuals is a concern, but my experience is that TB is a fairly malignant disease in people who are HIV-infected. If you have at least two visits, one month apart, before giving IPT, most patients/most people who are HIV-infected and who have got active TB are not going to be walking around feeling good for more than a month.' However, he also said he thought 'that anyone who is HIV-infected should have a TB culture'.

Dr Martinson set some targets for the future, calling for CD4 counts to be routinely available at the time of HIV diagnosis (perhaps with point-of-care testing): for at least 20% to be investigated with a TB sputum culture; for 60% of those who do not yet qualify for ART to be put onto IPT; for an 80% adherence rate; and for less than 2% breakthrough TB cases.

As Dr Vincent Tihon of the SA Department of Health noted, putting this into operation in clinics will take real-world models and tested tools - but these are currently being developed. Dr McCarthy described the development and implementation of a systematic method of integrating TB/HIV services at urban clinics in Johannesburg. Before starting the effort, 'there was no systematic screening. IPT uptake was limited and in 2007, less than 100 people in the entire city of Johannesburg had TST done,' she said.

'Now to do this we used what we call the "Roadmap of Care" - a framework for integrated TB/HIV services that uses a "Provider-initiated testing and counselling register" and a "Wellness register"; as well as other materials to facilitate implementation' (for copies contact Padma Dayah, pdayah@rhru.co.za).

Data collection in the registers is manual, which increases staff workload, so staff training in data collection is critical. However, now 'we are able through the register, to track and understand all of the factors involved in TB and HIV integration and see month by month, exactly, the progress towards implementation'.

After successful piloting in four inner city clinics, the Roadmap of Care is being rolled out on a larger scale in Johannesburg, North West Province and Ekurhuleni. 'IPT in fact represents a success for TB/HIV integration. It's not only just the value of the preventive efficacy of INH - this represents the tip of the iceberg of the population that is reached through HIV services,' she said. 'IPT will not only do those individuals a service by preventing TB, but we access the entire spectrum of the population for HIV testing, TB screening and all of the other services that go along with it.' Good follow-up mechanisms are also essential to ensure adherence, detect cases of active TB if any are missed, and appropriately treat and monitor those patients.

'Political commitment to IPT is essential, and community and activist awareness as well as promotion of TB prevention activities are critical. Client awareness of IPT can drive prevention efforts and improve health-seeking behaviour,' she said.

'Community mobilisation has also supported the rapid and large-scale uptake in Thibela,' said Professor Churchyard. 'It creates the awareness of both TB and IPT and it has created a demand for IPT, and strong support for this study. Communication is essential to the community mobilisation and underpins all of those processes.'

TABLE I. PRELIMINARY DRUG SUSCEPTIBILITY OF TB ON IPT

Active TB	IPT (*N*=66)		Comparison (*N*=129)	
	First episodes, *N*=53 % (95% CI)	Retreatment, *N*=13 % (95% CI)	First episodes, *N*=97 % (95% CI)	Retreatment, *N*=32 % (95% CI)
Any INH	7 13.2% (5.5 - 25.3)	1 7.4% (1.9 - 36.0)	8 8.2% (3.6 - 15.6)	8 25% (11.5 - 43.4)
MDR	1 1.9%	1 7.7%	3 3.1%	4 12.5%

As for political commitment, the meeting's final word came from the South African Department of Health.

'The political commitment has increased significantly in the past few months where TB and HIV have really gone high on the agenda,' said Dr Tihon. First, the department is considering several proposed changes to the IPT policy that may remove some of the barriers to access. These include removing the TST requirement; considering IPT for pregnant women with HIV, as benefits outweigh the risks; and considering IPT for patients who have been stable on ART for 6 or more months who have no signs and symptoms of TB.

'It is quite critical to start talking about how we are going to implement it,' he added. Consequently, the Department of Health has instructed the provinces to develop clear operational plans for IPT implementation.

'It will require training, standard operating procedures, technical guidance that is very practical, how to exclude TB, who is eligible and how to monitor people who are starting on IPT,' he said, noting that RHRU's work could serve as a model. But ultimately, he said, successful implementation of IPT will be dependent upon the delivery of quality HIV services, effective TB screening, adherence support and follow-up. 'The HIV programme really has to take the responsibility and the leadership in strong collaboration with the TB programme so that people will say: It works, it's safe and let's just do it!'

We thank the Chairs and presenters for sharing their expertise. Mr Theo Smart is thanked for preparing the final report.

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APPENDIX 1. SA BUILDING CODES OF PRACTICE, THE PROPOSED SANS 10400, SECTION 0, PARA 4.4.10

Occupancy	Minimum outdoor air requirements		Pressure relative to adjacent area
	Air changes per hour	l/s per person	
Health care facilities			
Surgical and critical care			
Operating theatres and suites	20	-	Positive
Wound intensive care (burns)	6	-	Positive
Critical and intensive care, treatment and delivery rooms	6	-	Positive
Trauma, ER waiting rooms, radiology waiting rooms and triage	12	-	Negative
Diagnostics and treatment areas			
Bronchoscopy, sputum collection, examination and treatment room (general)	12	-	Negative
Medication room	4	-	Negative
Physical therapy and hydrotherapy	6	-	Negative
Inpatient nursing areas			
General wards, paediatric wards and labour/delivery/recovery/postpartum rooms	2	-	Positive
Airborne infection/protective environment wards and anterooms or airlocks	12	-	Negative
Laboratories			
Microbiological (molecular)	6	-	Positive
Bacteriological P1	6	-	Negative
Bacteriological P2, P3 and P4	12	-	Negative
General biochemistry, cytology, histology, nuclear medicine, pathology and serology	6	-	Negative
Radiology			
General radiology areas	6	-	Negative

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