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it's time to integrate tb/hiv care on a national scale

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Progress has been slow towards getting TB and HIV programmes to work together to reduce the burden of both diseases in countries where TB/HIV coinfection is common, but recent dramatic improvements in the delivery of integrated TB and HIV services on a national scale in Kenya and Rwanda show that it is possible to move beyond pilot projects to full scale implementation.

A coordinated response between national TB (NTPs) and HIV/AIDS programmes is urgently needed to improve diagnostic, care and prevention services for people living with HIV and TB. In fact, it is overdue, as the Global Plan to Stop TB called for full scale-up of "collaborative TB/HIV activities" by 2007 in the 63 countries with the highest burden of HIV-related TB.

But first to define an awkward term: "collaborative TB/HIV activities" are both the key actions required to get TB programmes and HIV programmes working effectively together, as well as the actual healthcare services targeting each respective disease that each programme should either be providing directly or making more accessible to the people it serves (these activities are described more fully below).

Yet despite changes at the policy level in some countries to endorse better TB/HIV collaboration to deliver these services, and despite the development of a number of vanguard or pilot projects offering integrated TB/HIV services, the impact on the ground in most countries so far has been modest.

Only 10% of TB patients screened for HIV in Africa

Programmes have been slow to get even the most basic collaborative activities online, such as regularly screening people with HIV for symptoms of TB, or HIV testing and counselling of all TB suspects. For instance, through the end of 2005, only 7% of all TB patients were tested for HIV globally (10% in the African region), though PEPFAR-focus countries are doing a bit better than most other countries (at around 12%) according to a WHO survey presented at the HIV Implementers' meeting in Kigali, Rwanda in June. During the same period, HIV programmes within the same countries reported screening less than 0.5% of all people living with HIV for TB, (though only a handful of programmes appear to be reporting consistently).

"Having said that, from the few numbers that were screened, there were large numbers of TB cases detected," said Dr Alasdair Reid, the HIV/TB adviser to UNAIDS, who initiated the survey while at WHO and presented its findings. For instance, in South Africa, 38% of those screened for TB symptoms were eventually diagnosed with active TB. "So there's a lot of undiagnosed TB out there," he said.

TB screening and HIV testing are the entry point to care for each respective disease — but they are only the first step. The numbers of people with TB or HIV who subsequently receive further collaborative services, such as being put on cotrimoxazole prophylaxis or on antiretroviral therapy (ART), is improving but it was also disappointingly low in most programmes. Only about 26% of the TB patients who tested HIV-positive were then placed on ART in PEPFAR countries.

"That is far from an ideal situation," said Dr Reid. "We are missing many opportunities to provide better care. These are people who are in front of us, who are already in the care system. There's a whole manner of barriers that people have to get through to actually reach the health service, the least we can do is offer them integrated prevention, care, and treatment when they get there — and in doing so, we avoid unnecessary deaths."

However, in the last year or so, a few countries, such as Kenya and Rwanda among the PEPFAR-focus countries, have achieved dramatic breakthroughs in screening and other service delivery, demonstrating that where there is a will, integration of TB/HIV service delivery on a national scale is indeed achievable — and quite quickly at that.

For instance, Kenya began provider-initiated testing and counselling (with opt out testing) for people in its TB programme in October 2005. By the fourth quarter of 2006, 67% of Kenyan TB patients

“ where there is a will, integration of TB/HIV service delivery on a national scale is indeed achievable ”

were being tested for HIV — 85% of those testing positive are getting cotrimoxazole, though the programme is still struggling to get more than a third of the eligible people onto ART.

Similarly, Rwanda recently began PITC in its TB patients and TB screening in people at risk of HIV. But by the first quarter of 2007, 87% of TB patients were tested for HIV, while 76% of people living with HIV enrolling at ART sites were screened for TB. In addition, of those who tested positive, about 46% and 31% received cotrimoxazole and ART, respectively (around a 3-fold improvement from the previous year). Results in both countries' model TB/HIV integration centres have been even better.

Their successes and ongoing challenges, plus the experiences from several other projects and countries, were described over the course of the Third South African AIDS Conference, the HIV Implementers' Meeting, and at a meeting just afterwards, organised by US Office of the Global AIDS Coordinator (i.e., PEPFAR) and WHO on behalf of the Global TB/HIV Working Group of the Stop TB Partnership. The latter PEPFAR/WHO meeting was held to highlight the lessons learned in these programmes and pilot projects about what does and doesn't work well, and to identify key activities to help improve TB/HIV integration on a nationwide-scale.

Several good reasons for TB/HIV service integration

The case for improving collaboration between TB and HIV programmes was made in several presentations, starting with a plenary speech made at the South African AIDS Conference by Dr Kevin de Cock, Director of WHO's Department of AIDS.

“What patients need is to be treated in a manner that is effective and convenient for them for both diseases. And that is the non-negotiable bottom line,” he said.

Better patient care

“Before we offered TB services and HIV services separately and this posed a lot of challenges for both the patients and the health workers,” said Hellen Muttai, a clinical care manager who shared data from Kenya's Kericho District Hospital at the Implementers' Meeting. Before integration, patients had double queues, drug prescriptions, sets of labs, and had to attend two separate clinics on different days. Unsurprisingly, the uptake of TB/HIV services before integration was extremely low. “If patients with TB had HIV, the clinician just made a referral, they didn't follow-up to see whether that patient had accessed services later on. And patients had to move from one clinic to another so they spent a lot of time in the hospital to receive TB and HIV services separately,” she said.

In the case of Kericho District Hospital, TB/HIV integration meant bringing HIV services into an existing TB clinic, offering people with TB HIV-related services including provider-initiated HIV testing and counselling (PITC), and if HIV-positive, providing subsequent services such as cotrimoxazole and ART (as long as they continued to be on TB treatment). After integration, 94.2% of the TB patients were tested for HIV; 45.4% were indeed coinfecting; they *all* received cotrimoxazole and other HIV care and treatment services; 78% were deemed eligible for ART and they *all* received it, most before they had completed TB treatment.

There is no question that this intervention saves lives.

Likewise, TB/HIV services have been integrated in Mulago Hospital in Uganda since August 2005, when it began offering both provider-initiated HIV testing to all TB inpatients and outpatients, enhanced TB screening in the HIV clinic, and concurrent TB and HIV screening of all medical inpatients. 96% accepted HIV testing and 33% of the people with TB were coinfecting.

"We had a very large number of patients that we identified who had both TB and HIV disease and because of this we found it necessary to introduce a clinic where we were able to provide both TB and HIV services concurrently," said Dr Rhoda Wanyenze. So a combined TB/HIV clinic was set up operating on one day of the week within the TB unit offering the basic package of HIV care and ART and CD4 monitoring during the course of TB treatment. 327 out of 706 coinfecting people who have so far received services from the integrated TB/HIV clinic have started ART while there.

Even TB treatment and non-ART HIV care alone improved the immunological status of people with HIV and TB according to an analysis of 792 patients enrolled between July 2005 and December 2006 at Kericho District Hospital.

"We noticed that the patients who were not eligible for ART, or who were not treated for ART, even if you just treated the TB without offering them ART, their CD4 cell count still improved," said Muttai. Those given just HIV care and TB treatment had a mean increase of 78 CD4 cells six months after enrolment, while those who received ART as well had an increase of 139 CD4 cells ($p < 0.001$).

"Clinicians treating patients with TB/HIV should be aware of the benefit to HIV infection by treating TB and offering supportive care alone, and also additionally offering ART," she said.

Better TB control

But beyond improving the care and treatment of people with both illnesses, better collaboration between HIV and TB programmes may also be the only way to help overstrained health systems cope with the unparalleled dual burdens of the TB and HIV epidemics.

Just to review recent data from the WHO/STOP TB Partnership: 14 million people are co-infected with TB and HIV, globally; but around 80% of those who are coinfecting live in sub-Saharan Africa. In some parts of the continent, up to 80% of the people with active TB are HIV-infected. TB is by far the most common opportunistic infection diagnosed during the first three months on ART — particularly in Africa. 200,000 people with HIV die of TB each year, again, most of them in Africa.

HIV has thrown fuel on the flame of TB.

- People with HIV are at increased risk from both TB reactivation and rapid TB progression
- TB manifestations may be more severe or atypical with more frequent extra-pulmonary TB especially in people with advanced HIV disease
- TB can be more difficult to diagnose, with higher rates of smear negative TB, and chest X-rays can be more difficult to interpret (although in a departure from a few years ago, experts are again recommending their use when affordable and feasible)
- A higher rate of mortality: even though TB is curable, it is the leading cause of death reported for people with HIV in many countries, with a mortality rate around 25% within two years in patients not receiving ART
- There is an increased risk of TB recurrence following treatment in people with HIV

HIV can also impact the care delivered to HIV-negative people with TB. For instance, the dual stigma of HIV-associated TB affects the health seeking behaviour of TB suspects regardless of their HIV status. This has sometimes been used as an excuse not to integrate TB and HIV services within the same facility.

But according to a survey of TB patients in KwaZulu-Natal presented at the South African AIDS Conference, people in the community are already well aware "of the link between TB and HIV/AIDS... On becoming ill with TB, many patients feared they may have HIV/AIDS. This fear led to them delaying accessing health services" (Loveday). This in turn leads to delayed diagnosis, poorer outcomes and increased transmission within the community. Additionally, the increased numbers of people with TB taxes the TB programme's capacity and can decrease the quality of care for all patients.

The net impact of the dual epidemics on public health systems has been that well-organised programmes that had once been making good progress towards containing TB before the HIV pandemic can no longer do so. Although the annual incidence of TB is stable or falling in most of the world, the total number of cases has been increasing in Southeast Asia and Africa — especially where HIV coinfection is more common.

But it isn't necessarily because the TB programmes have been poorly managed. At the South African AIDS Conference, Dr de Cock referred to a study from Dr Gavin Churchyard and colleagues that found an increasing incidence of TB in the gold mines in Welkom, Free State, South Africa, despite a model directly observed therapy (DOTS) TB programme. "They showed that even with a tuberculosis control programme that meets all of the WHO recommendations, TB continued to escalate in incidence under the pressure of HIV," he said. "So clearly TB programmes alone cannot reverse this tide."

HIV is the main reason why TB programmes have been unable to reach their targets.

"With a TB burden last year of about 300,000 reported cases, we're definitely not winning this battle against TB," said Dr Margot Uys of the Department of Health in both KwaZulu Natal, the Northwest Province and the US Centers for Disease Control, at the South African AIDS Conference. "With a success rate of about 54% in our treatment outcomes, it's far away from the WHO recommendations of 80%. And on top of that we've got an HIV prevalence in our TB patients averaging at around 55% but spanning from 30% to 72%, and following last year's outbreak of XDR-TB we have also got this MDR-TB burden of at least 6,000 MDR-TB cases per year, of which a considerable portion would be XDR-TB."

"It will be vital to shift into a higher gear on tuberculosis control. The emergence of XDR-TB is a dramatic wake up call, not only for South Africa but for the whole world," said Dr Peter Piot, the Director of UNAIDS at the South African AIDS Conference, and then, paraphrasing a comment made by Nelson Mandela himself just a few years earlier: "If we don't factor and integrate tuberculosis into everything we do, we will get nowhere. We are doomed to fail in our treatment programmes."

Collaborative TB/HIV activities

"We need to integrate TB/HIV services," said Dr. J. Muhwa Chakaya of Kenya Medical Research Institute and the National Leprosy and TB Control Programme (NLTP) at the Implementers' Meeting. "It's the only way to effectively deliver services."

To help countries get started, WHO Stop TB Department and Department of HIV/AIDS released basic suggestions for how to better integrate TB and HIV care and treatment in 2004 in the Interim Policy on Collaborative TB/HIV Activities (http://www.who.int/entity/tb/publications/tbhiv_interim_policy/en/index.html).

The policy recommends twelve activities divided into the “policy-making level” activities required to set up, plan and monitor TB/HIV collaboration; the activities carried out by the HIV programme to reduce the burden of TB disease among people living with HIV; and the activities carried out mostly by the TB programmes to reduce the burden of HIV disease among TB patients, by providing prevention services, diagnosing those with HIV and providing or making certain that they receive adequate and appropriate care (see table below).

Establishing mechanisms for collaboration/ creating a conducive policy environment

The following section is meant for anyone involved with or concerned about the delivery of care to people with or at risk of TB and or HIV infection, whether a healthcare worker, nongovernmental organisation (NGOs), civil society, community-based organisation (CBOs) or a person with HIV and/or TB. Mobilisation of the HIV community and other stakeholders at national and local level is necessary to change policy, hold governments and programmes accountable, and make certain that policy is translated into practice both nationally and locally, keeping in mind that the most important level of implementation is at the point of healthcare delivery.

Engaging stakeholders and building advocacy

“One of the problems in TB/HIV is that both sides of the equation are viewed as someone else’s problem,” said Dr de Cock.

Before setting up collaborative bodies for TB/HIV, or fixing ineffective ones, it helps to understand the nature of the programmes that are being dealt with — and how and where they function in each country. TB and HIV/AIDS programmes have traditionally been separate vertical programmes with their own distinct cultures.

“The TB culture traditionally has been emblematic, epitomising the public health approach with rigid algorithms, very clear sharp outcomes and a standardised simplified approach,” said Dr de Cock. “TB services are oriented in the short term — six months to nine months — have limited diagnostic capacity and have paid little attention to infection control. The TB establishment typically thinks that HIV is an intruder, upsetting the carefully perfected system.”

“In contrast, HIV culture is focused on individuals with an emphasis on human rights, has guidelines that are far from standardised, and of course needs to offer long-term services. It

has limited understanding of tuberculosis epidemiology and is dismissive of TB as just another opportunistic illness which is difficult to treat,” he said. One way of fostering better understanding between the two programmes suggested during the PEPFAR/WHO meeting might be to involve TB programme staff in HIV planning cycles and vice-versa.

But another challenge in some countries is that HIV and TB governing bodies operate at different levels in government structures (ministries, etc), which can make collaboration difficult and the convening power of any TB/HIV bodies that may be established weak.

Funding streams are also usually separate for TB and HIV — with TB programmes less well funded, and it may be difficult to use earmarked funding for collaborative TB/HIV activities within the TB programme.

Dealing with such entrenched and often mismatched programmes takes great political commitment, from the grass roots up to high levels, and involvement of all the key stakeholders.

“What are the kind of things we did for these results to be achieved?” said Dr Chakaya. “I think that one of the critical things was political will and leadership.” In the case of his country, he said that the TB programme, the more established of the two “took this to heart and provided the requisite ‘push’ for these activities to happen.”

Likewise, Dr Greet Vandebriel, Deputy County Director Programs for the International Center for AIDS Care and Treatment Programmes (ICAP) in Rwanda, stressed that high-level government commitment to integrating TB and HIV programmes and services, was a crucial ingredient in “the Rwandan ‘recipe’ for success.”

But how does one create high-level political leadership around collaborative activities where there is little or none? At the PEPFAR/WHO meeting, one roundtable group suggested using the examples and evidence from Kenya and Rwanda or model national pilot projects (there are also model projects in Uganda and South Africa to name a couple) to “sensitise politicians” and other stakeholders to the need for TB/HIV activities. These can be used to demonstrate that collaborative TB/HIV activities are possible in a similar setting, much as the Botswana ART programme was once an example to the rest of Africa that ART scale-up was achievable. “Showing how our activities can help reach international (MDG), donors’ and national targets could be particularly important,” they added.

Grass roots political pressure may also help.

Recommended collaborative TB/HIV activities

A. To establish the mechanisms for collaboration	B. To decrease the burden of TB in PLWHA	C. To decrease the burden of HIV in TB patients
A.1 Set up a coordinating body for TB/HIV activities effective at all levels	B.1 Establish intensified TB case-finding (basic TB screening is a part of this)	C.1 HIV testing and counselling
A.2 Surveillance of HIV prevalence among TB patients	B.2 Treatment of latent TB infection (TB preventive therapy)	C.2 HIV prevention methods
A.3 Joint TB/HIV planning	B.3 TB infection control in health care and congregate settings	C.3 Cotrimoxazole preventive therapy
A.4 Monitoring and evaluation		C.4 HIV/AIDS care and support
		C.5 Antiretroviral therapy

These activities are described in more detail in the Interim Policy and in *A Guide to Monitoring and Evaluation of Collaborative Activities* (http://whqlibdoc.who.int/hq/2004/WHO_HTM_TB_2004.342.pdf). But with the experiences described from the conferences in June, and particularly from the PEPFAR/WHO meeting, it’s possible to expand a bit more on some of these activities.

“A crucial partner in all of this is the affected community,” said Dr Reid, “and it should be engaged and involved in designing, advocating for, implementing and especially monitoring the collaborative response.”

Coordinating or harmonising donors, technical agencies and funding sources with the programme was also identified as important at the PEPFAR/WHO meeting. Though donors clearly don’t set policy, their resources can certainly help catalyse it.

“I think what is very critical is that we were provided with finances to be able to do all the things that we needed to do,” according to Dr Chakaya, who said that there had been an exponential growth in funds dedicated to TB/HIV from PEPFAR, the Global Fund, and others. “The funds from PEPFAR and the Global Fund allowed for the first time many other people to become involved in TB/HIV. So multi-stakeholder involvement became possible with this funding which stimulated civil society involvement and private sector involvement and that was extremely important.”

The provincial, state, district levels

A common pitfall is to focus solely on the national programme level —but the best efforts at the national level may go nowhere without engagement of local government, programmes and other stakeholders at the provincial or state, and district levels.

For instance, Dr Annalies van Rie, of the University of North Carolina at Chapel Hill and colleagues were asked by the national government in the Democratic Republic of Congo for technical assistance integrating some HIV services into the TB programme. So they helped develop a national policy for TB/HIV, which included providing provider-initiated HIV testing and counselling of all TB patients, plus cotrimoxazole to those who tested positive (the country has Global Fund funding for the HIV test kits and the cotrimoxazole). Then they rolled the programme out at 14 pilot sites, training the staff, and providing onsite technical assistance.

It worked extremely well, with over 5000 patients tested (around 16% of whom were HIV-positive) even though access to CD4 cell counts and ART (provided by referral to the HIV clinics) was still quite low.

“We showed that it’s really feasible to do it and you can do it with the existing healthcare workers,” said Dr van Rie. “The healthcare workers were motivated, and did not want any premium to be paid to take on this extra work. You do not need massive input of funding, if you have the tests and the cotrimoxazole, but you do need [government] ‘buy-in’ and organisation.”

They had a written agreement with the National TB Control Programme, that on the 1st of January they would take the project over. But this didn’t happen, and the health centres ran out of HIV tests, and many ran out of cotrimoxazole.

“There just wasn’t the political will to take it over. That is what’s missing, which is a great contrast when you see Kenya where it’s also initially set up with international funding, but it’s driven by the national government,” said Dr van Rie. “I think the difference doesn’t lie in the extreme poverty of the Congo, it doesn’t lie in the capacity of the facilities. To me it really lies in taking ownership and wanting to take ownership of it by the local government. We had anticipated this, so we wrote this memorandum of understanding but it was with the national control programme. But what then happened is, the facilities are under the control of the *provincial programme* and so the provincial programme says, ‘Well, we didn’t sign this!’ and the

national programme says, ‘They are not under our responsibility, we do the national programme.’”

Kenya has tried to avoid this problem. “We set up coordinating committees at all levels,” said Dr. Chakaya. “We don’t always know how well the provincial and district committees are working but we have really tried – and we are still trying – to get a lot of more joint planning between TB and HIV.”

Developing operational protocols, training and reporting materials

As Dr Peter Piot emphasised at the opening of the South African AIDS Conference: “Let’s not forget that it is action at the district, at the local level, that will make the ultimate difference for people,” he said. “A national plan is as good as every district plan, and as every district can deliver.”

“Although most WHO strategies to reduce the burden of HIV in TB patients form part of revised TB-HIV policy in South Africa, uptake has been limited,” said Dr Margot Uys at the South African AIDS Conference. “It seems like there’s integration at the policy making level but not at the programme implementation level.”

So Dr Uys and colleagues from the Medical Research Council and the Foundation for Professional Development developed an operational framework for a model TB and HIV services integration site implemented in Richmond Hospital, in the midlands of KwaZulu-Natal, which has had some success in identifying and enrolling people with TB and HIV into HIV care (at least those who voluntarily choose to get an HIV test).

This programme — TB HIV AIDS Treatment and Integrated Therapy (*that’s it*) — is now being expanded to three or four other districts in different geographical regions in the country focusing on sites where there is little infrastructure.

There are also several other model TB/HIV integration sites within South Africa, but a perusal of the handful of poster presentations at the South Africa AIDS Conference suggested that some districts are largely being left to their own devices about how to implement collaborative activities — with mixed results (Dhlamini, Stephens, Scott, Verkujt, Ndlhovu).

But must each district in the country go through the process of developing its own operational protocols independently? It does make one wonder whether there isn’t a lot of reinvention of the wheel going on — and whether there isn’t a way to scale up more efficiently, rapidly and equitably. And how reporting and monitoring and evaluation from these districts will be synchronised is anyone’s guess.

In contrast, the national leadership in Rwanda and Kenya drove the process. As soon as the countries had convened their coordinating bodies and had adopted the WHO TB/HIV collaborative activities into their national policies, they wasted no time in revising their TB and HIV technical manuals and guidelines, developing operational protocols and training manuals that mainstreamed TB/HIV, and *disseminating* them to all the treatment sites. In Rwanda, informational, education and communication (IEC) materials were also developed and distributed. The whole process took around a year.

Both countries developed and implemented systems for monitoring and evaluation (M&E) of TB/HIV services — and started recording and reporting their TB/HIV indicators immediately (both by the third quarter of 2005). M&E is crucial for a host of reasons as it allows programmes to measure performance (see whether they are

reaching their goal and to identify problems if they are not). Furthermore, it serves as the foundation and measure for any subsequent efforts in quality improvement.

Registers were adapted so that TB components were included in HIV registers (such as whether the patient has been screened for TB) and HIV components in TB registers (HIV test, cotrimoxazole, CD4 counts), and data recording and reporting was harmonised between TB and HIV programmes. Using internationally recommended registers and tools could facilitate this, and WHO is close to completing the standardisation of its recording and reporting forms for care and treatment to include TB/HIV integration indicators.

Both Rwanda and Kenya also performed intensive and continuous staff training and technical support. In Rwanda, "The TB/HIV model centres served as practical training sites," said Dr Vandebriel. "Between April - June, 2007, 21 nurses and nine MDs from the TB and ART services were trained." Training consisted of a two-day visit to complement theoretical TB and HIV care and treatment trainings.

In Kenya, training and technical support was possible despite human resource constraints, including a hiring moratorium, according to Dr. Chakaya: "We had to use some crazy mechanisms to get people in and we were lucky that we were among the countries that were selected as the first tier for the Intensive Support and Action Countries (ISAC). And of course we had PEPFAR, which allowed us to get 36 additional coordinators to stimulate action at high TB/HIV burden districts. So we were able to train people in all our districts; and we provided technical support for the development of guidelines or checklists."

And taking a page from the books of TB control, Kenya set national targets for implementation of the TB/HIV activities.

"We provided targets, and this was the key thing. Every service delivery point was provided targets for TB, HIV and all other elements of TB control. This was extremely important," said Dr Chakaya. Kenya aimed at testing 80% of TB patients for HIV, and providing cotrimoxazole and ART, and screening 20% people living with HIV for TB. Nationally, they are reaching the target for cotrimoxazole already — so perhaps they should start aiming for 100%.

Virtually everything Kenya and Rwanda did found its way onto a list of critical enablers to successful scale-up of TB/HIV services, presented Dr Haileyesus Getahun of WHO's Stop TB Department at the PEPFAR/WHO meeting, but target setting was at the very top of his list, followed by setting the national policy, and producing and disseminating operational guides and training manuals.

It was a message that some participants at the PEPFAR/WHO meeting seemed eager to take home.

"The second lesson [we've learned] is the value of both guidelines for TB/HIV integration and supporting those with operation protocols at the implementation side of guidelines, recognising that there are multiple models of TB/HIV integration," said the representative from South Africa.

Collaborative TB/HIV services

The remaining collaborative activities constitute actual healthcare services that should be provided to people living with or at risk of either HIV or TB.

"These interventions cannot be taken up by only one programme, it must be both," said Dr Chakaya. "The TB control programme

must do their part and HIV control programmes must do their bits. In terms of who takes the lead for which intervention, I think that activities decreasing the burden of TB among HIV patients should really be up to the HIV control programme while the TB control programme should take care of the activities decreasing the burden of HIV disease among TB patients. That to me makes the most sense."

But different models have been developed for how the services are delivered in different settings:

- 1 Setting up a good cross referral system between separate TB and HIV sites, where the provision of TB-related services is primarily through the TB clinics and the HIV-related services mostly through the HIV clinics. Some TB services still must be integrated into the HIV clinics: HIV clinics should still screen people for TB (or assess their current TB status, such as whether they are on TB treatment, etc) and practice good TB infection control. However, people identified by TB screening as being TB suspects (possibly having TB) will need to be referred to facilities that can complete the TB diagnostic process.
- 2 Partial integration: TB clinics provide some HIV services, but refer patients out for others (such as CD4 testing or ART). This is particularly common where clinics are required by the government to go through a rigorous accreditation process or install security before being able to distribute antiretroviral drugs. In South Africa, accreditation delayed the ability of Richmond Hospital to deliver ART, although it is now accredited to do so. One nice work-around that it has developed, to bring ART and other HIV services to TB clinics in outlying areas in Gauteng Province, is a roving clinic with a dedicated staff and pharmacy.
- 3 Complete integration with one stop shopping for the patient, as at Kericho and Mulago Hospitals and in Rwanda (see box). For instance, while patients have TB, they receive all their HIV services, including ART, from an existing TB clinic or new combination clinic.

One stop services for TB patients with HIV in Rwanda's model TB/HIV clinics

- HIV counselling and testing (PITC)
- Enrollment into care for new patients (or if a person with HIV is already in care when they are diagnosed with TB, their file is shifted to TB service)
- Venopuncture for CD4 count
- Medical consultation, prescription of cotrimoxazole, ART
- Distribution of cotrimoxazole and ART (shift pharmacy tools, follow-up of ART and cotrimoxazole stock cards):
 - Cases already on ART through monthly provision and auto-administration
 - Newly enrolled patients under DOT (directly observed therapy)
- At the end of TB treatment the patient is referred and 'accompanied' to the ART clinic for further follow-up.

These models may have strengths or weaknesses in different settings, or in some instances, may simply be compromises for what can be achieved at a site given the “policy” environment or available resources at the time.

However, it’s important to recognise that at every point along a chain of referrals, whenever a person is referred, there is a risk of losing them. Some programmes have developed systems with active follow-up when making referrals, sometimes using with community-based workers. Even so, it is more difficult to capture and record outcome data on referrals, for instance, in settings where TB clinics have to refer people out to separate sites for HIV testing.

But it does not have to be all or nothing — it may also be possible for HIV or TB clinics to start out with a referral system, and decrease reliance upon referrals gradually as resources and capacity become available to integrate more services in-house.

“As far as the specific models of care go,” said Dr de Cock, “although delivery models may differ, outcomes should be identical: diagnosis of both diseases; successful treatment of tuberculosis to cure or completion, reduction in HIV disease progression and mortality, and a decrease in the transmission of both diseases.”

However, from the presentations at the PEPFAR meeting, it was clear that some approaches to TB/HIV service provision were critical enablers of success.

Services to reduce the burden of TB in people with HIV

HIV programmes in most countries have not been implementing TB-reducing services aggressively.

1 Intensified TB case-finding

Intensified case-finding consists of regularly screening all people with or at risk of HIV (especially in congregate settings like prisons) for symptoms and signs of tuberculosis, referring them for prompt diagnosis and treatment, and doing the same for their household contacts.

“There’s a real opportunity, when people present for HIV care or to the HIV care clinic to collect their ARVs, to actually simply screen them for TB. We’re not talking excluding TB in this case, we’re simply talking about using a screening questionnaire to see if they are symptomatic and if they are, then entering into the diagnostic process,” said Dr Reid.

HIV screening can be performed quickly and cheaply using a questionnaire asking patients whether they currently are on TB treatment, and if not whether they have any of the following symptoms: usually cough (for more than 2 or 3 weeks), fever, night sweats, recent weight loss, lymphadenopathy.

The screening tool will probably capture too many suspects than too few — since this is only the start of the diagnostic process. Nevertheless, Dr Willie Were and colleagues from CDC Uganda presented a study at the HIV Implementers’ Meeting showing that a few basic clinical symptoms were highly predictive at identifying TB in HIV-infected patients. The analysis involved 71 (3.6%) cases of TB diagnosed out of 1995 subjects. No symptom alone was 100% sensitive, however, a combination of any of the following parameters: cough >3 weeks, fever >1 month, lymphadenopathy, and BMI <18 had a sensitivity of 99%, specificity of 66% and negative predictive value of 100% for TB. During follow-up of

patients on ART, the presence of any of cough > 3 weeks or body weakness of > 2 weeks had a sensitivity of 100%, specificity of 66 % and negative predictive value of 100%.

It is unclear why HIV programmes haven’t taken up screening (or at least reporting it), as there are several examples suggesting it is easy enough to implement. Mulago Hospital screened 4835 of its HIV clinic patients, focusing on cough for 2 weeks, and then looking at other clinical symptoms (fever and weight loss) before entering into the diagnostic process (which includes chest X-ray). 17% were found to have active TB. Rwanda developed a questionnaire with five questions, and currently screens over 90% of the people in its model TB/HIV clinics (and 76% nationwide). Rwanda is now introducing TB screening into its community based outreach HIV testing and counselling programme (screening up to 68% of the people in the families visited).

Haiti has also implemented TB screening in its VCT clinics by simply assessing whether the client has a cough. 30% of those with cough were found to have active TB, 9% of the all VCT clients overall (Grand’Pierre).

Likewise, TB screening should also be introduced at PMTCT clinics, STI clinics and anywhere else people at risk of TB are likely to gather.

Establishing good referral systems between these sites and tuberculosis diagnostic and treatment centres is crucial however. In several programmes, large numbers of patients were lost between screening and ultimate diagnosis. According to Dr Vandebriel in Rwanda, patients were lost after repeated visits to the TB clinic required for repeated sputum samples, and particularly when they had to pay services charges (e.g., for chest x-rays).

2 Treatment of latent TB infection (isoniazid preventive therapy (IPT)

“Probably the least well implemented activity, and we understand the reason for this, is isoniazid preventative therapy,” said Dr Reid.

If active TB has been excluded, IPT is given to people with HIV and latent infection with Mycobacterium tuberculosis to prevent progression to active disease. However, only about 25,000 people living with HIV are currently being treated with isoniazid for latent TB infection and about 84% of them are participants in the Botswana IPT programme.

Many programmes are afraid of the development of isoniazid resistance, and also lack the capacity to introduce widescale IPT (though why this should be more difficult than cotrimoxazole prophylaxis is unclear). HATIP has described some of the issues surrounding IPT fairly recently (see <http://www.aidsmap.com/cms1199982.asp>). At the Implementer’s meeting, there were several reports of pilot IPT projects starting in other countries, including Nigeria, and Kenya. However, most countries seem to be waiting for the outcome data from the pioneering Botswana programme, some of which are expected to be released at the World Union TB meeting this November.

3 TB infection control CAN be implemented in the HIV clinics

Likewise, TB infection control is not in place in most settings where people are treated for HIV but this is changing since the XDR-TB outbreak in South Africa.

Five steps for preventing TB transmission in HIV care settings

from WHO guidelines

Step I	Screen	early recognition of cases or suspects
Step II	Educate	cough hygiene
Step III	Separate	cases or suspects in OPDs and wards
Step IV	Provide HIV/AIDS services	prompt services to reduce exposure
Step V	Investigate for TB or refer	TB diagnosis on site or prompt referral

There has been much criticism of South Africa for the XDR-TB outbreak, with many experts attributing it to a “failure to adhere to DOTS” in its TB programme, a “by product” of weak TB control. There may be some truth to this: overwhelmed by the burden of coinfection, some South African TB clinics have been unable to meet targets for case detection and supervised patient adherence support. Countrywide, TB treatment completion rates are only around 65% and the default rate is 14%. There are also issues with the widespread availability of second-line TB drugs, such as fluoroquinolones in the private sector for less serious medical indications.

But the outbreak may be due in part to the delay in integrating collaborative TB activities — in particular, infection control — into the HIV programme. In the case of last year’s outbreak, 85% of the XDR-TB was due to nosocomial transmission of a single XDR strain — so it did not arise independently in hundreds of patients receiving inadequate TB care. But in the absence of functioning TB infection control, one case of XDR-TB can quickly spread among other people living with HIV because they tend to use health services more frequently.

“There is a lot of undiagnosed TB out there, and that means TB that is continuing to be transmitted in the ART clinics and in the community,” said Dr Reid. “Most of these clinics don’t have TB control policies and people are sitting in those waiting rooms for hours on end to collect their medicines. If one person has TB or worse, XDR-TB, the whole room will likely be infected.”

“There is paradoxically the possibility of worsening the situation in the longer term if we run bad programmes,” said Dr de Cock. “Because ART will keep HIV infected patients alive but vulnerable and susceptible to tuberculosis and also to transmit tuberculosis to others.”

An increased association with HIV and TB drug resistance has also been observed in other countries. For instance, at the Implementers Meeting, Dr Reynold Grand Pierre of Haiti said that the rate of MDR-TB is three times higher among people with HIV in his country.

Many countries, including the Ministry of Health in South Africa have expressed an interest in establishing broad infection control policies, though it is unclear how soon these policies will be put into practice.

In the meantime, HIV clinics can establish infection control strategies based on good work practice and administrative measures. These include: A written infection control plan for each facility, administrative support for procedures in the plan, including quality assurance, staff training, education of patients and increasing community awareness and coordination and communication with the TB programme.

Services to reduce the burden of HIV among people with TB

The services to reduce the burden of HIV among people with TB are much more self-explanatory. However, some countries and projects were much more successful at scaling them up than others. Some of the successes and failures and ongoing challenges are described below.

1 HIV testing and counselling

Without HIV testing and counselling, countries will never recognise the true scale of the burden of HIV and TB coinfection, and people with TB who are coinfecting with HIV will go unrecognised and untreated.

Repeated again and again at the Implementers Meeting, far and away, the most critical enabler for the success of TB/HIV service scale-up at various sites was provider-initiated HIV testing and counselling. Without it, the turn-around in the

programme in Kenya, Rwanda, Mulago Hospital and other sites would not have been possible.

“One of the key landmark things that happened in Kenya was setting the policy for provider initiated HIV testing in clinical settings,” said Dr Chakaya. “Before 2004, all of our TB patients were being referred to VCT sites for HIV testing and with a lot of problems. But in 2004, the Minister of Health came up with a policy document on HIV Testing in Clinical Settings which [said] that: ‘if you don’t offer HIV testing to persons presenting with an HIV-associated illness, then you are providing, as a clinician, a sub-standard care.’”

“That statement was extremely prominent in that document, and it made a lot of difference. No clinician wants to offer sub-standard care,” he said, noting that it was reinforced in trainings. “It was a major, major event that really, really paved the way for a lot of testing of TB patients.”

In other countries, however, programmes continue to rely on VCT. Unfortunately, even though it is easy enough for TB clinic staff to recommend VCT, most people don’t follow through on the referral.

“VCT uptake initially was very poor in the Richmond Hospital,” said Dr Uys, “Because we had to use the voluntary counseling and testing approach because of the ethics requirement. It increased temporarily when we increased group counselling sessions but then relaxed unfortunately.”

The proportion of people with TB who actually get tested in the Richmond programme is only 30%. And this is higher than reported by some other posters at the South African AIDS Conference. For instance, after intensive training of nurses by the excellent Practical Approach to Lung Health and HIV/AIDS in South Africa (PALSA PLUS) programme, VCT uptake among TB patients more than doubled — but only from 10.1% to 21.2% (Fairall).

The experience of a TB/HIV collaborative programme set up to in Jakarta, Indonesia is also telling.

“There has been some hesitation to introduce testing and counselling for HIV in the TB programme (PPTI), due to the worries that it will become a double stigma, and reduce TB detection, reducing people from coming in for TB treatment,” said Dr Flora Tanujaya, a senior clinical officer for Family Health International in Indonesia

But in September 2004, they set up a VCT site at the TB clinic (and a variety of other collaborative services for people with HIV). But during the first few months, hardly anyone they referred used it (around 14% uptake overall, about 30% among those who attended an HIV education session). So for 2005, they adopted an opt-in approach. Nothing changed. In 2006, they introduced an educational video that increased access to the HIV education session to 100%.

“But still, the uptake for pre-test counselling (and testing) was only around 30%,” she said. “It is time for an opt-out strategy, but we are waiting for the national policy to change.”

Changing the national policy includes changing who is allowed to conduct the HIV test. In some settings, non-laboratory staff (including nurses) are not authorised to perform rapid HIV tests, in others medical staff can perform the test but trained lay counsellors cannot.

HIV programme have in some cases been unwilling to give up HIV testing to TB programmes, resulting in delays in the scale up of collaborative activities. But the conclusion of one roundtable discussion at the PEPFAR/WHO meeting was that HIV testing should be available at every TB microscopy site.

One final point that was often repeated at the HIV Implementers’ and PEPFAR/WHO meeting is that HIV testing should be performed on all TB *suspects* — not just the TB patients. Several teams noted that other HIV-related conditions often turn out to be the reason why someone is referred to the TB clinic.

2 HIV prevention methods

With training and steady supply of materials, most integration sites were able to introduce and implement comprehensive HIV prevention strategies for their patients.

Aspects that programmes may still need to attend to include providing their clients with, or providing referrals for PMTCT, sexually transmitted disease screening, and family planning services.

3 Cotrimoxazole prophylaxis

Most TB programmes at the conference reported little difficulty in introducing cotrimoxazole preventative therapy, other than occasional supply chain management problems, and a lack of an alternative to cotrimoxazole (such as dapson) in case of contra-indications in the DRC.

4 HIV/AIDS care and support

TB clinics may need to bring on more staff if they are providing integrated HIV/AIDS care and support services (rather than referring patients to the HIV clinic).

“Counselling and support for patients who are concurrently taking anti-TB drugs and ART requires a lot more support. They usually are very ill and there are more reports of missing pills and trying to switch round the timing for taking medications amongst these patients, so they need a lot more support,” said Dr Wanyenze. “Because there was increased workload in terms of counseling and preparing patients for ART, for example, and for the lab investigations, we had to bring in some additional staff there to help them.”

“We used some of the resources that we received from PEPFAR to hire additional personnel,” she said.

5 Antiretroviral therapy

TB programmes have had mixed success getting their coinfecting patients onto ART, depending largely upon whether they rely on referrals to existing ART clinics or are able to initiate it themselves. In the DRC, about 7% of people who were referred got onto ART, while at Kericho District Hospital, 100% did (although for a small proportion it was after they had completed TB treatment).

But for obvious reasons, every TB clinic in high burden countries cannot offer ART right away — so referrals continue to be necessary. But this causes problems when TB clinics are more decentralised than ART clinics.

“Although the absolute numbers of HIV-infected TB patients receiving ART has increased tremendously, the proportion of HIV-infected TB patients not receiving ART is not declining,” said Dr Chakaya. “TB services have been decentralised... but ARV treatment sites have not yet decentralised to the same

extent. We believe that may be the major reason why a lot of our TB patients who are HIV infected, are not yet receiving ARV treatment," said Dr Chakaya.

Another issue is when exactly to initiate ART in people who present with TB and HIV. Policies differ by country, but the system at Kericho District Hospital seemed to work fairly well.

"Initially, on the first day when they are found to be coinfecting, we take a baseline CD4 and a baseline work-up and we start them on TB treatment and tell them to come back after two weeks," said Muttai. Family members or friends are counselled to provide the patient with DOTS.

"At two weeks, we review their HIV results and give them their TB refill. If the CD4 count is very low, we want to initiate ART right away but we give them a minimum of two weeks in order to observe whether they are doing well on their TB meds, and that way if there are any side effects on ART later, you will be able to make a clinical judgement whether it is the TB or HIV meds that are causing it... When they complete their TB treatment then we hand them over to the HIV clinic," she said.

Continuing to treat someone with HIV and cured TB at the TB clinic could clearly put them at risk of re-exposure to TB, so most programmes recommend referring people on ART to their most convenient TB clinic. But this has proven somewhat tricky in some cases.

"We have had some challenges with the transferring out of patients after they have completed TB treatment," said Dr. Wanyenze. "They get attached to the clinic and they get a bit uncomfortable with transferring out."

Ongoing challenges

There are of course various ongoing problems that will continue to limit success of any of collaborative TB/HIV efforts. For instance, resource-limited countries still need to strengthen their health systems and add to their health workforce. Although assistance from PEPFAR, the Global Fund, DFID and other partners has enabled some programmes to bring on more staff, and other programmes are finding ways to "task shift" activities to new cadres of workers (volunteers and/or paid lay staff from the community), long term and sustainable solutions are needed.

Despite an increase in funding to laboratory scale-up and diagnostics, the capacity to quickly diagnose TB, including smear negative and drug resistant strains continues to be a problem. One roundtable group at the PEPFAR/WHO meeting suggested that HIV programmes might want to consider using some of their funds to improve TB laboratory capacity, since, given the high coinfection rate, there is a good chance that this would improve outcomes in their patients.

Finally, supply chain management needs to be updated and improved to prevent stock-outs of HIV test kits, condoms and cotrimoxazole.

Time to scale up

But at the end of the day (and of the conferences), it was clear, based on the example of Kenya and Rwanda and at several of the pilot sites, that these issues should not stand in the way of immediately implementing collaborative activities.

"I think it's time we move beyond pilot sites," said Dr Anand Date of the CDC as we both boarded our plane leaving Kigali. "It's time to scale up."

References

- Dhlamini N et al. HIV & AIDS, STI, tuberculosis (HAST) integration. 3rd South African AIDS Conference, Durban South Africa, abstract 223, 2007.
- Chakaya JM. TB/HIV: Integration of services and stopping the newest epidemic—XDR-TB. The 2007 HIV/AIDS Implementers' Meeting, Kigali, Rwanda.
- Fairall L. Practical approach to lung health and HIV/AIDS in South Africa (PALSA PLUS): a best practice model for primary care nurse training in integrated healthcare. 3rd South African AIDS Conference, Durban South Africa, abstract 733, 2007.
- Getahun, H. Enablers for nationwide expansion of collaborative TB/HIV activities. Accelerate HIV/TB activities in PEPFAR focus countries. Kigali, Rwanda, 2007.
- Grand'Pierre, R et al. HIV/TB integration in a network of VCT centers in Haiti. The 2007 HIV/AIDS Implementers' Meeting, Kigali, Rwanda. The 2007 HIV/AIDS Implementers' Meeting, Kigali, Rwanda abstract 303.
- Loveday, M et al. The awareness and effect of HIV on TB patients and health service provision for TB patients. 3rd South African AIDS Conference, Durban South Africa, abstract 710, 2007.
- Mwesigire, D.M A model for integration of TB and HIV care and treatment services in Mulago Hospital, Uganda. The 2007 HIV/AIDS Implementers' Meeting, Kigali, Rwanda, abstract 1062.
- Muttai HC, Hamm TE, Sigei, CK. Integration of HIV and TB services within the district hospital: experiences from the Kericho District Hospital in Kenya. The 2007 HIV/AIDS Implementers' Meeting, Kigali, Rwanda, abstract 678.
- Natpratan, C et al. TB/HIV public-private partnership for most-at-risk-groups in Jakarta, Indonesia. The 2007 HIV/AIDS Implementers' Meeting, Kigali, Rwanda, abstract 831.
- Ndhlovu L et al. Challenges to integrating ART and TB services in Health Facilities in South Africa. 3rd South African AIDS Conference, Durban South Africa, abstract 230, 2007.
- Reid A et al. Global progress in implementing collaborative TB/HIV Activities — comparison with the 15 PEPFAR 'focus' countries. The 2007 HIV/AIDS Implementers' Meeting, Kigali, Rwanda, abstract 1771.
- Scott V et al. Evaluation of an integrated HIV/TB/STI strategy in Cape Town. Addressing the challenge of turning the policy of HIV/TB integration into action. 3rd South African AIDS Conference, Durban South Africa, abstract 586, 2007.
- Stephens D et al. Integration of tuberculosis (TB) treatment in HIV And AIDS programming. 3rd South African AIDS Conference, Durban South Africa, abstract 445, 2007.
- Van Rie A et al. Roll-out of provider-initiated HIV counselling and testing for patients with tuberculosis in Kinshasa, Democratic Republic of Congo. The 2007 HIV/AIDS Implementers' Meeting, Kigali, Rwanda, abstract 763.
- Vandebriel G. Early results of implementation of a national policy on TB screening in people living with HIV attending ART clinics in Rwanda. The 2007 HIV/AIDS Implementers' Meeting, Kigali, Rwanda, abstract 596.
- Verkuijt SE et al. TB and HIV services integration in TB hospitals at the Buffalo City Local Service Area, East London, South Africa. 3rd South African AIDS Conference, Durban South Africa, abstract 684, 2007.
- Weyer K et al. Improving access to HIV care for TB patients in South Africa: a best-practice approach. 3rd South African AIDS Conference, Durban South Africa, abstract 362, 2007.
- Were W.A et al. Clinical predictors of active tuberculosis in HIV-infected people attending an antiretroviral treatment program in rural Uganda. The 2007 HIV/AIDS Implementers' Meeting, Kigali, Rwanda, abstract 1280.

Resources

WHO STOP TB Department
<http://www.who.int/topics/tuberculosis/en/>

The STOP TB Partnership
http://www.stoptb.org/wg/tb_hiv/

Studies present reassuring data on the use of ART in patients on TB treatment

Two studies presented at the 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention in Sydney provided reassuring data about the dosing and effectiveness of both efavirenz and nevirapine-based antiretroviral therapy (ART), although questions still remain about the best ART regimen to use and when is the best time to start it in people coinfecting with HIV and TB.

reproduced from the www.aidsmap.com/news coverage of the IAS Conference on HIV Pathogenesis, Treatment and Prevention in Sydney, 2007

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Background

Rifampicin is the cornerstone of the combination of drugs used to treat TB, however, studies have shown that it lowers the serum concentrations of efavirenz by up to 20%, and nevirapine levels by 20-50%. Because of fears that coadministration might thus compromise antiviral efficacy, many doctors in resource limited settings (where other regimens are not available or are too costly) have been afraid to start ART in people with HIV already on TB treatment — even though the patient may desperately need HIV treatment. In addition, clinicians may be unsure what to do if someone on either efavirenz- or nevirapine-based ART regimens should develop active TB. Delaying TB treatment is not an option. Should the antiretroviral doses be increased?

Efavirenz

In the case of efavirenz, a few studies now suggest that this is unnecessary. One of these, by Dr Ketan Patel and colleagues at the Infectious Diseases Clinic, Ahmedabad, India found that coadministration of standard doses of efavirenz (600 mg once daily) with TB treatment did not appear to reduce its short-term clinical effectiveness, while other studies reported that increasing the dose to 800 mg once daily did not necessarily lead to dramatically better trough levels of the drug, but did significantly increase side effects.

Nevertheless, there is a chance that coadministration could reduce the long-term effectiveness of efavirenz-based ART, so Dr Patel assessed the data from extended follow-up (at least 12 months and out to three years) of the previous cohort to ascertain whether prior TB treatment predicted an increased risk of treatment failure.

195 HIV-positive patients with TB and 188 without TB were treated with an efavirenz-containing combination antiretroviral regimen. Patients with TB received the same antiretroviral regimen plus nine months of rifampicin-containing TB treatment, and then continuing with efavirenz-containing combination antiretroviral treatment alone. All patients were medically evaluated every month with CD4 counts done every three months.

Among patients co-infected with TB, baseline median CD4 counts were lower in those with TB (90 versus 126) ($p = 0.0005$). However, similar improvements in CD4 count were seen in both groups at each time point up to 3 years of follow-up. The rate of irregular follow-up and those lost to follow-up or death were also similar in the two groups ($p = 0.494$).

There appeared to be no significant differences in long-term treatment outcomes. Immunological failure was observed in 11.79% and 10.10% of subjects with and without TB ($p=0.715$) respectively. When losses to follow-up were treated as failure, there was still no significant difference. Nor was there any

difference in time to treatment failure. However, it should be noted that the study has no viral load results in its subjects.

A significantly higher number of people on treatment for both TB and HIV developed hepatitis (13.3% vs 2.2%, $p < 0.0001$) but Dr Patel said these resolved when the hepatotoxic drug was discontinued.

“Rifampicin-based TB treatment at the onset of efavirenz-based HAART didn’t predict or increase risk for efavirenz treatment among HIV infected patients, for up to three years,” concluded Dr. Patel.

Nevirapine

Because of the previously described studies, efavirenz is recommended by WHO guidelines when people on TB treatment need to start ART.

However, some people cannot take efavirenz due to allergies, side effects, pregnancy or unavailability. In these cases, nevirapine may be the sole option, but the best dosage has been unclear. So Dr Anchalee Avihingsanon of the Thai Red Cross AIDS Research Centre, Bangkok, Thailand and colleagues conducted a randomised study to find the appropriate dose of nevirapine in HIV/TB co-infected patients also on rifampicin.

The team investigated 32 HIV/TB co-infected patients, with CD4 counts < 200 cells/mm³, who were receiving rifampicin for two to six weeks. The subjects (mostly male) had extremely advanced HIV disease, with baseline CD4 cell counts of 45 and 40 for the NVP400 and the NVP600 arms respectively.

Nevirapine dosing is already somewhat complicated. Participants were randomised to receive nevirapine 200mg once daily for 2 weeks then twice daily (NVP400 arm) or 200mg twice daily for two weeks then three times daily (NVP600 arm) plus two nucleoside reverse-transcriptase inhibitors. Plasma nevirapine levels were checked at weeks 2, 4, and 12.

They found that median nevirapine trough levels (C_{min}) at week 2 were significantly lower in the NVP400 arm than the NVP600 arm ($p = 0.001$). More patients had C_{min} levels < 3.1 mg/L at week 2 in NVP400 (79% vs 19%, $p = 0.002$). However, nevirapine C_{min} was comparable between the two arms at week 4 ($p = 0.06$) and week 12 ($p = 0.24$).

“ many doctors in resource limited settings have been afraid to start ART in people with HIV already on TB treatment — even though the patient may desperately need HIV treatment ”

The 24-week efficacy showed no difference. In an intent-to-treat (ITT) analysis 63% vs 56% had HIV RNA < 50 copies/mL, while in an on-treatment (AT) analysis 83% versus 100% of the NVP400 and NVP600 had HIV RNA < 50 copies/mL. The median (inter-quartile range) CD4 rise was actually greater on the NVP400 arm but this did not reach statistical significance ($p = 0.07$).

However, NVP600 had a higher trend to hypersensitivity (25% vs. 6%, $p = 0.07$) and study discontinuation (44 vs 25%, $p = 0.23$).

Although drug levels were suboptimal in the NVP400 group's lead-in period, the NVP600 lead-in period was associated with more drug hypersensitivity. Because of these data, the NVP600 arm was discontinued. Longterm follow-up data of NVP400 at 60 weeks show that 68% of subjects have viral loads below 50 copies/ml by ITT, 87.3% by AT.

“NVP 600 with a 400 mg lead-in is not recommended due to a high rate of hypersensitivity,” said Dr. Avihingsanon. However, despite suboptimal doses in 80% of the patients at two weeks, nevirapine dosed at 200mg twice daily as part of combination antiretroviral therapy with 200 mg once daily lead-in “provided potent virological suppression and good CD4 response over 24 weeks observation,” so this regimen “should be sufficient for most Thai HIV-infected patients” receiving rifampicin.

However, it is unclear how applicable these findings are to other populations. According to Dr Avihingsanon, Thai subjects tend to have higher drug levels of nevirapine than other ethnicities. Also, the weight of the participants in this study was quite low compared to some populations (between 46-54 kg).

References

Avihingsanon A et al. 24-week efficacy and safety of nevirapine: 400 mg versus 600 mg based HAART in HIV-infected patients with active tuberculosis receiving rifampicin. Fourth International AIDS Society Conference on HIV Treatment and Pathogenesis, Sydney, abstract MOAB102, 2007

Patel K et al. TB co-infection treated at onset of therapy does not affect long-term risk of treatment failure among HIV-1 patients initiating efavirenz (EFV)-based combination antiretroviral treatment (cART). Fourth International AIDS Society Conference on HIV Treatment and Pathogenesis, Sydney, abstract MOAB103, 2007.

Botswanan study finds low concentrations of TB drugs common in HIV-positives, predict TB treatment failure

A pharmacokinetic (PK) study conducted in people on directly observed tuberculosis (TB) treatment in Botswana calls into question whether the standard TB drug dosing is really adequate for all populations, particularly among people with advanced HIV living in sub-Saharan Africa.

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The study, which was presented at the 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention in Sydney, Australia, found that low concentrations of TB drugs were common in the population, regardless of HIV status.

However, when people also had advanced HIV disease, concentrations of some of the TB drugs were significantly lower — which could have contributed to poorer treatment outcomes. However, having a low level of pyrazinamide, in particular, was independently associated with having a worse outcome on treatment.

Background

First-line TB treatment has for many years relied chiefly on a combination of four drugs: rifampicin, isoniazid, ethambutol and pyrazinamide, but the pharmacokinetic profiles of these medications were typically established in healthy adults in Europe and the US.

Over the years, lower than expected levels of some TB drugs have been reported worldwide, associated with gastrointestinal illnesses, drug-drug interactions, patient demographics and HIV infection. This could potentially lead to prolonged infectiousness, treatment failure and/or death as well as the development of drug-resistant TB.

“Given this, we think it is very important that population-specific pharmacokinetic norms be established for those in whom they are relatively unknown, and who make up the majority of cases in the TB epidemic today, mainly people living with HIV and AIDS in sub-Saharan Africans,” said Dr. Sekai Chideya of the US Centers for Disease Control and Prevention, who presented the study’s findings.

Furthermore, she believes that the emergence of extensively drug resistant TB (XDR-TB) indicates a pressing need to reassess how the PK parameters of TB drugs affect patient outcomes worldwide.

So she and her colleagues performed a study to determine the incidence of sub-therapeutic drug levels among adults with TB (both HIV-infected and uninfected) in Botswana, to look for associations between patient risk factors and low drug levels, as well as the associations with poorer outcomes.

Between 1997 through 1999, the study enrolled consenting adults with TB at Gaborone, Botswana’s largest public outpatient clinic, who agreed to have an HIV test and who had initiated TB treatment within the previous seven to 13 days.

Participants were hospitalised, and fasted for eight hours before receiving all four TB drugs simultaneously. Serum was drawn at 1, 2, and 6 h after TB treatment dosing. Specimens were then frozen and shipped to a US laboratory that specialises in drug level analysis (using high performance liquid chromatography, however

this was only recently performed). "Low drug levels" were defined using previously published reference points for the maximum serum drug levels (C_{max}).

Patients were then discharged and monitored regularly for 18 months for either treatment failure (defined as either being sputum-positive after six months of treatment or showing no clinical improvement after 6 months on treatment) or death during TB treatment.

Results

The final sample size was 225; 69% were HIV-infected and none were taking antiretrovirals. The median CD4 cell count was 269, (606 in the HIV-negative patients and 189 in the HIV-positive).

Low concentrations of rifampicin occurred in 84%; ethambutol in 39%; isoniazid in 37%; and pyrazinamide in 5% of patients. However, the median C_{max} in people with HIV was significantly lower ($p < 0.04$) for rifampicin and pyrazinamide. This was mostly powered by those with CD4 cell counts < 200 (93% of those with CD4 cells below 200 had low rifampicin levels, vs 80% in those with CD4 cells above 200, $p = 0.005$).

27% of the people with low CD4 cell counts had poor treatment outcomes, vs 11% in the HIV-negative group and 12% in the HIV-positive subjects with higher CD4 counts. In a multivariate analysis, having a CD4 cell count < 200 put people at a higher risk of a poor outcome (Odds Ratio 3.2 (95% confidence interval 1.1- 11.7, $p = 0.3$).

In a multivariate analysis, having a low concentration of pyrazinamide was also a risk factor for poorer outcome (OR 7.7 (95% CI 1.8-3.3; $p = 0.003$). After controlling for HIV status, and CD4 cell count, the relative risk for treatment failure was 5.7 (95% CI 1.5-20.7) and for death during treatment, 4.5 (95% CI 1.5-13.3).

Discussion

The study is somewhat unique because it is a prospective cohort with a rather large sample size (most PK studies are much smaller). However, the results may look particularly bleak because of the very high mortality rate due to HIV (no one was receiving antiretroviral treatment). Also, the study only evaluated PK on one day during the course of treatment.

“ Over the years, lower than expected levels of some TB drugs have been reported worldwide. This could potentially lead to prolonged infectiousness, treatment failure and/or death as well as the development of drug-resistant TB ”

The importance of pyrazinamide was rather surprising, although it should be noted, that low levels generally occurred within the context of the other drugs being low as well. It however, appeared to be the proverbial straw that broke the camel's back. "We're still not quite sure why," Dr Chideya said, but she suspects that when the drug level is low, it may be more difficult to sterilise mycobacteria from some parts of the body.

According to Dr Chideya, the low levels were not associated with poor gut absorption in these patients — and appeared to occur in those with normal liver function tests. This suggests that there could be some change in drug metabolism brought on by HIV.

This does not mean that she recommends increasing the dose of any of these drugs (in fact, this could cause unwanted toxicity and may not have the desired effects on serum drug levels anyway). Nevertheless, it suggests that some of the assumptions about the optimal doses of TB drugs may have to be re-evaluated.

"We are hopeful that future steps will include establishing TB drug pharmacokinetic norms for people living with HIV/AIDS, people of colour and women," concluded Dr. Chideya.

References

Chideya S et al. *Incidence of sub-therapeutic tuberculosis drug concentrations and associated treatment outcomes among predominantly HIV-infected tuberculosis patients, Botswana*. Fourth International AIDS Society Conference on HIV Treatment and Pathogenesis, Sydney, abstract MOAB104, 2007.



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We are a community based organisation, now 20 years old, that supports you by producing reliable, impartial, up to date information based on the latest TB, HIV and AIDS research.

If you are a healthcare worker or other professional who treats or supports HIV-positive people then you will find NAM produces a resource that could make your work easier.

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You might have met us before without realising it!

If you have ever visited our website **aidsmap.com**, then you have already met NAM and seen the range of materials we produce for you.

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