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Catalysing HIV/TB research: a meeting report

By Theo Smart

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Introduction

"The consequences of inattention to TB research are not just embarrassing, they are tragic and shameful," said Dr Anthony Fauci, Director of the US National Institute of Allergy and Infectious Diseases (NIAID) at a meeting held in Cape Town just prior to IAS 2009.

"Generations of research advances and technologies have bypassed the field of TB research. All of the great breakthroughs that we have seen in molecular biology — there was nobody working on it in TB. Nine million people develop active TB each year and yet we still don't have an effective vaccine. There have been no newly licensed drugs for TB in forty years [with the exception of rifabutin]. The therapeutic regimens, although they work, are cumbersome and prone to the development of drug resistance. The diagnostics are ridiculous, they are antiquated, non-standardised and imprecise."

The meeting entitled "Catalysing HIV/TB Research: innovation, funding and networking" was organised by the World Health Organization (WHO) in collaboration with the International AIDS Society, the Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE), Treatment Action Group (TAG) and the Desmond Tutu HIV Centre of the University of Cape Town. The goal of the meeting was to review the ongoing research activities around TB/HIV, serve as a forum for exchange of new findings and challenges, and to identify gaps and priorities in the HIV/TB research agenda. The meeting was attended by about 250 HIV researchers, activists and representatives from funding agencies.

As HATIP [described earlier this year](#), TB research has long been neglected and under-funded. But the participation of Dr Anthony Fauci, Director of NIAID, of Nobel Prize winner Dr Françoise Barré-Sinoussi of the Institut Pasteur, and many others from the HIV research establishment was a clear sign that some of the world's pre-eminent research institutions are finally moving to make TB research a priority.

"We must aim at transforming the research field," said Dr Fauci, "We are playing 'catch up' after decades of neglect, so incremental changes are not sufficient. TB is an ancient disease, but we must understand it in modern terms, using cutting edge technologies to ask and answer questions that have never been adequately addressed."

Some of the most critical goals include forming a better understanding of TB pathogenesis, the development of a safe and effective vaccine, moving TB therapeutics into the 21st century and last but not least the development of point-of-care diagnostics for TB.

In her talk, Dr Barré-Sinoussi underscored the need for much better understanding of the host-pathogen interaction as a leverage to generate new ideas and areas of TB research particularly for diagnostics and drugs. She noted that there are unique challenges involved in screening and diagnosing TB in people with HIV, especially extrapulmonary TB and in children.

Treatment of TB does have to be improved, given the burden of coinfection, and research needs to address when and how to co-administer TB treatment and ART in the same patient; and how to recognise and manage TB immune reconstitution inflammatory syndrome (TB IRIS). Finally, in addition to operationalising isoniazid preventative therapy, new and better preventive measures, such as vaccines, must be developed.

While funding for basic science is essential, she stressed that it must be balanced with translational and clinical research to quickly move advances into the field.

The remaining speakers addressed a variety of issues, which were summarised in the satellite session into four topic areas: TB prevention, TB/HIV diagnosis and treatment, childhood TB/HIV, and TB drug resistance.

Online materials from the meeting

Most of the slide presentations from the meeting can be found here: http://www.stoptb.org/wg/tb_hiv/meetingevents.asp, while outcomes and key findings of the meeting were presented at a satellite session held later during the IAS 2009 conference. References for the studies cited below can be found in those presentations. A webcast and powerpoint presentations from the satellite symposium are available at the [IAS 2009 conference website](#). This article summarises some of the highlights of the meeting and satellite session.

Preventing TB in people with HIV

The TB epidemic has been fuelled by HIV, which greatly increases the likelihood of developing active disease after exposure to TB bacilli and infection and increases the number of infectious cases and ongoing transmission. Research is needed to explore ways to reduce TB transmission and the reactivation of TB and develop other interventions to reduce the prevalence of tuberculosis in people with HIV. Much of this research involves refining key strategies that HATIP has previously reported on, including preventing TB by scaling up access to ART, and the package of interventions known as the '3 I's': Isoniazid Preventive Therapy (IPT), Intensified Case Finding (ICF) and Infection Control (TB IC). (A collection of the previous reports on the 3 Is is available in a publication called Think TB in People with HIV, which can be [downloaded in pdf form here](#), file size 2.3mb).

ART to prevent TB

Dr Robin Wood of the Desmond Tutu HIV Centre of the University of Cape Town reviewed findings from his team and others demonstrating that TB incidence risk is inversely related to CD4 cell counts both on and off of ART and that ART's effect on TB incidence in the population and community depends both on the CD4 cell count at initiation of ART and the sustained CD4 response. Rates of TB are extremely high in people who have very low CD4 counts, ART reduces the incidence of active TB as CD4 cells increase, but the TB rates remain elevated above what is seen in the general population until the CD4 cell count goes above 500.

Dr Wood also previewed what would be some of the most exciting data from the IAS conference ([see this report](#)), showing that the delivery of ART to cover 90% of eligible people in a small, tightly demarcated periurban community near Cape Town, led to a marked decrease in HIV/TB-associated mortality and a population level effect in the community — a reversal of 10 years of increasing TB incidence probably due to a major decline among those on ART.

These findings need to be replicated elsewhere, as they make a strong and important case for the continued push towards universal access for HIV treatment — and for the initiation of ART at much higher CD4 cell counts — at a time when funding partners and programmes have been shying away from honouring funding commitments.

Isoniazid preventive therapy (IPT)

Professor Gavin Churchyard described some of the lessons learned in the huge Thibela TB study being conducted in the South African goldmines, which has randomly allocated about 70,000 miners, according to which mine they work and live in, to either the standard approach to TB control or to TB control including community-wide IPT. To date, the study has had great success enrolling participants, and starting those who are eligible on IPT. Community mobilisation has been essential for engaging participation — and this was affected by a well-orchestrated communications strategy in which the study was given a strong brand identity, and simple key messages that were reiterated through a variety of media.

The study has observed very few serious side effects (mostly peripheral neuropathy seen in one out of 500 subjects), and while there have been some deaths on study, only one or two could possibly be related to isoniazid toxicity. Another plus was that the screening process for the study (which included chest x-rays) identified many previously unrecognised cases of TB. Finally, there was no evidence of an increase in IPT resistance compared to the general population, but this could possibly be because the study did such a thorough job screening participants for active TB.

While these are encouraging data, Professor Connie Benson of the University of California San Diego pointed out at the meeting that there are still many outstanding questions around IPT. For instance, how generalisable will Thibela TB's findings be to other settings — particularly where facilities do not have the capacity to perform chest x-rays on patients? How long will the preventive effect last, especially in communities at high risk of reinfection? What is the optimum duration of treatment? What are the costs and staffing required to implement IPT properly? Might other regimens be more effective? What is the safety and efficacy of IPT in co-administration with ART, including second-line regimens? Finally, what sort of preventive therapy should be given to people at high risk of exposure to MDR-TB?

TB infection control

Dr Rod Escombe of the Imperial College, UK, described what is currently known about TB infection control that includes facility level managerial (such as having a TB infection control plan) and administrative controls, environmental controls and personal respiratory protection. Administrative controls include the rapid identification and separation of TB suspects (*triage*), cough hygiene, minimising the time spent in health care facilities and a prevention and care package for health care workers. There is good evidence that these work in lower middle-income countries, but only as a package of interventions. However, the relative contribution of the individual interventions to the effectiveness of IC is unknown.

Environmental controls seek to eliminate or kill any infectious TB bacilli that might be circulating in droplets in the air. There is a lack of epidemiological data showing that environmental measures work — most of the recommendations are based on modelling evidence, animal studies and theoretical data based on measuring air changes. Emerging data suggest that although optimally designed mechanical ventilation systems can be quite effective, they are

expensive, difficult to maintain, and may be prone to failure in resource limited settings. When possible, a better option would be to optimise natural ventilation; and Dr Escombe has been involved in work [demonstrating that natural ventilation \(simply opening windows\)](#) can dramatically increase the number of air changes per hour.

He noted that another low-cost option is to install wind turbines on the roof, which can increase ventilation significantly, especially on windy days. Building layout and movement of people through a facility can also be optimised to enhance natural ventilation.

Nevertheless, Dr Escombe noted that there are also a number of disadvantages to natural ventilation — namely that it is climate dependent; there is no control over the direction of contaminated air — which should be considered when choosing the location of TB wards. Also, noise pollution, security and fire safety can be issues.

In situations where ventilation cannot be increased as much as one would like (such as in cold climates or at night), guinea pig studies have shown that ultraviolet radiation of the upper-room air could reduce transmission — provided room air is circulated towards the lights. These also require expert design and installation, plus routine bulb cleaning and changing. There is also a need to develop low-cost fixtures for use in resource-limited settings.

There is very little evidence that personal respiratory protection prevents TB transmission, though there is good evidence to show that N95 respirators can catch the particles. The challenges are operational: fit testing, durability of the mask (how long can one effectively be used?) and in getting people to wear them when necessary.

This behavioural component may actually be critical for the success of all the TB IC interventions and should be studied. How can hospital staff be motivated to perform administrative controls? How are any of these interventions put into operation and maintained? What sort of training and supervision is necessary? What elements of infection control or specific interventions are most critical to implement in resource-limited settings?

Additional research needs include the duration of infectiousness (particularly of patients with drug-resistant TB and also infected with HIV). How long should infectious patients (particularly those with drug-resistant TB) be in isolation? Novel methods for evaluating the implementation and impact of TB infection control in health care settings such as to measure the concentration of viable TB in the air are needed, as is translational research that promotes the implementation of existing policies such as the newly released WHO policy on TB infection control.

Intensified case-finding

Studies have shown that there is a huge burden of undiagnosed TB in many communities, especially among people with HIV. The early detection and treatment of these cases may have a role in preventing the spread of TB within the community, in congregate settings and health facilities. Although further research is needed to optimise screening tools, even the use of an insensitive tool should detect additional cases sooner, lead to earlier treatment, reduce the burden of TB and decrease opportunities for onward transmission.

One approach to increase detection is to routinely screen for TB in people with HIV in health facilities. Another approach is to go into the communities to find TB cases. Dr Helen Ayles gave a presentation on the Zamstar study which is a large cluster randomised trial, allocating different communities (in the Western Cape, South Africa and Zambia) to either strengthening the existing health system or an enhanced case finding strategy that links three elements:

- 1 Community mobilisation (information, education and sputum collection points)
- 2 A schools intervention (encouraging children to take messages home) and
- 3 An open access approach to sputum microscopy where anybody who wants can have their sputum screened. The idea is they should be able to deliver their sputum within a 30 minute walk of their home and be guaranteed to get the results within 48 hours.

While the approach is likely to increase case-finding, the primary outcome of the study will be the prevalence of tuberculosis across the different communities, after three years of intervention.

Dr Ayles also presented data from Professor Liz Corbett's "DetectTB study" which is also a cluster randomised study comparing door-to-door screening for chronic cough or by using a mobile van, to see which will find cases more efficiently and reduce the prevalence in the western suburbs of Harare.

A common finding of both studies is that health-seeking behaviour among people suspected of having TB is very low. In DetectTB, 70% of cases had not attended the health service. A significant number of these cases are actually among HIV-negative people, who are both more likely to be smear-positive (and infectious) and who survive with TB much longer than HIV-positive patients.

"This means that we shouldn't be just thinking about intensified case finding - which tends to focus on people living with HIV - but that if we want to prevent tuberculosis, a major focus should be on people who are HIV-negative and who may transmit tuberculosis for a long time," said Dr Peter Godfrey-Faussett, of the London School of Hygiene and Tropical Medicine during the satellite symposium. These people may be living right next door to a clinic and yet refuse to go there — one person in Dr Corbett's study reportedly said 'I feel it is better to go home and die than to stay and be insulted.'

"We have to think how the health system engages with the community and how patients engage with the health system when they get there," said Dr Godfrey-Faussett. "Access is not only geographical access but may also be due to much more complicated psychosocial questions of access."

Likewise other societal measures need to be considered as prevention because TB is contracted in societies that are structurally weak due to poverty and social inequity.

Finally, Dr Godfrey-Faussett stressed that the effectiveness of these preventive strategies is challenged by the lack of good diagnostic tools.

"Diagnosis remains the 'Achilles Heel' to several of these attempts to prevent TB," he said. For instance, a point-of-care while-you-wait TB test would simplify TB screening, it would be much easier to give IPT if it were easier to exclude active disease, and it would make it easier to comply with administrative infection control.

Clinical challenges for diagnosing and treating TB in PLHIV

Another major focus of the Research Meeting was how to improve the management of people living with TB/HIV.

Subclinical TB

One speaker, Dr Haileyesus Getahun of WHO's STOP TB Department tackled an issue that has led many clinical programmes to avoid implementing IPT to prevent TB: the fear that they might accidentally under-treat sub-clinical TB, so leading to drug-resistant TB.

Dr Getahun performed a systemic literature review to determine whether subclinical TB actually exists, and if it does, what would be its standard case definition.

He found a number of case definitions across several studies, but nothing standardised, and none of the studies specifically addressed sub-clinical TB as a primary objective. There were some common elements to this syndrome, however, namely that the patient was asymptomatic by symptom screening, the definition of which varied from study to study but which did not mean that the patients were necessarily free of any signs and symptoms. The diagnosis of TB was generally made on culture-positive results except for one study that used AFB smear to confirm TB. Some of the case definitions included cases that were extrapulmonary TB.

There is no workable case definition and evidence is too scarce at this point to draw meaningful conclusions on the implications of sub-clinical TB (or base policy upon its theoretical existence).

Dr Charlie van der Horst from the University of North Carolina pointed out that it also depends on how, where, when and who asks the questions to solicit symptoms from patients. Stigmatisation of specific symptoms may lead the patients to deny or not to recognise their presence.

While there is a possibility that there may be a clinical entity, somewhere on the continuum between latent and active disease, of asymptomatic subclinical TB that can only be detected by culture, this needs to be demonstrated using a standardised case definition. Only at that point can we determine how common it is, the risk factors, how long this disease state lasts, and its clinical implications.

The role of TB in early mortality on ART in people living with HIV

The issue of subclinical TB might be of particular relevance in people who are about to start taking ART, particularly if it contributes to poor outcomes. Data from the ART-LINC study suggest that the cumulative probability of death during the first 12 months on ART in resource-limited settings is much higher (6.4%) than in industrialised countries (1.8%) and that much of this may be due to TB.

According to Dr Mina Hosseini, from the University of North Carolina, this increased mortality occurs early on ART, with an increased hazard-ratio in the first three months, particularly in people in lower CD4 strata. The analysis adjusted for cohort, sex, age, baseline CD4, the ART regimen, and the stage of disease. The risk factors for early mortality were low BMI, low CD4, WHO stage 3 and 4 disease and low haemoglobin. TB was in fact the leading diagnosis associated with death.

In fact, TB was the leading cause of death in five out of six cohort studies (five in South Africa, one in Haiti) looking at the causes of mortality on ART. TB was also likely to have been underreported, due to the difficulty of making a diagnosis, and high loss to follow-up rates. After TB, other diagnoses listed as causes of mortality included invasive bacterial infections, wasting (potentially TB-related), cryptococcal meningitis and Kaposi's sarcoma. Most causes of death were actually unknown, but it was pointed out that this may well have been undiagnosed TB in many cases.

There are few data to show whether causes of death in the community have a similar pattern to in-patient death, and this should be studied. Other research questions include whether it might be possible to optimise ART to reduce early mortality, adjust for toxicity that may complicate the management of coinfections, and look at drug interactions. Finally, would a strategy of aggressive

screening for TB or empiric TB treatment reduce the risk of early mortality in high-risk patients (such as those in low CD4 cell strata)?

TB IRIS

Another treatment issue that may emerge after initiating ART is TB immune reconstitution inflammatory syndrome (IRIS), which is characterised by clinical deterioration during ART that is thought to be due to an immunopathological reaction to mTB as mTB-specific immune responses improve. It may manifest in one of two forms: people already on TB treatment who experience a paradoxical reaction after starting ART (*paradoxical TB IRIS*). Another reaction occurs in people who begin ART who are not on TB treatment. TB incidence rates remain high especially during the first months of ART in settings with a high burden of TB. A subset of these new TB cases may manifest with a particularly exaggerated inflammatory presentation and are regarded as being *unmasking TB-IRIS*.

Dr Graeme Meintjes of the University of Cape Town told participants at the Research Meeting that paradoxical TB IRIS may occur in up to 25% of people on TB treatment starting ART in sub-Saharan Africa. Major risk factors include low CD4 counts, disseminated TB and a short interval between TB treatment and ART. Their TB is typically improving on TB treatment but usually one to four weeks (but up to three months) after starting ART, they may get new and recurrent clinical manifestations of TB, such as increased lymph node involvement, pleural effusions, ascites, cold abscesses and tuberculomas in the brain.

Dr Meintjes and colleagues published case definitions for paradoxical TB IRIS, (and unmasking TB IRIS) in [Lancet Infectious Diseases](#) (registration is required). Dr Meintjes believes there is still a need to assess the performance of the consensus case definition for TB IRIS, especially since there is no diagnostic test for paradoxical TB-IRIS and diagnosis is made on clinical grounds after exclusion of other plausible explanations for the clinical deterioration.

He has also presented results of a study demonstrating that corticosteroids can reduce hospitalisation time in people with paradoxical IRIS, though its impact on survival has yet to be determined.

"This is clearly not the final word on corticosteroids for IRIS," he said. "In making the decision regarding using steroids clinicians also need to weigh up the potential side effects. There was an excess of mild infections in our study, and there may be greater risks in other settings, for instance where strongyloides is endemic. But more importantly in settings where diagnostic capability is limited, more harm than good could be done by prescribing corticosteroids to patients who may not have TB IRIS but instead have another opportunistic infection or have undiagnosed MDR-TB."

Although there are many case reports of unmasking TB-IRIS, it can be difficult to distinguish from a normal case of TB arising on ART – unless there are overtly inflammatory presentations. But again, rates of incident TB are extremely high in people starting ART, especially in lower CD4 cell strata. Research is needed to determine how much of this TB is really unmasking TB IRIS and to identify its role in early mortality; and there is also a need to conduct a study of empiric TB treatment in people with low CD4 cell counts starting ART.

Treatment

TB treatment in people starting ART is complicated by drug interactions due to rifampicin, which induces several enzymes in the

cytochrome P450 isoenzyme system, affecting levels of nevirapine, efavirenz and protease inhibitors. Consequently, there are many unanswered questions about how to best treat both TB and ART in the same patient.

There is a perception that the question of whether it is better to use nevirapine or efavirenz as first-line treatment alongside rifampicin-based TB treatment has been settled (in favour of efavirenz), but according to Professor Gary Maartens of the University of Cape Town and Groote Schuur Hospital, the data may not be definitive.

In early pharmacokinetic (PK) studies, when rifampicin was coadministered with nevirapine, about half of the subjects had less than the recommended nevirapine concentrations. But this effect may only be significant during the first couple of weeks of the lower nevirapine lead-in dose. A small Thai study which looked at increasing both the nevirapine lead-in dose, and the treatment dose, achieved higher nevirapine concentrations, but also observed hypersensitivity reactions in 25% of the subjects. But it is possible that increasing the long-term dose was unnecessary. The safety and effectiveness of omitting the lower lead-in dose before beginning standard doses of nevirapine still needs to be addressed in a clinical trial.

Several PK studies suggest that efavirenz is not affected by rifampicin, although the package insert says that the area under the curve concentration of efavirenz is reduced by 26%. Meanwhile, a retrospective therapeutic drug monitoring database found a significant reduction in efavirenz concentrations in people on TB treatment.

Prof. Maartens believes that there still need to be adequately powered randomised controlled trials comparing efavirenz to nevirapine in people on TB treatment – which has not really happened to date. Similar studies are also needed in children (see below).

Rifampicin also reduces levels of protease inhibitors including ritonavir-boosted lopinavir (*Kaletra*), which anchors second-line regimens in most resource-limited settings. The response has been to either double the dose or increase the ritonavir component. But sub-therapeutic *Kaletra* concentrations were observed in 60% of the children in a study in which the *Kaletra* dose was doubled, leading the data safety and monitoring board to terminate the study.

Healthy volunteers who took adjusted dose protease inhibitors with rifampicin had serious problems with hepatitis, especially if rifampicin was started first. But should these findings be extrapolated to people with HIV? In practice, the combination is used a lot in people with TB/HIV without similar degrees of liver toxicity being reported, but studies are needed to determine how safe it really is.

Recently, rifabutin (150 mg three times weekly) has been added to the essential medicines list, in the hope that it would provide an alternative to rifampicin in TB treatment regimens for people on ART. Rifabutin does not have the same potent interactions with protease inhibitors. However, Prof. Maartens believes there aren't yet enough efficacy data to use rifabutin in TB treatment. Furthermore, it's not part of a fixed-drug combination for TB, which makes it difficult to administer; and there are still issues with its procurement and distribution.

There are a number of clear research priorities for coadministering TB medications and second-line ART regimens. There is an urgent need for more data on rifampicin's interaction with the available protease inhibitors in adults and children as more patients move to second-line antiretroviral treatment, including characterising the risk of liver toxicity. More evidence is also needed

on the efficacy of rifabutin to treat TB in coinfecting patients. Finally, alternative antiretroviral regimens, including new drugs such as raltegravir, need to be evaluated in PK studies with rifampicin, and efficacy studies in people with TB/HIV.

TB in children

The management of TB in children, especially those with HIV poses numerous issues for researchers need to address. HATIP has previously described some of these in a series of articles on TB in children (see [Childhood TB - the overlooked epidemic](#); [Childhood TB - presentation and diagnosis](#), and [Childhood TB - treatment and prevention](#)) particularly the difficulties defining the actual burden of TB in children; the severe morbidity of disseminated TB (including TB meningitis); as well as how TB infection can move very rapidly from infection to disease in young children, and the dilemmas regarding treatment and prevention of TB in children with HIV.

Diagnosis

But the problems begin with diagnosis and Dr Anneke Hesselning from Stellenbosch University, South Africa, presented on the challenges of diagnosing TB in HIV-positive children. Challenges include the fact that symptom-based diagnosis – often the only recourse in remote low resourced settings – has low sensitivity in HIV, especially when children have an atypical presentation. It can be difficult to distinguish between a chest x-ray of miliary TB and lymphoid interstitial pneumonia (LIP), which is very common in children with HIV – and this leads to over-treatment of TB.

Then there are difficulties obtaining good respiratory specimens from children who do not expectorate sputum that can be used for bacteriological diagnosis. Early morning gastric aspirates are an option, though data suggest that induced sputum (increasingly performed in South Africa) is more productive. Other techniques such as nasopharyngeal aspirates and string tests need further evaluation. Fine needle aspiration may also be useful if there are superficial and enlarged lymph nodes, but this technique is also under-utilised.

There is therefore a need to evaluate and optimise all the new TB diagnostic tests that are in development in children as well as adults. These include the interferon gamma-release assays, such as the ELI-SPOT and Quantiferon Gold assay, which is more sensitive for exposure than tuberculin skin tests (TST); and the urinary lipoarabinomannan (LAM) tests. Likewise line-probe assays and nucleic-acid amplification tests (NAAT) need to be studied in children but may need to be optimised for a specimen other than sputum to be useful in children.

Prevention of TB in children and their mothers

It is policy in most countries to administer isoniazid preventive therapy to children under five who have a household contact with TB, though implementation is lacking. After a study demonstrated a clear survival benefit in children who were given IPT, there were questions about whether IPT should be given to all infants with, or exposed to, HIV.

A subsequent study could not reproduce the earlier findings when infants in the control arm were routinely screened for TB contacts and offered IPT when exposed. However, the take home message from this study should be that HIV-exposed or infected children need to be assessed routinely for TB exposure and offered IPT when necessary.

According to Dr Amita Gupta from John Hopkins University, another approach to prevent TB and TB-related mortality in infants is to reduce the burden of TB in their mothers (which clearly should be a priority for the mother's health too).

TB is the most common HIV-related illness and cause of mortality in women of reproductive age in Asia and Africa. Data suggest that infant mortality rates are also much higher when the mother has TB – even when adjusted for CD4, viral load, hemoglobin, age, and educational status in the mother, and when infant mortality is adjusted for HIV PCR status, preterm birth (<38 weeks), birth weight and the maternal factors already listed.

Likewise, rates of TB are estimated to be ten times higher in HIV-exposed uninfected children, and thirty times higher in HIV-infected children under 5 years of age. The highest rates have been found in infants under the age of 12 months, perhaps because they are in close contact with the mother and other adults and family who may have TB.

TB transmission can occur in utero, intrapartum and postpartum. In addition, HIV transmission to the infant is more likely when mothers have active TB.

So a number of studies are evaluating the safety and efficacy of providing IPT during pregnancy and post-partum. While IPT should be safe to the foetus, in breast milk and to children generally, there are concerns about its liver toxicity in the mother, especially when there are underlying risk factors such as age, pre-existing liver disease including hepatitis B, or when IPT is being combined with ART.

These studies include TB APPRISE - IMPAACT P1078, a multicountry study in India and African sites (comparing IPT to active case-finding alone in 1600 women), and the TB/PMTCT Study in Soweto. The CDC-BOTUSA study of IPT in Botswana is also following outcomes in infants born to mothers participating in the study, as well as assessing how best to implement TB screening and IPT in PMTCT clinics.

Other related research questions include how best to screen for latent and active TB in pregnant women in TB/HIV endemic areas. For instance, what is the role for chest x-ray, which is often avoided for fear of irradiating the foetus? Also, what are the safety, tolerability, and pharmacokinetics of the new and second-line TB drugs in pregnant and lactating women, including their interactions with antiretroviral drugs?

Treatment in children

Children metabolise drugs differently than adults, but there are only limited pharmacokinetic data to guide dosing of TB drugs in children. There is also evidence that severe malnutrition can affect metabolism, and that metabolism may vary greatly across different populations. Data from Professor Donald of Stellenbosch University suggest that doses currently being used may be sub-optimal. Studies are needed to find the proper dosing in regimens, and possibly shorten the time needed for treatment.

Dr Philippa Musoke from Makerere University Uganda reminded participants that treatment choices in children with HIV coinfecting with TB are even more difficult. What is the optimal regimen in different age groups? If using nevirapine, how should it be dosed? As noted above, doubling the dose of *Kaletra* doesn't work in children taking rifampicin, so the best regimen for a child who needs a protease inhibitor is unclear and needs further study. Strategies are needed to deal with these interactions. Studies are needed to investigate whether newer antiretrovirals might be an option. Likewise, studies need to evaluate whether rifabutin might be a suitable alternative to rifampicin in children with TB on ART.

Also, when is the best time to start ART in a child on TB treatment? These studies have not been performed in children.

Vaccines

While the BCG vaccine doesn't prevent TB in adults, it does seem to protect young children against disseminated and neurological forms of the disease — and therefore BCG is part of most national programmes and is given at birth. However, in children with HIV, it has been associated with high rates of BCG IRIS in about 0-15% and disseminated BCG disease in about 1%, but this has very high case fatality rates. WHO has recommended that BCG not be given to children who are known to be HIV-positive, regardless of symptoms, but how can this be put into practice when the vaccine is given at birth?

So researchers are looking at alternative strategies. According to Jerald Saddof from Aeras Global TB Vaccine Foundation, one might be a prime-boost vaccine regimen where the infant is primed with a recombinant BCG vaccine containing specific antigens, and then weeks later given a booster with either a protein/adjuvant or a non-replicating viral vector. These recombinant BCG organisms over-express proteins most likely to induce a strong immune response to mTB, and so appear to be quite potent at relatively low doses. Some of the recombinant BCGs (though not all) do not appear to cause disease in animal models — and so may be safer in children with HIV. The booster vaccines should also be safe in children.

There are quite a few of these vaccines in the pipeline (see [WHO's initiative for vaccine research](#)), including some that have moved into randomised phase II and IIB efficacy studies.

Vaccine Efficacy Trials
<p>MVA85A/AERAS-485 First efficacy trial of a new TB vaccine in infants in more than 80 years (proof of principle) 2,800 infants – 90% power for 60% efficacy compared to BCG</p> <p>AERAS-402/Crucell Ad35 Planned multicentre study including SATVI (South Africa), Makerere University (Uganda), KEMRI/CDC (Kenya), Manhica Health Research Centre (Mozambique)</p> <p>GSK M72 to be tested late 2010</p> <p>AERAS-rBCG to be tested in infant Phase III non-inferiority trial vs. BCG in 2011</p>

Of course, the safety and efficacy of these approaches needs to be demonstrated in people with HIV. This will first be done in adults with HIV, with two studies currently planned: the AERAS-402/Crucell Ad35 study starting this year in South Africa and other sites for safety and efficacy, and the MVA85A/AERAS-485 in people with HIV in 2010.

The hope is that a new and better vaccine for children, both with and without HIV, will be available in the next five to ten years.

TB drug resistance in people living with HIV

“MDR/XDR-TB and HIV are converging on an increasing scale and posing huge challenges; but there is a great paucity of evidence in the understanding and magnitude of this convergence,” said Dr Getahun during the satellite session.

“Research results to address and ease the bottlenecks — either involving patients or healthcare delivery systems — for the diagnosis and treatment of MDR/XDR-TB, among people living with HIV, are a priority and crucially needed.”

Multidrug resistant TB (MDR-TB) is TB that is resistant to at least isoniazid and rifampicin, while extensively drug resistant TB (XDR-TB) is MDR-TB that is also resistant to the fluoroquinolones and at least one of the three injectable second-line drugs (amikacin, kanamycin and capreomycin).

The burden of drug-resistant TB

The most recent data suggest that the global burden of MDR-TB was around 510,000 with 150,000 deaths in 2007; while there were an estimated 50,000 XDR-TB cases leading to approximately 30,000 deaths. Dr Paul Nunn of WHO's STOP TB Department underscored the fact that we do not know how many of the M/XDR-TB cases are in people with HIV, and participants at the research meeting felt that this was unacceptable.

“I don't want to see TB statistics without HIV information,” said Dr Ken Castro of the US Centers for Disease Control.

Data from country surveys suggest that the greatest burden of TB drug resistance is in the countries of the former Soviet Union, China and a handful of other countries, but there were few survey and surveillance data from sub-Saharan African countries. Meanwhile, by April 2009, fifty-five countries worldwide had reported at least one case of XDR-TB. Most sub-Saharan African countries reported no cases, but this may be because there are no laboratories in Africa, other than the supranational laboratory in South Africa, that are able to do second-line drug susceptibility testing. According to Dr Getahun, this raises the question of whether there are any other possible clinical indicators or clinical parameters that could help assess the magnitude of XDR-TB in the absence of surveillance data. Also, what is the best way to strengthening the laboratory capacity to perform drug susceptibility testing for second-line TB drugs?

Data are also needed to better understand the mortality associated with MDR and XDR-TB. Early data from the Tugela Ferry outbreak in South Africa suggested rates of mortality above 85% and a very short median survival time (29 days) in people with HIV and XDR-TB. The same researchers concluded that survival with MDR was similar, with a median survival of around two months. But more data are needed on the pattern of mortality in people without HIV. Developing a clearer understanding of the dynamics and reasons for the high rate of mortality will be an important matter for research.

Diagnosis

Some of the excess mortality could be due to delayed diagnosis, because the existing ways to diagnose drug-resistant TB take time, space, and are labour-intensive. Liquid culture and DST may speed diagnosis in the few settings that can do it.

Some countries are also attempting to roll out line probe assays (LPA), a PCR-based technique that can reduce the turnaround time for detecting MDR-TB to two to four days.

These technologies are best suited for large referral laboratories – and the operational usefulness will depend upon getting healthcare staff to routinely send specimens in for testing and follow-up on the results.

However, according to Dr Giorgio Roscignio, the CEO of the Foundation for Innovative and New Diagnostics (FIND), the goal is to develop diagnostic tests that can be progressively rolled out to more decentralised levels of care.

After LPA, the next stage will be an automated desktop system, Cepheid's Xpert MTB integrated nucleic acid amplification test, which can be used in district hospitals or microscopy centres (with electricity). It uses a common platform to diagnose TB and rifampicin resistance (which would probably indicate MDR-TB); TB that is resistant to fluoroquinolones (which could flag potential XDR-TB); and could potentially perform HIV viral load tests. Results are provided in less than 2 hours, and since it is a closed system there is no risk of contamination or need for a safety cabinet.

Dr Roscignio shared exciting results from using this platform in at least five sites (including two sites in South Africa with high HIV prevalence and two sites with high MDR prevalence) with over 1500 TB suspects, in which they found greater than 90% sensitivity (95% confidence interval 84.9 – 93.8) in smear-negative/culture-positive cases and even higher sensitivity in smear-positive/culture-positive cases. Specificity was 98.1% (95% CI 96.6-98.9). In other words, the test could also dramatically increase the diagnosis of smear-negative TB. In addition, sensitivity and specificity for rifampicin resistance were also above 90% in both smear-negative and smear-positive cases. However, one drawback is that, so far, the machine only uses sputum and hence will miss cases from people with extrapulmonary TB and children who do not produce sputum.

Further demonstration projects of the Xpert system are ongoing at microscopy centres and district hospitals in seven countries, and FIND expects to submit the findings to the WHO in 2010. Development of the platform for XDR-TB will take longer (probably until 2013), although an adaptation of LPA that will screen for XDR-TB may become available sooner.

In the meantime, what are the best diagnostic algorithms to diagnose MDR/XDR-TB in people living with HIV? In addition, do we have the best case finding/screening model for MDR/XDR-TB among people living with HIV?

Treatment

The number of people with drug-resistant TB who actually receive appropriate treatment is shockingly low: only 30,000, or about 6% of the nearly 510,000 estimated MDR-TB cases in 2007. Clearly there are treatment issues that need to be researched. One is, where is the best place to treat these individuals, in the hospitals or in the community? What are the barriers for patients accessing not only second-line TB drugs but also ART and newly developed drugs?

A case in point was [a recent study of the new TB drug TMC207](#), which included 47 cases, only six of whom were HIV-positive. The key barrier to enrolling more people with HIV was the lack of data on potential drug interactions with antiretroviral drugs. But such barriers must be addressed as soon as possible, because it is essential to know the safety and effectiveness of such second-line TB drugs in people taking ART.

According to Dr Neel Ghandi, treatment of MDR-TB should be thought of in a different paradigm than the centralised treatment programmes that currently exist. Care should be decentralised to provide shorter times to referral and treatment initiation. In addition, antiretroviral therapy should be integrated into MDR and

XDR-TB treatment programmes; it needs to be as much a part of their treatment as their second-line TB drugs, because these two diseases are working together to compromise the health of these patients.

Transmission and prevention

There is substantial evidence, particularly from the outbreak in Tugela Ferry, of nosocomial transmission of XDR-TB, including subjects who have been infected by multiple strains. However, Dr Paul van Helden of the Centre of Excellence for Biomedical Tuberculosis (TB) Research in South Africa, and Stellenbosch University presented data at the research meeting suggesting that most XDR-TB is actually being generated in people who have MDR-TB.

Notably, during the course of moving from susceptible TB to MDR-TB to XDR-TB, the percentage of cases acquired through transmission reduces as the disease progresses (thus acquired XDR-TB may be less infectious than contracted XDR-TB). Thus, prevention research needs to look both at how to reduce the generation of drug resistance and its transmission.

Research questions include: How and where are MDR and XDR being created? Does poor drug quality play a role? There are some signs of this in Eastern Europe, and there is currently a multi-country study trying to identify the reasons for poor drug quality. What is the contribution and nature of healthcare delivery failures or problems on the part of the patient?

Are there any preventive treatments, like IPT, that could be used to treat someone who has been exposed to XDR or MDR-TB? What are the best methods of separating infectious cases from susceptible contacts? How much impact do different infection control measures have? Do surgical masks on patients work? Do respirators really protect staff and visitors? What indicators do we use to monitor their effectiveness?

Human costs of neglecting TB research

With all the figures, and all the data, it is easy to forget the real purpose of TB research - getting the answers that will make a difference in the lives of people with HIV. But Dr Getahun concluded his report during the satellite session by reminding the audience that there are human costs attached to not prioritising TB/HIV research.

"Thembi Ngubane died a couple of weeks ago," he said. "She was a person living with HIV who served as a reporter for [a radio programme](#), documenting her diaries of living with HIV to teach others about HIV based on her personal experience. She inspired millions of young people and met both former President Clinton and President Obama. Thembi was serving as a UNICEF ambassador and she had a young child. But despite living with HIV for several years on ART, she died in a hospital, of MDR-TB."

Just 24 years old, the loss of Thembi is yet another example of how tuberculosis (TB), especially drug-resistant TB, can steal away even champions in the fight against HIV, and cheat HIV prevention and treatment services of their hard-fought gains. These things should not have been allowed to happen.

Of course, there is a lot that can be done to put what we know in practice and the implementation of a number of relatively simple interventions could significantly improve outcomes of people with or at risk of TB/HIV. But sometimes these interventions are only partial solutions and stop-gap measures. Even for the best-operating programmes, it can be difficult to prevent, diagnose and treat TB/HIV cases in time using tools and technologies that are decades, if not more than a century old, and that were never meant to be

used in such difficult clinical settings in people with a coinfection such as HIV that changes all the rules.

The time has come for research that will transform the field, even if for some, that time has come too late.

about HATIP

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The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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