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TB, HIV, mothers and children: time for action

By Theo Smart

This edition of HATIP was kindly supported by the STOP TB department of the World Health Organization. This is the first of a two-part edition: the second half of this World TB Day special edition will examine TB case finding, diagnosis and preventive therapy in children.

TB in pregnant women and children

This year's World TB Day edition of HATIP focusses on the needs of pregnant women and children with TB – and the need for greater integration of TB/HIV activities into maternal and child health services.

There is remarkably little information about the impact of TB in either women with HIV or in children, and in the wider tuberculosis field a narrow focus on `TB control` has led to a neglect of the disease's impact on pregnant women and children. For instance, one reason why children have not been prioritised by TB programmes is because children with TB aren't viewed as highly infectious, and so are not a priority for case-finding or treatment. Also, said Dr Mario Raviglione, head of the STOP TB Department of WHO at the opening of the STOP TB Symposium, a pre-meeting of the Union World Conference on Lung Health, held last October in Lille France, "childhood TB was often mistakenly perceived as a mild disease. But contrary to that perception we know that there are severe forms of TB that is often fatal, such as meningitis and miliary forms of TB."

Similarly the high incidence of TB in pregnant women has not been recognised as an opportunity for greater TB casefinding efforts in antenatal clinics – or as a reason for greater vigilance for TB in infants.

Over the last few years, however, the TB community has begun to wake up to the needs of vulnerable populations — including women and children. Consequently, the theme of the 2011 STOP TB symposium was "meeting the unmet needs of women and children for TB prevention, diagnosis and care: expanding our horizons.

"Although the exact magnitude of tuberculosis (TB) among women and children is not known, the evidence is growing that they are disproportionately affected," said Dr Raviglione. Why the STOP TB Department is unsure of the scale of the problem is described below; nevertheless, WHO has begun tallying up with the available research does show, and the estimates are frightening.

- Over half a million women and at least 64,000 children die of TB each year (the real tally in children is difficult to say)
- TB is common among pregnant women, and has been reported in up to 11% of pregnant women living with HIV in high burden settings
- TB causes 6%–10% of all maternal mortality, up to 15% in high prevalence settings, and 15%–34% of indirect obstetric maternal mortality
- There is an increased risk of transmitting TB and HIV to infants born to mothers with TB/HIV coinfection
- TB has resulted in nearly 10 million cumulative orphans due to parental deaths

But while it is good that TB experts are turning their focus to the issue, to effectively reach women and children, TB services will have to be provided by those parts of the health system that they are likely to access.

"It's time for the TB community to reach out most forcefully to all those working on issues such as women and children's health," said Dr Raviglione. "I bet they don't realise it. Because when we start talking about the number of deaths in women and children, people — those who take care of women and children, in their own professional community — don't know about it.

Accordingly the 2011 STOP TB symposium explored whether TB diagnosis, prevention and treatment could be mainstreamed into maternal and child health services, programmes to prevent vertical transmission, and family planning services. Where should services be integrated and how can referrals be made effectively when services can't be integrated? What is the best route forward to improve prevention, diagnosis and treatment of TB among women and children?

TB programmes will need to examine the technical support that is necessary to respond to the specific needs of women and children affected by TB in their country. But this will not be a conversation if it just goes in one direction — programmes need to listen to the people who are currently working with women and children to learn what barriers, challenges and solutions there might be to increasing integration of TB management into their services. "Invite the *unusualsuspects* to the forum where policy decisions are made," said Stacie Stender, a nurse implementer working with JHPIEGO said later at the symposium. "TB case finding does not start with the national TB programme."

This HATIP summarises the presentations of the STOP TB symposium including innovative approaches to tackling the issue in different parts of the work. In addition, we describe some related reports at meetings over the past year. Finally, this edition reports on key recommendations from WHO's Stop TB Department that released this week to coincide with World TB Day. We hope to continue the discussion on the HATIP blog, and to compile a collection of tools and educational materials targeting the community, midwives and other healthcare workers working in MCH.

The 2011 Global TB Control Report: Progress at least, but uncertainty regarding women and children

Dr Katherine Floyd of WHO's STOP TB Department gave an overview of the current status of global TB control, implementation of TB/HIV activities and progress towards 2015 Millennium Development Goal (MDG) targets, before reporting on what global notification and survey data can and cannot tell us about the burden of disease among women and children.

Dr Floyd stressed that major improvements in TB surveillance data collection and reporting have made estimates in this report more reliable than in the past. Better data partly explain the bigger story, which has already been widely reported, that there have been significant reductions in global TB incidence, prevalence and related mortality over the last few years. For instance, the absolute number of TB cases has been falling since 2006 (rather than rising slowly as indicated by previous global reports).

"This is the first time that we've published estimates that suggest that the absolute number of TB cases is falling globally," said Dr Floyd. TB incidence rates have been falling since 2002 (two years earlier than previously suggested); likewise estimates of the number of deaths from TB each year have been revised downwards,

and have fallen, from a peak of 1.8 million per year in 2003, to 1.4 million in 2010.

The world is on track to reaching the MDGs (with the exception of halving TB prevalence rates by 2015 compared with 1990, which the HIV epidemic made unlikely. However, the recent Global Report also noted improved scale-up of TB-HIV activities such as HIV testing of TB cases, cotrimoxazole preventive therapy and ART, but higher rates are possible, and "more needs to be done to reach the Global plan targets for 2015," she said.

However, there are problems reliably estimating the burden of TB disease among women, because about 30% of countries are not disaggregating cases by sex. Both case notification and survey suggest a lower prevalence of TB among women, but there is significant variation by region – with a higher percentage of cases among women in Africa and the Eastern Mediterranean Region.

Similarly, in children, many countries are not disaggregating cases by age. On the basis of the available data, it is estimated that at least 6% of global notifications are among children.

"But what we also know is that not only are we not picking up all of the cases in children from the routinely reported notification data but probably the notification data don't actually capture a lot of those cases because of under-reporting. For example, because there aren't good links between national TB programmes and paediatricians, or other reasons," said Dr Floyd.

Using the available data, the figures show that there is a very substantial burden among women and children.

- There were an estimated 3.2 million (range 3.0 to 3.5 million) new cases among women in 2010
- Approximately 10% of cases occur in children
- There were an estimated 320,000 deaths among HIV-negative women in 2010 and ~500,000 deaths among women including HIV-associated TB.

In order to better assess the burden of TB in women and children, Dr Floyd said, "what we really need is to have notification data disaggregated by age, sex from all countries that would be facilitated by having case or patient-based electronic recording and reporting systems. Prevalence surveys in Africa will also be important for telling us more about the share of cases that are recurring in women in that part of the world. Finally, studies need to quantify the under-reporting of cases among children and use that data as a basis for introducing interventions that will enable better reporting of TB among children" (to reduce under-reporting (and over-diagnosis).

During the discussion, Dr Floyd emphasised the importance of having good surveillance data on TB in children. "There are a lot of countries that aren't reporting any information about TB in children at the moment," she said. It is recommended that childhood cases be reported in two age categories, zero to 4, and 5 to 14. "If we had the data from all countries, we would certainly know a lot more about the real burden and would also know a lot more about what is driving TB epidemics. If there are high rates among young children then it obviously shows that there is more transmission. So surveillance data on TB in children are very important."

Decreasing TB mortality by integrating TB/HIV services into maternal and child health platforms

"The question has to be asked, are we doing enough for pregnant mothers and their babies to prevent, diagnose and treat their TB?" said Dr Robert Gie of the Desmond Tutu TB Centre and Stellenbosch University.

In his presentation, Dr Gie focussed upon the links between TB in mothers and TB and other poor health outcomes their young children — especially in the context of HIV. He proposed that relatively simple TB interventions, such as the Three Is for HIV/TB, delivered within the context of maternal and child health services could both improve maternal mortality and reduce TB transmission and related mortality in the infants.

He described a few cases of children with severe and mysterious illnesses that he had recently seen in the wards. In each case, the child's illness had been investigated extensively by his staff — only to later discover their mothers were also ill. "All these very expensive tests were completely unnecessary, after speaking to the mother, because here was the mother's chest x-ray with smear-positive TB."

Similarly, there was a cluster of cases among infants in a kangaroo care setting, where one mother proved to be the source case not only for TB in her infant, but for several cases of severe TB in other exposed children at the site.

Cases like this were inevitable if one considers how and when HIV and TB, a dangerous combination at any time, tend to join forces during one of the most vulnerable period of a woman's life. In high TB burden countries such as South Africa, over the course of a childhood, a growing proportion of young women are exposed and latently infected with TB. Then, as many young woman start to become sexually active and look for a partner, HIV slips in and begins to undermine the immune defences. Over time, the virus releases TB from the granulomas (scar tissue) where the immune system may have held mycobacteria captive indefinitely, and as the mycobacteria begin to grow and spread in the young woman's body, she goes about her life unaware that she is infected until she becomes pregnant.

In the high prevalence countries of Southern Africa TB case notification rates are highest in women of childbearing age

Consequently, in the high prevalence countries of Southern Africa, TB case notification rates are highest in women of childbearing age. In fact, although globally, prevalence rates among women in surveys are lower than in men, in southern Africa (the region with the highest global HIV prevalence), women aged 15-24 have rates of TB 1.5 – 2-fold higher than men of the same age, and the pattern is consistent across each of the countries in the region.[1]

What's more, as Dr Amita Gupta, of Johns Hopkins University pointed out, TB in these women often has an untypical presentation. For example, being female is an independent risk factor for developing extrapulmonary TB. In a US cohort including more than 250,000 cases, only 18.7% were EPTB cases. But compared to pulmonary TB, EPTB was significantly associated with female sex (odds ratio 1.7; 95% Confidence Interval (CI) 1.7-1.8).[2] In resource-constrained settings especially, EPTB can be much harder to recognise as TB and diagnose.

TB/HIV coinfection can complicate pregnancy considerably. In one cohort of women for example, pulmonary tuberculosis was one of the major causes of maternal mortality – after stage IV HIV disease, pneumonia and sepsis.3 Dr Gupta noted that a study in Durban, South Africa, had found that TB and HIV are both independent risk factors for morbidity and mortality — but there was a 3.2-fold higher risk of death in coinfected women than in women with TB alone.[4] "Maternal TB can have negative consequences for both the mom including increased antenatal hospitalisation,

adverse pregnancy outcomes (such as postpartum haemorrhage), and negative infant outcomes such as increased prematurity, IUGR, low birth weight and mortality," said Dr Gupta. [5, 6]

Additionally, not only HIV but TB too can be transmitted from mother to child in utero, intrapartum and postpartum. For instance, in one study in Durban involving 107 mother-infant pairs where the mother had TB, 15% of neonates sampled in the first three weeks of life had TB bacilli.[7] Some small studies suggest that women living with HIV who are coinfected with TB may also have an increased risk of in-utero HIV transmission. One study of women with HIV infection and confirmed TB found an in-utero infant infection rate of 19% among the neonates of 42 HIV/TB pregnant women compared to 5–10% among women with HIV alone.[8]

Dr Gupta then examined the association between maternal TB and several other characteristics, with mother-to-child HIV transmission in a larger study of 783 HIV-infected young women (median age 23) in India, 33 of whom had either prevalent or incident cases of TB diagnosed during a median follow-up of 365 days.[9] The characteristic most strongly associated with vertical transmission was having a high viral load (> 5 log/ml), with an adjusted odds ratio of 10.8 (95% CI 4.25-27.70); however maternal TB was also significantly associated with HIV transmission, with an adjusted odds ratio of 2.51 (95% CI 1.05, 6.02), as was a having CD4 cell count below 250 and practicing an extended period of breastfeeding (more than four months). Although the association between maternal TB and vertical HIV transmission lay close to borderline significance, and some of the women with TB may also have had low CD4 cell counts and higher viral loads [check] than those without TB, "nevertheless, when a mom develops TB, we should also be thinking about the possible risk of increased HIV transmission," said Dr Gupta.

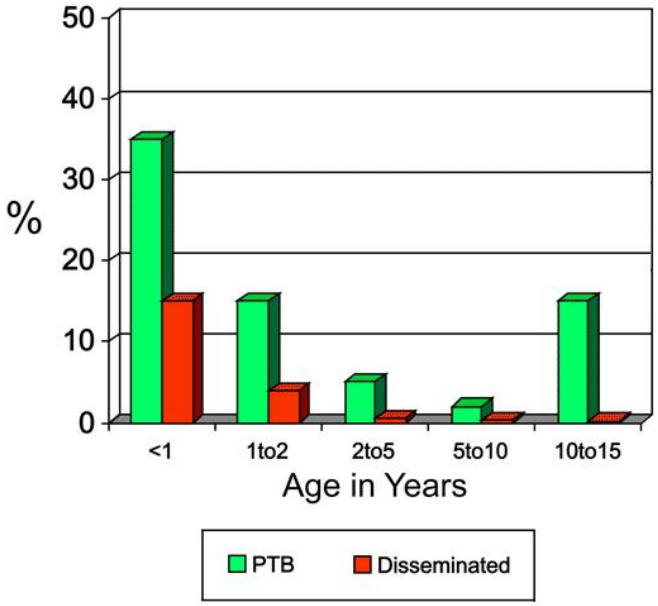
"When a mom develops TB, we should also be thinking about the possible risk of increased HIV transmission"

Studies have also shown that when a mother has TB, there is a dramatically increased risk of death in the child, not only from TB but from other illnesses too. In an earlier study in Pune, India, comprising a cohort of 715 women living with HIV, Dr Gupta found that TB increased the risk of postpartum mortality in HIV positive women by 2.2-fold (p=0.006) from a mortality incidence of 0.4/100 patient years up to 0.9/100 patient years, while the probability of infant death increased by 3.4-fold (p=0.02) from 2.5/100 patient year to 8.5 deaths per 100/patient year when the mother had TB.[10]

In other words, Dr Gupta said, "a sick mom equals a sick child."

Some of this sickness is due to TB contracted from the mother, as Dr Simon Schaaf found when looking at hospital records, 36% of culture-proven TB cases in children could be matched to signs of TB in their maternal caregivers — especially amongst the youngest children.[11] [Note other studies have reported both high rates of undiagnosed TB among child contacts of people with tuberculosis, although, some of these have also reported that the child's TB was from an unrelated strain: see box]. Notably, when Dr Mark Cotton of Tygerberg Hospital was screening for TB exposure in infants for an IPT study, 10% of them had already been exposed to TB cases by just three months of age.[12]

This is particularly frightening when one considers the risk these children have of developing active TB —infants less than one year of age who are latently infected by tuberculosis, have about a 35% chance of developing pulmonary tuberculosis, and about a 15% chance of developing disseminated tuberculosis in the first year of life according to Marais et al (see chart).[13]



Again, HIV amplifies these effects — another study estimated the incidence of culture-confirmed tuberculosis in HIV-infected infants less than a year old to be 24-fold higher than in uninfected infants.[14] A follow-up study using the same data set reported that 32% of infants less than a year old with culture confirmed tuberculosis and HIV-coinfection died within the first year of life either of TB or as a result of a secondary complicating condition.[15] Notably, in a study in Guinea-Bissau, the relative risk of mortality from any cause amongst 52 HIV-infected infants was 8 fold higher for those whose mothers had active tuberculosis than for those whose mothers did not.[16]

These data clearly illustrate the need to concentrate on mothers and pregnant women, according to Dr Gie.

He cited studies suggesting that integration of TB services such as intensified case finding (TB screening) into programmes to prevent vertical transmission "is feasible and a very simple and potentially very vital addition to maternal and child health," said Dr Gie.[17,18]

"There are very simple interventions that we can do to screen for tuberculosis amongst mothers into maternal and child healthcare. If we're successful in this, the tuberculosis programme will contribute tremendously to the Millennium Development Goals 4, 5 and 6: We would reduce the mortality in children, by diagnosing tuberculosis in their mothers and preventing disease in their children; decrease the maternal mortality rates by getting the TB diagnosed in the mothers; and contribute to a reduction in the number of people dying from tuberculosis, worldwide."

Some of these studies are described in the following section — though it isn't clear whether all the TB screening approaches are equally 'simple.'

As data now show that early coadministration of antiretroviral therapy and TB treatment generally improves outcomes in people living with HIV on TB treatment, integrated TB/HIV services implemented by MCH services could further reduce maternal and under-five mortality.

While sharing Dr Gies' conviction that TB and TB/HIV have an important impact upon maternal and child health mortality, and need to be addressed, the next two presentations addressed some of the technical challenges, barriers and noted where there are knowledge gaps that could complicate integration of TB/HIV services into programmes targetting women during pregnancy, childbirth and breastfeeding.

A closer look at diagnosis and treatment of TB and latent TB in HIV-positive women

"The antenatal and prevention of mother-to-child transmission programmes, which have really been the focus for a lot of the HIV planning for women, are a key entry point for healthcare for women in general and represent an opportunity to detect active and latent tuberculosis, and to educate women about TB, particularly if they are HIV-infected because they really are the greatest risk," said Dr Gupta.

She also noted that research has shown women tend to have less TB literacy compared to their male counterparts.

Indeed, a large national survey documented low awareness of TB among women in Nigeria. As many as 28.9% of the women in a survey said that they had never even heard of TB (compared to 11.6% who were unaware of HIV). Looking over the demographic data, implementers puzzled about how to reach these poor young rural women with little education — the original plan had been to integrate a TB/HIV literacy component into family planning services.

However, these particular women did not commonly use those services. On the other hand roughly 30-40% of them had accessed antenatal care — suggesting that that would be the most logical place to focus their TB/HIV efforts and reach this underserved population.[19]

Screening

There have already been several studies introducing TB screening into antenatal clinics but they used somewhat different screening approaches. Most have relied on symptom screens, but others added or substituted tuberculin skin tests (TSTs) and some added chest x-rays to identify TB suspects for further diagnostic work-up. However, the role of shielded chest X-rays and tuberculin skin testing in this population continues to be debated (and indeed continued to be debated later in the symposium and conference (see below).[20]

In 2006, a programme in Soweto, South Africa integrated TB screening into the post HIV test/counselling session at the antenatal clinic.[21] A nurse/lay counsellor was given a 7-minute symptom screen to administer to the patients that looked specifically for cough greater than 2 weeks as well as other signs and symptoms of TB. Symptomatic women were then referred for further investigation. They screened 370 women and identified TB symptoms in 120 (32%). Ultimately, eight women (2.2% of overall group, 7% of symptomatic group) were diagnosed with active TB –each one was smear-negative.

Earlier in 2003, Nachega el al performed TB screening specifically during the post-natal follow-up period in women living with HIV and their male partners by performing tuberculin skin tests (TST) to identify those who had been exposed to TB.[22] Participants were to return two or three days later to have their reaction read. A positive result was defined as an induration (bump) over >5mm, and these were sent for a complete diagnostic work up.

But there were problems with this strategy. Out of 438 HIV-positive patients given a TST, 120 (27.4%) did not return for results. A little under half (157) of subjects who returned for TST reading were TST-positive, but only about 120 of these came back for the full diagnostic work-up (a loss of another 24%. Out of the 120 with an evaluable diagnostic work-up, 13, or 11% had active TB (as they were TST-positive, the remaining 107 had latent TB infection (LTBi) — and thus were candidates for isoniazid preventive therapy (IPT).

In addition to the loss to follow-up there are a couple of other downsides to using TSTs as a screen. Tuberculin supplies require cold chain management, which makes it difficult to implement in remote lower resourced settings. In addition, people living with HIV are often anergic (fail to have a immune reaction on the TST) but that doesn't mean that they are not latently infected and therefore at risk of developing active tuberculosis.

On the other hand, TSTs do identify those most likely to benefit from IPT — which may be a useful piece of treatment information for a person living with HIV in a high TB burden setting, who is faced with the decision of whether to take continuous IPT to prevent TB due to reinfection(see below). It might also conserve laboratory capacity by reducing the number of specimens sent to the lab — especially with such appalling losses during referral.

Nevertheless, a case detection rate of 11% is exceptionally high, and if a way were found to retain patients in care (perhaps by having a community healthcare worker make home visits to read the TST), including access to TST in maternal-child health services might prove useful.

Indeed, in India, Dr Gupta performed a study that found a 1.4% prevalence of active TB among women screened around the time of delivery in India, using either the WHO symptom screen or TST.[23]

Grounder et al reported on a study in Soweto in which she and her colleagues implemented TB symptom screening at six antenatal and prevention of parent-to-child transmission clinics, with the specific objective of getting as much of the diagnostic process done during the patient's very first antenatal visit — in a valiant effort to minimise the opportunities for the patients to be lost to referral during the process. So the TB symptom screen was actually performed during the HIV pre-test counselling session, and if the symptom screen was positive, a sputum specimen was taken on the spot for smear, culture, and drug sensitivity testing.

Including all the women, irrespective of HIV-status – they found that 23% of the HIV-positive women had a positive symptom screen, compared to 14% of the HIV negative women; and after the diagnostic workup they identified 15 active TB cases out of a total of 3963 women, of whom 37% were HIV-positive. Ten active TB cases were identified out of 1454 HIV positive women (0.6%; 688/100,000 persons/years) and five active TB cases were found among 2483 HIV-negative women (0.2%; 201/100,000 persons).[24]

WHO's 4-symptom screen

Most of these studies used symptom screens that are now considered old and out-dated since the introduction of the WHO 4 symptom screen to rule out TB. Based on a meta-analysis including data on over 8,148 people living with HIV, Getahun et al identified four symptoms: any current cough, fever, night sweats or weight loss which were only somewhat sensitive for TB (78%) and poorly specific (50%) for TB, but the negative predictive value (NPV) was quite high at 98% in a context of 5% TB prevalence among people living with HIV (though the NPV falls to 90% if there is a 20% TB prevalence).[25]

In other words, it isn't a very precise test for identifying TB cases, but a patient who does not have any of the four symptoms is highly

unlikely to have active TB, and could be given IPT without having to worry about undertreating an active case of TB.

Of course, a few cases could slip through anyway, so WHO recommends that the symptom screen be performed any time a person living with HIV has any interaction with the health system, *especially* if they are on IPT and come back to the clinic to collect the next month's supply of medicine. This reduces even further the likelihood that any breakthrough active TB cases will undergo prolonged monotherapy — and TB cases that are detected while on IPT, still respond well to standard treatment that includes isoniazid (unless it is a case of transmitted drug resistance.

The symptom screen isn't for everyone however. While the meta-analysis included large numbers of women, it did not include small children. WHO does not recommend its use for TB screening in children, in whom symptoms and the natural history of the disease can be very different.

But what about pregnant women? Getahun et al make no reference to them in their paper, and just like children, one cannot simply assume that a meta-analysis based a general population can apply to a specific and different population.

Fortuitously, Dr Gupta decided to evaluate the WHO symptom screen retrospectively in their Indian cohort of 841 HIV-positive women around the time of delivery (they had previously performed symptom screening and TST screening at delivery, and women received a diagnostic workup if either was positive. as part of their early symptom screening).

"We found similar findings to the meta-analysis in non-pregnant populations [a negative predictive value of 99.3%] … no symptoms for this population means that it's going to be quite reasonable to consider IPT," said Dr Gupta.

The negative predictive value was slightly lower, 97.8% in women with CD4 cell counts below 350. (Notably, the inclusion of TST in this study increased the negative predictive value to 100% regardless of CD4 cell count).

GeneXpert

Dr Gupta believes the GeneXpert assay could be a "game-changer" given its high sensitivity in both HIV-positive and HIV-negative individuals, in smear-positive and smear negative case, and its potential to significantly decrease in median time to case detection.

Dr Gupta described a paper that had been recently published that proposes integrating GeneXpert into antenatal clinics — as a point-of-care test, "where a woman who would be coming in for antenatal care would get educated about HIV and TB and then get registered with the symptom screen. If she's symptom positive, she would then give a sputum sample for the GeneXpert, and carry on based on the results of that test. Certainly these kinds of models need to be tested – particularly in terms of cost-effectiveness. Whether such a model would really prove to be feasible in such a setting remains to be answered."

"I also believe that GeneXpert is fabulous, but its not feasible to roll out at the level of where the antenatal clinic is, and it never will be. Particularly if you look at the economic barriers, you have to diagnose many many cases to make it cost-effective," said Stacie Stender of JHIPIEGO, who gave the next presention.

Indeed, GeneXpert is something like the iPAD of the TB diagnostics world — everyone would like to have one on their desk. While HATIP does believe GeneXpert to be a significant technological advance, an upcoming issue will more closely investigate operational issues related to its implementation and its likely clinical impact.

Latent TB, diagnosis and treatment

Dr Gupta next turned her attention to screening for latent TB infection to identify those at highest risk of reactivation disease who are most likely to benefit from IPT or other preventive treatments. However, the challenges of implementing TST (the return visit to read it, operator dependency and a degree of cross reactivity and false positivity) have held this strategy back, which is something of a shame since it is inexpensive and low-tech.

Alternatives such as the interferon gamma release assays (IGRA) initially created a bit of excitement because they don't require a return visit, nor do they cross-react with the BCG vaccine (which complicated the interpretation of TSTs in children). But they are expensive, require a fresh blood sample and there are issues around cut-offs interpretation and reproducibility. Another issue is that TSTs and IGRAs are often in disagreement, and they appear to be measuring somewhat different things. For instance, IGRAs could potentially be detecting an immune response that has developed in someone exposed to TB, but who did not become latently infected, and who may not be at risk of active disease.

"We're not really quite sure what that means, and how to interpret that," said Dr Gupta.

IPT and other preventive treatment

The WHO ICF/IPT guidance recommends offering at least six months of IPT in any adolescent or adult living with HIV who screens negative on the WHO Symptom Screen, including, now, pregnant women. Dr Gupta had some reservations about how widespread the implementation of IPT should be, given that the prevalence of latent TB varies significantly from place to place.

Clearly in a population where at least 25-30% are known to be latently infected, we're likely to see a benefit of wide implementation of IPT. But in other settings where there may be a low burden of latent tuberculosis, there may be less benefit.

Tanzania	30% where antenatal HIV prevalence 5%	Sheriff BMC Infect Dis 2010
South Africa	49%	Nachega AIDS 2003
India	20% where antental HIV prevalence 2 – 3%	Gupta CID 2007
United States	11% in HIV-positive women	Mofenson Arch Int Med 1995

But while it is helpful to have the WHO recommendation to implement IPT in pregnant women — which could be particularly beneficial for TST-positive women, Dr Gupta believes that a pregnant woman has a number of things to consider when thinking about TB preventive options.

"When we think about maternal health, ART, administered to women during pregnancy and beyond, clearly has a huge impact on reducing TB incidence. But we need to understand some of the side-effects that potentially can occur when we coadminister ART with IPT, and with cotrimoxazole — and if a woman is hepatitis B surface Antigen positive (HBsAg+)— there may be issues about safety to consider," she said.

Many healthcare providers have raised concerns about hepatotoxicity as one of the reasons not to necessarily implement IPT across the board in pregnant women.

"We know that hepatotoxicity is increased during the state of pregnancy, by itself. Certainly some of the antiretrovirals are

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associated with hepatotoxicity. And there are old data from the pre-HIV, pre-HAART era suggesting that INH, at least during pregnancy, caused some hepatotoxicity," said Dr Gupta.

In fact, because of the concerns related to using IPT in pregnant women, pregnancy has been an exclusion criteria for all IPT trials to date. But Dr Gupta feels evidence on IPT during pregnancy is needed to convince providers and programmes.

So the NIH-funded IMPAACT trials network will be conducting a randomised trial, the TB Apprise trial (IMPAACT P1078) looking at the safety and timing of IPT — should it be given early in pregnancy or should it be deferred into the postpartum period? — to provide some additional evidence on the risks and benefits of IPT in pregnant women, particularly in those taking ART.

The study will randomise 950 pregnant HIV-infected women living in countries with a high burden of TB/HIV to immediate vs. deferred (3 months postpartum) IPT. Many women will be on ART and IPT concurrently, and between 2 – 10% are expected to have occult HBsAg+. The primary endpoints is safety — effectiveness will be a secondary endpoint.

Adherence on IPT is commonly reported to be suboptimal — and in settings where the risk of re-exposure is not high, there is a need for new short TB preventive regimens to be evaluated. Recently, a regimen of weekly isoniazid and rifapentine given for 12 weeks and was shown as efficacious as a nine-month regimen of IPT in mostly HIV-negative individuals. Soon a very large AIDS Clinical Trials Group Study will study the effectiveness of daily isoniazid with rifapentine for 4 weeks in 3000 people living with HIV above 13 years of age (participants are permitted an NNRTI-based ART regimen).

Naturally, there are no pharmacokinetic or safety data for rifapentine in pregnancy.

"Clearly I think we need to push to say we need to study these drugs in women – specifically pregnant women - at the same time, so that we can have the data ready to implement as soon as these big trials release results," said Dr Gupta.

Issues related to treatment of active TB in women including during pregnancy

Similarly, given the greater risk of liver toxicity and other safety issues in pregnant women, there are questions of when to start ART while taking TB treatment. Three recent studies indicate that ART should be started no more than two weeks after TB treatment in patients with CD4 counts below 50 cells/mm^3 (unless there is CNS involvement in which case immediate treatment could be dangerous),[26] while it may be safe for women with CD4 cell counts above 50 to delay ART until after the intensive phase of TB treatment.

New TB drugs are in development and as is the case with rifapentine, data are needed on their safety and efficacy in women –in particular, pregnant women, as well as the the optimal treatments and dosage strategies, drug interaction and pharmacokinetic studies when these drugs acre combined with HIV treatment.

Generally adherence and outcomes in women and pregnant women on TB treatment are good. The biggest challenge is that woman who may have difficult to diagnose EPTB, and higher levels of stigma, low TB literacy and poor or belated health seeking that can make it difficult to obtain an early diagnosis and get her on treatment.

Rifampicin drug interactions with antiretrovirals continue to pose a challenge for coadministration of ART with TB treatment in women, particularly pregnant women.

Rifampicin interactions with antiretroviral drugs	
NRTIs (AZT, 3TC, TDF, etc.)	No significant interactions
NNRTIs (EFV, NVP)	RIF decreases NVP exposure 40 – 50%, EFV 20 – 35% (but effects highly variable)
Protease inhibitors (LPV/r, DRV/r, ATV/r, etc.)	RIF decreases exposure > 80%, in most cases Increasing the PI dose can lead to hepatotoxicity
Integrase inhibitors (raltegravir)	RIF reduces raltegravir exposure by 40 – 60%

First line drugs in pregnancy

Drug	**FDA**	**Crosses placenta**	**Breast-feeding**	**Issues in HIV pregnant women**
INH	C	Yes	Yes	Hepatotoxicity especially Hep B, NVP
RIF	C	Yes	Yes	Drug interactions with NVP, PIs
Rifabutin	B	Unknown	Unknown	Drug interactions with PIs
EMB	B	Yes	Yes	
PZA	C	Yes	Yes	

Brost Obstet Gyn Clin 1997; Bothamley Drug Safety 2001; Shin CID 2003; Micromedex
Key to grading:
A) Adequate well controlled studies; B) Animal studies no harm but inadequate human studies or animal studies show harm but human data do not; C) Animal studies show adverse effects and inadequate human data; D) Risk to fetus but use in life-threatening situations may be warranted; X) Risk of fetal abnormalities AVOID.

Second-line drugs for TB

Drug	**FDA**	**Crosses placenta**	**Breast-feeding**	**Issues in HIV pregnant women**
Streptomycin/ AGs	D	Yes	Likely, Yes	Ototoxicity
Capreomycin	C	Unknown	No data	
FQs *Cipro* Moxi	C C	Yes Unknown	AAP Yes, WHO No Unknown	
Cycloserine	C	Yes	Unknown	

Italics: Case reports of use in pregnancy
(Brost Obstet Gyn Clin 1997; Bothamley Drug Safety 2001; Shin CID 2003; Micromedex online)

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Other drugs

Drug	FDA	Crosses placenta	Breast-feeding	Issues in HIV pregnant women
TMC 207	?	Unknown	Unknown	No data
Rifapentine	C	Unknown		Teratogenic in rats/rabbits No data
Ethionamide	C	Unknown	Unknown	
Amoxicillin-clavulanate	B Unknown	Yes Unknown	Yes	

Italics: Case reports of use in pregnancy
(Brost Obstet Gyn Clin 1997; Bothamley Drug Safety 2001; Shin CID 2003; Micromedex online)

Efavirenz is generally the preferred antiretroviral anchor drug when taken with TB treatment, but there are the concerns regarding efavirenz use within the first trimester. However based on meta-analysis data WHO guidelines – and British HIV Association guidelines – no longer recommend against the use of efavirenz during the first trimester, due to the lack of evidence of an excess of birth abnormalities in infants exposed to efavirenz.[27]

Rifabutin may be an option with PIs, but is expensive and hard to access.

Dr Gupta noted that there are few data on MDR-TB in pregnancy: "When we look at the world's literature on the issue, there are approximately 57 published case reports – only a few that are specific to HIV, and we know that there's obviously a lot more out there. So this is a plea to try and also address this issue better with data."

She concluded by reiterating the need for research to develop new paradigms to rule in active TB; and new paradigms to assess latent TB assessment to better target preventive therapy. Finally, "when we think about treatment for prevention, and active TB in women, we need to think about including pregnant and breastfeeding women. "

Integrating TB case finding into maternal health services

"I'm not a researcher, I'm an implementer in Africa," said Dr Stacie Stender. Her presentation described the human resource constraints and priorities of those working in maternal and child health services, which the TB field is now trying to convince to integrate TB/HIV services, and JHPEIGO's efforts to engage them.

"Every year, 150 million women become pregnant and half of these are unwanted pregnancies, there are 20 million unsafe abortions; 10 million maternal morbidities; 358, 000 maternal deaths and 7.5 million stillbirths and newborn deaths," she said, noting that this all has been occurring in a context where there is a severe crisis in human resources for health.

In the countries with the highest TB incidence/burden in sub-Saharan Africa, most health care is provided by nurses and midwives. In the case of MCH, much of the care is provided by midwives, supporting focused antennal care, the WHO recommended service package that involves a four-visit approach to the ANC.

"Maternal death is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy regardless of the site or duration of the pregnancy, from any cause related to or aggravated by the pregnancy, but not by accidental or incidental causes. It can be classified either as direct: obstetrical complications of pregnancy, labour or the postpartum period, or indirect: previously existing diseases, or diseases arising during the pregnancy which are aggravated by the physiologic effects of pregnancy. In 2010, the definition was revised to include HIV as a direct cause.

It is important to remember that sub-Saharan Africa generally has the highest maternal mortality ratio, with over 300 deaths per 100,000 live births in many countries. Stender noted that the maternal mortality ratio and TB epidemic overlap closely in Africa.

- 99% of maternal deaths occur in developing countries
- More than 50% occur in Africa
- Haemorrhage is the leading case of death
- Infections (but a mix, not just HIV or TB)
- Eclampsia
- Obstructed labour
- Unsafe abortion

Stender cited the 'three delays'model of maternal mortality from the book *Too Far to Walk: Maternal Mortality in Context*,[28] which states that maternal mortality comes from delays:

- in the decision to seek care
- in reaching care
- in receiving care

"This is where we can an impact from a clinical standpoint," she said, "and it applies to TB and HIV mortality as well, so I think we can take a lesson from this."

The book addressed many of the challenges in provision of care in resource-limited settings, include challenges related to weak health systems, such as understaffing, poorly equipped facilities, which TB care advocates may not be able to affect in maternal and child health services, however "one factor affecting quality of care 'incorrect diagnosis and action' is where we can have an impact," said Stender "where we can increase the index of suspicion among health care workers, particularly midwives, when it comes to maternal health, that they consider TB in their list of differential diagnoses."

JHPIEGO's framework for engaging MCH involves advocacy and policy work, education and training, and facility based implementation work.

"Advocacy mean we can't just talk to ourselves, we have to have the unusual suspects at the table," she said.

Education and training

Another area Stender has been working on is to try to improve TB/HIV competencies in pre-service education. She noted that the reality in most of sub-Saharan Africa is that pre-service training rarely supports country health priorities or actual practice. "Health systems analysis and interventions are needed to realign education and practice with country health priorities to ensure competent providers," said Stender.

She gave the example of one country in West Africa where she and her colleagues did an assessment of 19 colleges for midwives

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and community nurses looking at their equipment, logistics, reference material, skill and knowledge. Basic materials were either missing or totally out of date at most of the colleges. While 63% of facilities met achievement standards for family planning training, only 11% met the standard for HIV, and none for TB.

To address these shortcomings, their first focus is to improve the technical knowledge and update the skills of educators and preceptors to make sure that each school has the required teaching and resource materials, and then provide follow-up training on teaching skills.

JHPEIGO has also developed in-service training materials that integrate TB activities into focused antenatal care in Kenya, including TB screening in pregnancy and TB case management and referral. Just recently they have developed guidelines for integrating tuberculosis screening in the postnatal period in Kenya.

Midwife-driven interventions to prevent, diagnose, care, treat and support women and children infected and affected by TB and HIV

	TB	HIV
Prevention	Respiratory infection prevention and control; TB preventive therapy (IPT) in HIV	Primary HIV prevention: Condoms, early infant circumcision; Reproductive choices for women living with HIV
	BCG for newborn; TB preventive therapy for TB contacts < 5 years old	Prevention of infant HIV acquisition during pregnancy & childbirth: ARVs for mother; Prevention of infant HIV acquisition during breast feeding: NVP for exposed infant
Diagnosis	TB screening; Prompt laboratory diagnosis (sputum smear); Other investigations	Provider Initiated Testing and Counselling (PITC); WHO Clinical Staging; CD4 cell count; Other laboratory investigations to initiate treatment
	Recognising common signs & symptoms in children	PITC of infant at 6 weeks & again after cessation of breastfeeding
Care, Treatment & Support	Prompt initiation of TB treatment; Management of side-effects & drug interactions; Adherence support; Supervision of community workers	Cotrimoxazole preventive therapy (CPT); Antiretroviral therapy (ART) for women who need it for their own health Cervical cancer screening; Adherence support; Supervision of community workers
	TB contact screening and investigation	Exclusive breastfeeding support; CPT for exposed infants; ART for infants diagnosed with HIV

Facility-based implementation challenges

While the development of in-service training looks like progress, Stender says that patients still have to go through a series of referrals for the TB in pregnancy management cycle. This begins with triage at the antenatal clinic as the nurse screens for symptoms of TB, and typically leads to a chain of referrals, first the lab or to TB clinic, depending on symptoms, then the lab collects spot sputum #1, the client returns in the morning; and the lab collects spot sputum #2 and #3, if indicated. Then the lab provides results in written form to the client to give to the antenatal clinic nurse and TB clinic, if indicated, the antenatal nurse follows up, lab results/ TB clinic management.

Few pregnant women are likely to make it through this lengthy referral process if the service is not provided on site.

Some specific challenges of TB case finding she's identified in maternal health services in South Africa include provider bias in screening only those women perceived to have a higher risk of TB, poor clinical staff moral and motivation, and high rates of extrapulmonary TB, which are harder to screen for and diagnose, and high rates of smear-negative TB — something which is unlikely to be diagnosed in the antenatal clinic.

Meanwhile, in Kenya, there is no routine collection of data in the monthly summary sheets, and TB data summary sheet does not specifically capture referrals from the antenatal clinic, "so even if a person gets screened, there is no follow-up to be sure that they got their sputum done, they were diagnosed or ruled out."

In response to some of these challenges, JHPIEGO has developed tools to assist with integration.

Stender stressed that as services are linked, patient-centred care has to be considered. If introducing TB screening simply results a long line of referrals, sending the patient to other facilities, diagnosis will be delayed and timely access to treatment unlikely. "The fewer the referrals, the quicker the diagnosis," she said. When introducing new services at the primary healthcare level, it is important to remain cognisant of the human resource for health crisis and that providers in these facilities predominantly don't think or work vertically.

Finally, Stender said that she was concerned about the lack of specificity of the WHO Symptom Screen, which she thinks could lead to too many referrals to for diagnosis and potentially overwhelm the health system's capacity.

However, as Dr Getahun noted in the question and answer session, the Symptom Screen is designed to rule TB out so that preventive therapy can be implemented. Really the symptom screen's purpose is to identify "the well." The next step after screening positive on the symptom screen depends upon the local health system's capacity.

Indeed, there is nothing to stop programmes from introducing another step, such as a rule-in symptom screen, or even a tuberculin skin test, as a way to reduce unnecessary referrals to the lab.

WHO recommendations on actions to address the impact of TB on maternal neonatal and child health

To coincide with World TB Day, members of WHO's STOP TB Department have published a piece in a special Tuberculosis and TB/HIV Supplement of the *Journal of Infectious Diseases* that lays out the case for improving access to TB prevention, diagnosis and treatment services for pregnant women and their children.[29] They call for the following "low-cost, effective interventions" to be made a routine part of the integrated management of pregnancy and child health in much the same way as TB collaborative activities are now part of standard of care for HIV programmes in resource constrained settings.

Such collaborative activities have indeed become the standard of care for HIV programmes, though it took some time to happen, and

in most resource constrained settings, we still have a long way to go in implementing them. But there are also clearly a number of differences in how HIV services and MCH services are structured and delivered, and HATIPbe querying experts working in the fields of HIV and MNCH on these questions in the months to come.

WHO recommendations on key programmatic actions to address the impact of TB on maternal neonatal and child health

Integrated management of pregnancy and child health services

- Include TB prevention, diagnosis and treatment as core component of the integrated management of pregnancy and child health package.
- TB prevention, diagnosis and treatment should be included as key interventions at all stages of pregnancy, neonatal, postpartum and postnatal care, particularly in high HIV and Tuberculosis prevalence settings.

Prevention of mother to child HIV transmission services

- Include a sample clinical TB screening algorithm that relies on the absence of current cough, fever, weight loss and night sweats in prevention of mother to child transmission of HIV services to identify eligible pregnant women living with HIV for IPT
- Pregnant women living with HIV should be screened regularly using the algorithm at each of their encounters with healthworkers and based on the outcome of the screening should either be provided IPT or investigated further for TB.
- Facilitate the implementation of the integrated patient monitoring system of HIV (pre-ART and ART), PMTCT and Tuberculosis care recommended by WHO, UNICEF and the Global Fund to Fight AIDS, Malaria and TB with standardised indicators.

Integrated management of childhood illnesses services

- Strengthen the inclusion of TB prevention, diagnosis and treatment in integrated management of childhood illnesses for children less than five years old.

Family planning and infertility services

- Include TB prevention, diagnosis and treatment services to family planning and infertility services.
- Establish effective referral mechanisms with Tuberculosis services if inclusion is not possible

Family planning and infertility services

- Include TB prevention, diagnosis and treatment services to family planning and infertility services.
- Establish effective referral mechanisms with Tuberculosis services if inclusion is not possible

TB and HIV programme services

- Improve the recording and reporting of TB data disaggregated by sex and age.
- Encourage the use of case-based electronic recording and reporting systems and mobile phones and other e-health communications and processes.

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about HATiP

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