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HIV and TB in Practice: Moving towards combination TB prevention

By Theo Smart

Prevention highlights from the 3rd South African TB Conference and AIDS 2012

"What we really need is combination TB prevention," Dr Allison Grant of the London School of Hygiene and Tropical Medicine said on the final day of the 19th International AIDS Conference (AIDS 2012) in Washington DC. "Not just antiretroviral therapy (ART), not just ART plus IPT [isoniazid preventive therapy], but other things as well, and if we do all of these things — and *all of these things are achievable now* — we could really start to make a big difference in terms of TB prevention."

She suggested that the TB world should borrow the 'know your epidemic' message from the HIV field — meaning that the prevention strategy should suit the setting. In settings where TB transmission risks are low, it may be fine to focus primarily on preventing latent TB infection from becoming active TB disease — with short-course curative TB regimens — but in settings where the risk of being reinfected with TB is high, more drastic measures to prevent reinfection with TB may also be needed.

However, there is some controversy over whether some of these measures, such as continuous, lifelong IPT, are entirely necessary in the context of ART, especially for people without evidence of exposure to TB (as measured by a tuberculin skin test or TST), but widespread agreement that business as usual cannot be the response in high TB- and HIV-burdened settings.

"Therefore we have to intervene to break the cycle," said Dr Grant, "first, by preventing people who already have latent TB infection developing active disease, and secondly by reducing transmission to prevent new infections."

But a combination prevention approach will be needed to do it all. This point emerged very clearly in the 'Thibela TB' study for which Dr Grant was a principal investigator.

Further data from the largest trial of IPT ever: Thibela TB

The 'Thibela TB' study was the largest IPT intervention study ever to be conducted. As previously reported by aidsmap, the Thibela TB study showed that giving a nine-month course of isoniazid preventive therapy (IPT) to everyone working at randomly selected South African gold mines had no effect on TB incidence, TB prevalence or all-cause mortality in the population, when compared to a cluster of gold mines randomised to standard TB programme management. However, a post-hoc analysis found that IPT did have an effect at the individual level — reducing TB while people were taking it — but this effect was lost very quickly once IPT was stopped. This finding suggests that levels of TB transmission in the mining communities may be higher than realised — and that a longer, potentially continuous course may be necessary to better control TB.

Further modelling analysis, presented at the South African TB conference in Durban in June, shed some light on why the intervention studied may have been insufficient, and what more may be needed to minimise TB incidence.

Six months of IPT has very little effect on TB incidence

"Why did we get no detectable impact in Thibela?" asked Dr Emilia Vynnycky of the Aurum Institute, during a symposium at the conference in Durban. To find out, the researchers created a model describing the epidemiology of TB in each intervention cluster, incorporating both directly measured data and some key assumptions:

- 30% HIV prevalence
- 20% average annual risk of *M. tuberculosis* infection
- TB disease occurs either through reactivation or following reinfection at estimated rates
- Increased risk of disease if HIV+ and/or silicotic
- IPT protection against disease through reactivation/after reinfection, whilst on IPT — 63%: HIV- or HIV+, not on ART; 80%: HIV+ and on ART; No protection once stop IPT
- Six months of IPT cures an estimated fraction of latent infections.

"We assume there is no protection once people stop IPT — and we didn't really know what proportion of infections are cured by six months of IPT," she said.

So there were several unknown parameters in the model including the risk for developing disease — from reactivation, or following reinfection — and most importantly, the proportion of latent infections that are cured by six months of IPT is unknown. But the model had to reproduce what went on in the mines, and so they fitted models with the prevalence and incidence data until the models were able to produce the impact observed.

"It turned out that in order to match the low impact observed, the model really needed to assume that six months of IPT had a low impact," she said. "In fact, the best fitting model was one in which we assumed that ***6 months of IPT does not cure any latent infections***."

And once this was assumed, the model predicted that even optimal implementation of Thibela TB would have led to a modest additional impact of under 20%.

"If you'd actually improved the IPT retention to the best possible level, the overall additional impact would have been roughly 12% in addition to what we saw. And varying additional factors i.e. screening, treatment, migration, community contact ... additional reduction in TB incidence would have been up to 20%," she said.

What would it take to control TB in the mines? Combination prevention AND better prevention regimens

The Aurum Institute researchers then presented a further analysis to show what *would* have worked to control TB in the mines. On a Kaplan Meier plot, they added intervention after intervention, each showing the modest impact of interventions that included decreasing the delay before starting TB treatment, improving rates of diagnosis, then increasing IPT coverage to highest levels seen in the most successful round of this study. The last intervention, IPT, would have had a profound *initial* impact — cutting TB incidence by almost half during the course of treatment. But the effect doesn't last once IPT stops.

They showed that if IPT did not stop, and they could get around half of people in the community to take continuous community-wide IPT, the effect would be somewhat more durable.

Notably, they also presented the impact of using a three-month regimen that cured latent infection. This had the most profound impact of all, knocking TB incidence down by almost three-quarters. Here too, the effect was lost, but importantly, it took about three years for the TB incidence to rise to the level that would be seen with optimal IPT implementation and 50% of the community on continuous IPT.

Then the researchers looked at other factors such as better diagnosis with the *GeneXpert* test, which had an impact, but not as much as one might think; and addressing dust control/silicosis in the mines, which reduced TB incidence by only 10 to 20%. The most significant impact, which should come as no surprise, would be to put all the miners living with HIV onto ART. Alone, this intervention wouldn't be adequate either — additional interventions would be needed (as was shown in the randomised control study of ART and IPT in Khayelitsha (see this news report).

"However, combining interventions could reduce the TB incidence by over 50%," said Dr Richard G White, in Durban. The interventions included: reducing treatment delay, screening with Xpert in annual occupational health screening, ART coverage increased to 80% by 2009, an initial 9-month course of IPT, with coverage at highest levels seen in Thibela, followed by continuous community-wide IPT with 50% coverage.

Does the Thibela TB study add weight to the case for continuous IPT?

Both in Durban and in Washington DC, Dr Grant reported the team's conclusions about the potential ramifications of Thibela TB.

It *cannot* be that IPT does not work.

"We have lots of evidence to know that it works, so for example amongst people with HIV in clinical trials we know that, overall, people receiving IPT have a one-third reduction in their risk of going on to develop active TB. If they have a positive tuberculin skin test, they've got a two-thirds reduction in their risk of developing active TB, but in order to do that they have to take IPT for six to nine months," she said. "And clearly, we've got very consistent data suggesting that IPT works while you're taking it, but unfortunately it doesn't seem to have a durable effect after you stop."

She noted this poor durability of IPT was observed in a couple of other studies in high HIV prevalence settings, with high TB transmission. In the BOTUSA trial, 36 months of IPT was superior to a six-month course, and TB rates increased shortly after going off IPT even in the 36-month arm (in TST-positive subjects).[1,2] In a smaller study some patients took a short course of curative combination rifampicin and isoniazid (though this last observation was a bit more anecdotal).[3]

"So in high transmission settings, increasing evidence to suggest that IPT has limited durability is leading us to the thought that we need to very seriously consider continuous IPT for people with HIV," she said, adding that "more broadly than that, we need to think about a combination approach."

Taking IPT continuously is generally in agreement with WHO policy, which states: "IPT for a duration of 36 months is conditionally recommended in settings with a high transmission of TB among people living with HIV,"[4] and incidentally, also the conclusion reached by Professors Steven Lawn and Robin Wood of the Desmond Tutu HIV Centre, and the University of Cape Town. "Growing evidence therefore suggests that if IPT is used, to do so on a long-term basis would be a more rational approach," they wrote recently in the International Journal of Tuberculosis and Lung Disease (IJTLD).

They took exception to the next component of the WHO IPT policy, which emphasises that "a tuberculin skin test (TST) is not a requirement for initiating IPT in people living with HIV. However, in some settings where it is feasible, it can help to identify those who would benefit most from IPT."

Lawn and Wood argue that, if IPT is to be given lifelong, it is wasteful to give it to those who are not TST-positive.

"A shift in policy towards long-term or even lifelong therapy, however, would provide an even stronger rationale for targeting IPT according to TST status. Indeed, targeted provision of IPT for 36 months to TST-positive individuals in Botswana has been found to be more cost-effective than providing IPT without TST assessment or providing IPT for 6 months only," Lawn and Wood wrote, citing another recent paper.[5] Their main criticism is that the current South African IPT programme guidelines, as reported by Bristow and colleagues in IJTLD,[6] are not being properly targeted.

"The current rapid scale-up of IPT ... is not being targeted in patients who will benefit, and is being given for too short a duration that will not provide durable prevention. This policy is inefficient use of scarce health care resources. Current scientific evidence suggests that if the intervention is to be appropriately tailored to the local epidemiological situation, it should be given to patients who are confirmed to be TST-positive, and on a long-term basis," they concluded.

In her talk, Dr Grant conceded that the lack of benefit of IPT in TST-negative patients is indeed a bit of a quandary.

"I don't think we understand everything that there is to understand about the epidemiology of TB in these settings still. The results from the Botswana study, were very different amongst people who were tuberculin skin test positive and negative, and the people who were tuberculin skin test negative at the start of the study didn't benefit from continuous IPT. What I think is interesting though is, how is it that TB incidence remains so low in the placebo arm of people who are TST negative, even though their TST result was some years ago — if most TB [in these settings] is due to reinfection, it's a little bit difficult to understand that," she said.

South African activists have pointed this out too, and have also suggested that TSTs ought to be provided before anyone is put on continuous IPT (see recent HATIP blogpost on the debate over IPT in South Africa).

But Dr Grant is afraid that will take IPT programmes back to square one.

"If you can come up with another more effective way to do TSTs, maybe, the danger is that if you require TSTs, how will it be any different from the same old 'business as usual' which led to so many missed opportunities for TB prevention, and the failure to scale-up IPT?" she told HATIP.

Might ART make continuous IPT (and TSTs) unnecessary?

But one of the biggest TB prevention stories from AIDS 2012 was the suggestion — from Dr Molebogeng Rangaka's presentation of the randomised trial of ART with (or without) IPT — that the preventive benefits of one year of IPT appear more durable on ART. This suggests that, while the effect may wear off eventually, it might be possible to take IPT intermittently while on ART — so if IPT doesn't need to be taken continuously, perhaps TSTs aren't so critical either.

At least, that was what was being discussed in the impromptu celebration among many of the South Africans involved the study, right after the late-breaker presentation. It was pointed out that the

rate of TB in the first year after IPT doesn't increase much (unlike what was seen in BOTUSA). For instance, the hazard ratios for TB for the study overall (both ART plus IPT and placebo while on ART) was HR 0.52 (95% CI: 0-27-1.01) and only marginally higher 0.61 (0.3-1.21) in the following year.

Dr Rangaka and Dr Grant both showed a graph demonstrating the cumulative TB incidence in which the incidence lines began to converge towards the third year, but less than one-third of the participants have had three years of follow-up yet.

RCT of IPT plus ART

	Duration of study in years							
# at risk	Baseline	TB cases	Year 1	TB cases	Year 2	TB cases	Year 3	TB cases
ART + placebo	667	25	601	21	521	10	181	2
ART + IPT	662	13	609	13	539	9	195	2

It is possible that the longer duration of IPT — when given with ART — effectively clears up more of the TB that occurs shortly after going on ART. This is a particularly critical period, Dr Graeme Meintjes of GF Jooste Hospital in Cape Town told HATIP. After that, any TB reinfection that occurs may still progress to active TB disease — but it takes longer than in more immune-suppressed subjects not yet on ART.

Note, the median CD4 cell count at baseline in this study was around 214 to 218 — and TB rates might be expected to be even lower when ART and IPT are started together at higher CD4 cell counts. With further follow-up, it may be determined that 'continuous IPT' in combination with ART may only be necessary in a small subset of patients with lower CD4 counts or positive TSTs and that patients doing better on ART may be able to get by with an intermittent course of IPT.

This is likely to go down better with patients. As much as TB experts like to say in one breath that IPT is well tolerated — and indeed, there have been very few serious side-effects reported in these studies in people with HIV — with the next breath, they will say how difficult it is to get people to take IPT for twelve or nine or even six months.

For instance, earlier in her talk, when speaking about prevention regimens in low TB burden/transmission areas, Dr Grant said: "They have to take IPT for six to nine months — that's a long time and retention in a long care programme like that is typically quite difficult and completion rates are poor, so shorter regimens would be preferable if they were safe and effective."

Indeed. But if that's the case, if six to nine months is too long, what sort of uptake do we really expect to get with continuous IPT? According to the Thibela TB modelling study, the continuous IPT combination approach would cut the rate of TB in the mines in half — clearly a marked improvement.

But TB would still be occurring at outrageously high levels: ~1500 to 2000 cases per 100,000 people.

If TB in the mines — and TB in southern Africa — is an emergency, why just cut rates in half? Why not use more effective preventive therapy regimens, if there are any? The Thibela TB study clearly suggested that a more effective or curative regimen would do better.

Of course, a curative regimen could not be given continuously — but when taken with ART, we may only be talking about intermittent therapy anyway. If something like that could be given every other year, then perhaps it would be possible to begin to *eliminate* TB in the mines and in people living with HIV in southern Africa.

Perhaps the real problem is that IPT just isn't aggressive enough.

"Another potential contributor could be that IPT just isn't using the right drug. Isoniazid is not very good at curing latent infection," Dr Grant said in her talk, noting that this appears to be the case in mouse models where even six months of isoniazid is not enough to prevent relapse. "On the other hand, some of the newer regimens and in particular, the new drug TMC207 [bedaquilline], seem to have much more activity against latent infection," she said.

So of course, those new drugs aren't available yet, but what about other potentially curative TB regimens that are on the market or close to the market? What about the short-course regimens that have been tested for TB prevention in the United States, where Americans are considered to have too much trouble adhering to six months of IPT?

"In settings where transmission is rare we've got rifapentine and isoniazid looking very promising as a simpler and shorter regimen," said Dr Grant. She reviewed the results of the PREVENT TB trial, released last year which tested the novel TB preventive therapy regimen of rifapentine plus isoniazid given weekly, directly observed, for three months.[7] The short-course was non-inferior to the standard of care of nine months of isoniazid in the low TB burden setting where it was tested. There were not many people living with HIV in that study, so enrolment was continued to boost the numbers of HIV-positive people in the study.

Dr Tim Sterling presented the safety data in 393 people with HIV who were randomised to IPT versus the short-course regimen in the PREVENT TB study at AIDS 2012.[8] Rifapentine may interact with some antiretroviral therapies, particularly with protease inhibitors, so people entering the study could not be taking antiretrovirals and so had relatively high median CD4 cell counts (~500). Significantly, more people finished the short course regimen (89%), and only 11% discontinued it for any reason (compared to 35% who quit IPT over the nine-month period). About 4% of the participants discontinued IPT due to an adverse event in either arm.

Similarly, there are other, shorter preventive therapy regimens currently under investigation, including: another ultra-short-course regimen of rifapentine plus isoniazid given daily for one month; and a regimen of four months of rifampicin monotherapy versus nine months of IPT (in adults who are TST or gamma-interferon test positive for TB exposure, excluding people living with HIV if they are on incompatible ART). Both of those studies are underway.

There have been barriers to using rifampicin-like drugs for prevention — one has been the concern that the drugs are too important for treatment, and if over-used without direct observed therapy, resistance could be an issue — however, with new TB drugs with fewer side-effects and drug interactions approaching the market, it appears as though these concerns are not so pressing.

The other issue has been the difficulty in using the class of drugs with ARVs. However, AIDS 2012 attendees heard that not only were rifampicin's drug interactions with efavirenz less serious than once thought, there are also data to suggest that a newer class of ARVs (integrase inhibitors) may also be used in combination without serious drug-drug interactions — at least with rifampicin.

Unfortunately, data from these studies on preventing TB in people living with HIV won't be available for over a year — data from the PREVENT TB study in people living with HIV aren't due until the

end of 2013 — and even then it will take a while to introduce a new preventive regimen into the market.

Either way, despite the recommendations or the controversy, it doesn't look like IPT will ever really need to be "continuous" — more effective regimens appear to be on the way to take over.

Using IPT for now, in combination with widespread earlier ART, better diagnosis and less delay in getting onto effective treatment, could put us on the path to cutting the incidence of TB in half over the next couple of years. Then if the researchers, drug approval, drug purchasing agencies and health systems can start delivering better *curative* regimens, TB preventive therapy may truly begin to turn the tide turn on TB and HIV-related TB.

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TB and HIV news from the 19th International AIDS Conference

News coverage of AIDS 2012

NAM's team of writers published news throughout the conference, reporting on research presented on a wide range of subjects. Where possible, these include links to the original abstracts and webcasts of the presentations.

We sent out six conference bulletins, summarising news from each day, in English, French, Spanish, Portuguese, Italian and Russian.

All these news reports and bulletins are available on our website at www.aidsmap.com/aids2012. There you will also find selected news from other sources, a selection of tweets that caught our eye and our blogposts and photographs from the conference.

Taking isoniazid preventive therapy for one year reduces the risk of TB in people taking antiretroviral therapy

Theo Smart

Twelve months of isoniazid (INH) preventive therapy (IPT) significantly reduced the incidence of all TB diagnoses among HIV-positive people who were taking concurrent antiretroviral therapy (ART), according to results of a large randomised study presented as a late breaker study on Thursday evening at the Nineteenth International AIDS Conference in Washington DC.

"There was a 37% reduction in the rate of incident TB in the INH treatment group compared to those who were receiving ART alone," said Dr Molebogeng Xheedhe Rangaka of the University of Cape Town, who presented the study findings. Conversely, there was also suggestion of a higher risk of liver toxicity and no mortality benefit was observed.

Although the study wasn't powered to answer the question, the protective effect of IPT didn't seem to wear off very quickly in this context where ongoing TB transmission is believed to be exceedingly high. Although the protective effect of IPT seemed to be gradually lost over time, it did not wane as rapidly as has been reported in patients not on ART in the BOTUSA and THIBELA studies. This suggests that in patients on effective ART, IPT may not need to be given continuously to prevent TB, but could perhaps be taken intermittently, every second or third year.

Is IPT needed in people on ART?

"Antiretrovirals significantly reduce the risk of TB in HIV-infected persons," said Dr Rangaka. "In our high HIV/TB setting of Khayelitsha in South Africa, the rate of TB pre-ART was 30 per 100 person years and ART reduced that rate to 12 per 100 person years. Even with this massive 60% reduction, the rates on ART were still unacceptably high, suggesting that we required additional tools to prevent TB. Isoniazid preventive therapy or IPT is such an additional tool."

Three studies have suggested a role for IPT as an additional strategy for TB prevention in people taking ART. The first two were observational studies. The third was a randomised controlled study where the effect of continuous IPT on TB rates was evaluated in comparison to six months of IPT. In this study subgroups of participants started ART during the course of follow-up. All three studies suggested an added benefit of IPT to ART, but the comparisons were non-randomised.

The study in Khayelitsha

So in 2007, the study in Khayelitsha was initiated to determine whether IPT further reduce the risk of TB in HIV-infected people concurrently receiving ART — and furthermore, whether it is safe to take IPT with ART? (IPT and ART have overlapping toxicities including peripheral neuropathy, severe rashes, raised ALT and clinical hepatitis, raising the possibility of elevated rates of these treatment-limiting toxicities).

Khayelitsha is a township of Cape Town, South Africa with a total population of at least 600,000 and a TB case notification rate of 1600/100,000 population per annum. The HIV prevalence, drawn from test results at the antenatal clinic, is 33.3%. At the Ubuntu Clinic, where the study was performed, the HIV prevalence found among new cases of TB in adults is at least 70%.

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The study was a pragmatic (where the rest of treatment occurs as in the real world) randomised placebo-controlled trial. The patient, doctor and local pharmacy were all blinded as to whether the patients were taking IPT or a matching placebo, which was self-administered for 12 months, and dispensed with their ART.

The primary endpoint was all TB (definite, probable or possible). The secondary endpoints included drug adverse events; or death. The main exclusion criterion was active TB (based on a TB symptoms screen plus smear and/or culture.

The study enrolled 1369 volunteers. The study period was four years, with screening beginning in 2007 and a minimum follow-up of 12 months. The last patient was randomised in October 2010, and the study closed in September 2011. Only participants who completed the TB screening process were randomised; and they were stratified by whether they were new or established ART patients.

Tuberculin skin tests were not required to participate in the study. There is an ongoing debate in South Africa about how long IPT should be given. The BOTUSA and Thibela studies both showed that the effect of IPT began to decline rapidly after discontinuation of IPT in people living with HIV who had a positive tuberculin skin test (TST), leading some researchers to advocate for continuous IPT to be given in these high-burden settings to people living with HIV. The response from the community has been somewhat muted however, with some activists noting that since the benefit of IPT was only seen in TST-positive patients, continuous lifelong IPT might pose a risk to those who were TST-negative. The researchers however, have stressed that the logistical challenges of performing a TST, which requires cold chain storage for tuberculin and skin test reading two to three days after it is administered, constitute a barrier to providing IPT if a tuberculin skin test is a requirement to receive it.

During the intervention period, follow-up was monthly to 2-monthly in line with their regular ART appointments; liver function tests (ALT) were checked monthly for the first three months then every three months, and patients were monitored for adverse events and adherence for ART and study drug. Follow-up continued until they developed TB, a serious adverse event or study closure, and at each visit they were screened for TB with a symptom screen and went through TB diagnosis if necessary.

The results

Out of 2,138 subjects assessed for eligibility, 1369 were randomised and stratified by ART status (pre-ART 388, on ART 981). After some cases of prevalent TB were observed and excluded, there were 662 patients in the isoniazid arm who were included in the modified intention to treat analysis; and 667 in the placebo arm.

In the IPT arm, 482 patients finished the trial without clinical events, compared to 469 on ART alone; there were 69 events in the IPT arm versus 84 on ART alone and similar numbers transferred out or were lost to follow-up.

Baseline characteristics were fairly similarly distributed between the two arms; both groups had a median age of 34, were mostly female, and about 70% were established on ART. The median days on ART for those who were newly on ART or established on ART, was similar between the two groups. The groups had a median CD4 count of about 200 cells//mm^3. About 40% of patients had had a prior tuberculosis event.

"In total we had 95 tuberculosis cases develop over 3227 person years, giving us an overall tuberculosis rate of 2.9 per 100 person years. 58 of those cases were in the placebo group, 37 in the INH group," said Dr Rangaka.

'The rate of tuberculosis in the people who received placebo was significantly higher at 3.6 per 100 person years; compared to the rate in the INH group which was 2.3 per 100 person years giving us a hazard ratio of 0.63 [HR=0.63(95% CI 0.41-0.94), p=0.03]. In other words there was a 37% reduction in the risk of tuberculosis in the patients who received INH, versus patients who were only receiving ART."

The risk of stopping INH or placebo due to grade 3 or more raised ALT was twice as high on IPT (19 out of 662**)** as the risk in the placebo group (9 out of 667), (p=0.05).

"Lastly, looking at time to death from randomization, our study did not indicate any mortality benefit – the rate of death in the two arms was fairly similar," said Dr Rangaka.

During the discussion following the presentation, Dr Rangaka was asked whether the effect of IPT wore off in the patients who stopped treatment.

"There is a suggestion, although not significant, that the effect of IPT seems to wane by duration," she said. But that effect did not wane as rapidly as in patients not on ART, with the effect seeming stable for about a year. The study does not have statistical power to evaluate this waning effect fully, but it should be interesting to see whether these trends will be strengthened with continued follow-up.

Reference

MX Rangaka et al. *Randomized controlled trial of isoniazid preventive therapy in HIV-infected persons on antiretroviral therapy.* 19th International AIDS Conference, Washington DC, abstract THLBB03, 2012. (To view the abstract and webcast of this session, click here.)

Novel TB combination regimen shows potent activity in randomised short-term clinical trial

Theo Smart

A new TB drug, PA-824, showed very potent early bactericidal activity in a randomised 14-day study in people with TB, when used in combination with the established antibiotic moxifloxacin, and pyrazinamide, an existing TB drug, according to a presentation by Dr Stephen Murray of the Global Alliance for TB Drug Development (the TB Alliance) on Monday at the 19th International AIDS Conference (AIDS 2012) in Washington DC.

The study results (published on the same day in *The Lancet*), suggested that the early bactericidal activity in the combination arm was much greater than what was observed in the five other arms, one of which involved standard TB treatment – though the size of the study was not large enough to prove a significant difference between the arms.

Nevertheless, the findings in human patients seemed to match the activity predicted by a mouse model that Dr Murray said could be used to identify the most potent new TB combination regimens to take forward quickly into clinical development.

In addition to being the first clinical confirmation of a new TB drug's activity, the particular regimen is interesting for two other important reasons.

First, in addition to being potent against drug-sensitive TB, it is expected to be active against most drug-resistant strains of TB – potentially shaving more than a year off of the time it takes to treat a person with MDR-TB and possibly even extensively drug-resistant TB.

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Second, the regimen should not have any major drug-drug interactions if given at the same time as antiretroviral therapy (ART) to HIV-positive people with TB.

So many potential combinations, so little time

So, when there are already several established drugs with anti-TB activity, and several drugs in the development pipeline, there are hundreds of potential combinations that could be studied – and hundreds of thousands of people dying for lack of better TB treatment. Researchers can't take decades to test all the possible TB drug combinations with the new drug before it gets to market.

This is the very sort of problem preoccupying the TB Alliance, a not-for-profit TB drug development organisation supported by the Bill & Melinda Gates Foundation, Irish Aid, UKAid, USAID, and the US Food and Drug Administration. While there are a couple of companies with TB drugs a little further along in clinical development, the TB Alliance has made it their business to find as many potential new TB drugs as possible, and do what it can to speed the development of faster-acting, affordable TB drug regimens.

Their solution to the question of 'what combinations to test first' was to test them all in a mouse model of TB to see what worked best.

And, indeed, now they have evidence that what they see in the mouse model seems to happen in humans.

"The regimen of PA-824 plus moxifloxacin plus pyrazinamide has shown really very dramatic improvement over a number of other combinations, which is a reflection of its effect in reducing levels of tuberculosis in the lungs of mice in this particular model," Stephen Murray told the conference.

The NC-001 study

The data came out of the NC-001 study, which, Dr Murray noted, "is really the first novel combination early bactericidal study".

Early bactericidal studies have been used in the past to evaluate individual drugs, like TMC207 (bedaquiline). These studies take patients who are newly diagnosed with tuberculosis and treat them for a short time (after which they are given standard treatment immediately). As in the mouse model, the researchers count the amount of bacteria in the lungs, measured by taking serial sputum samples every 16 hours.

NC-001 randomised 85 people with TB at two sites in South Africa (only six were HIV positive). Fifteen patients each were randomised to one of six arms: *Rifafour* (the standard four-drug TB treatment) and five arms that contain single novel drugs or a combination of novel drugs.

After randomisation, the patients were treated for 14 days, with serial sputums collected to determine M.TB colony forming unit counts. In addition, they also inoculated the sputum to see the time to positivity (TTP) to evaluate the amount of bacterial load in the sputum using a liquid culture.

This was the first bactericidal combination study to include PA-824, which is a nitroimidazole, in the same class of drug as Otsuka Pharmaceutical's delamanid (which has moved into phase III studies and which *ought* to be available on expanded access). This means there is a decent chance such synergy will be seen with either drug, and also that a competitive drug in the same class marketed by a non-profit could keep prices of these new regimens low.

In this study, one of the arms provided TMC207 (bedaquiline) by itself, since it is known to have a bactericidal effect on its own. All the combinations however – of *Rifafour*, bedaquiline plus PA-824, bedaquiline plus pyrazinamide, PA-824 plus pyrazinamide, and PA-824 plus pyrazinamide plus moxifloxacin – were naturally more potent than monotherapy.

Of particular note, however, PA-824 plus pyrazinamide showed a dramatic synergistic effect, both in the mouse and the human CFU measurement model.

However, Dr Murray said that at best, PA-824 and bedaquiline had an additive effect. "When you look at PA-824 with TMC207, we don't see much of an enhancement, though it looks like it's a little bit better than TMC207 alone, but it really is no different than PA-824."

"But... as we saw in mice, the combination PA-824 plus PZA plus moxifloxacin has the largest effect. This effect really distinguishes itself from the other combinations with TMC207," he said. Though one wonders why there wasn't a three-drug combination with bedaquiline including moxifloxacin. Oddly, for a non-profit alliance, this seemed to be a rather proprietary treatment of their own not-for-profit product.

Nonetheless, the novel three-drug combination was profoundly potent; within two weeks, it killed more than 99% of patients' TB bacteria.

As noted within the press release from the TB Alliance, this particular regimen could treat both drug-sensitive and drug-resistant strains of TB.

"Treating drug-sensitive and drug-resistant TB with the same regimen can simplify the delivery of TB treatment worldwide," said Andreas Diacon, MD, the trial's principal investigator and lead author of the *Lancet* study.

A second trial called New Combination 2 (NC-002) was launched earlier this year to test the PaMZ combination over two months in patients, further advancing it through clinical development. NC-002 is currently enrolling patients and will be conducted at eight sites in South Africa, Tanzania and Brazil.

Dr Mario Raviglione, MD, Director of the Stop TB Department at the World Health Organization added that testing multiple new TB drug candidates simultaneously has already proven to be a major advance. "Because of testing drugs in combination, we have already saved several years in the research process to find new, effective regimens to treat TB," Dr Raviglione said in the press release.

S. Murray et al. *A phase 2 trial of novel anti-tuberculosis regimens with increased efficacy and low potential to interact adversely with antiretroviral therapy.* Nineteenth International AIDS Conference, abstract MOAB0305, Washington DC, 2012.

Reference

S. Murray et al. *A phase 2 trial of novel anti-tuberculosis regimens with increased efficacy and low potential to interact adversely with antiretroviral therapy.* 19th International AIDS Conference, abstract MOAB0305, Washington DC, 2012. (View abstracts and a webcast of this session here).

Determine LAM urine antigen TB test is highly cost-effective for use in hospitalised people living with HIV

Theo Smart

The lateral-flow urine LAM (liparabinomannan) test for tuberculosis — a simple inexpensive strip test for tuberculosis — is a feasible point-of-care test in hospitalised South African adults living with HIV and, if people are then quickly put on effective treatment, would be a very cost-effective diagnostic strategy in such patients, according to a South African study presented on Wednesday

afternoon at the Nineteenth International AIDS Conference (AIDS 2012) in Washington DC.

"It is a cost-effective diagnostic strategy, having an incremental cost-effectiveness ratio (ICER) of $1370 per disability-adjusted life-year (DALY) averted, and this is less than the per capita GDP in South Africa of over $7000," said Dr Di Sun of Johns Hopkins Bloomberg School of Public Health, who presented the findings. "This remained robust across a wide range of sensitivity and uncertainty analysis."

Five or six years ago, TB-HIV activists began drawing attention to the shocking inadequacy of the existing TB diagnostics — smear microscopy and culturing — which were relatively unchanged in over 120 years since they had been established by Dr Robert Koch, who discovered *Mycobacterium tuberculosis (M.TB)*. Smear microscopy fails to detect the majority of cases in people who are co-infected with HIV, resulting in delays in diagnosis and treatment, and all too often in death. Even culture fails to detect about a quarter of the TB cases that have to be diagnosed clinically.

As a field, TB diagnostics research and development was virtually non-existent. But the activists caught the attention of the Bill & Melinda Gates Foundation and others, who invested heavily in the Foundation for Innovative Diagnostics and other concerns, setting off a flurry of activity. A product pipeline evolved, out of which GeneXpert has emerged to great fanfare, despite being too expensive and having running requirements too complex to put into every primary health care facility — or for that matter even district hospitals.

"Dropping the machine with a parachute and cartridge will not do the job — you need quite a lot of logistical back-up to install this machine in lower resource settings — you need a stable electrical power supply which is very challenging in the settings we are working in, and you also need air conditioning for both the machine and the cartridges; the temperature should not rise above 30 degrees," said Dr Steven Van Den Broucke of MSF during a TB diagnostics session almost entirely devoted to the Xpert MTB/Rif tests at the conference on Thursday.

The only exception was during the overview on TB diagnostics given by Professor Gavin Churchyard of the Aurum Institute, who mentioned a couple of other assays entering into use, including those that try to detect lipoarabinomannan (LAM), a component of MTB's cell wall that can be detected in urine samples, when it gets released from metabolically active or degraded MTB.

Urine tests for TB are appealing for a couple of reasons, according to Dr Churchyard. "Urine is easy to obtain," he said, particularly from patients who may have trouble producing sputum – a common problem in people living with HIV who have extrapulmonary TB. Plus it lacks infection control issues associated with handling blood or sputum.

An earlier version of the LAM urine antigen test was ELISA-based, which would have to be used in a centralised laboratory. However, a new form of the test uses the Determine testing platform, requires no sample processing and produces results in 25 minutes.

In other words, it is a test that can be performed at the point of care, whichever medical facility the patient is in.

The test isn't perfectly sensitive or specific. Its highest sensitivity is in people with high MTB burden, who have more detectable antigen in urine, in immunosuppressed patients, and in those with disseminated TB.

The test seems to perform much better in people living with advanced HIV, particularly those with CD4 cell counts below 100. Dr Churchyard presented a table summarising the results using the point-of-care test thus far in people living with HIV.

Determine TB-LAM

Author/ Year	N	Setting	Sensitivity		Specificity
			Overall	CD4<100	
Peter, 2012	335	Inpatients	45%		96%
Lawn, 2012	516	ART clinic	28%	52%	99%
Dorman S, 2012 (Interim unpublished data)	561	Outpatients Inpatients	45%	80%	90%

Dr Sun noted that the lateral flow test has a few other profound advantages: it requires minimal training, and *no expensive additional equipment* that has to be airlifted to remote facilities in resource-limited settings.

The cost of each test is also profoundly less expensive than Xpert MTB/RIF, which was about $17 per cartridge test — though as cost-analysis studies in South Africa have shown, once shipping costs and other expenses were added in, the cost of the test was closer to $32 (See HIV & AIDS Treatment in Practice's review of LAM and other diagnostic assays for further information). More recently, UNITAID and other funding partners agreed to collaborate on a 'buy-down', essentially paying a percentage of the cost of the cartridge so that the cost to national TB programmes in resource-limited settings would be $10 each — though again, shipping and other costs involved in getting the cartridges into the country may not change that much.

The LAM lateral flow assays aren't bulky, don't weigh much and don't require air conditioning. They cost roughly $3.50 per test.

But that still doesn't mean it would necessarily be cost-effective to roll-out the test widely, or that it would improve upon the already available lab tests (smear microscopy, chest X-ray).

The purpose of the study presented this week was to evaluate the cost-effectiveness of a lateral-flow urine LAM assay in HIV-infected South African adults and the economic conditions under which it is most likely to be preferred.

This, other studies have suggested, would be for the most ill people living with HIV, who are waiting in the hospital for a diagnosis.

The cost-effectiveness analysis considered certain aspects of the diagnostic decision as being constant, such as:

1 ALL patients would receive the same existing diagnostic tests regardless of whether the LAM assay was added or not (and the costs of those tests would be a constant.
2 A positive result on smear microscopy or LAM would get treatment.
3 Undiagnosed, untreated TB in these patients would lead to death.
4 A proportion of undiagnosed cases would be treated anyway based upon the clinician's judgment.

Parameter values and unit costs were drawn from studies performed in the South African setting. The estimates (for instance, of life gained on treatment) used were conservative.

The primary outcome, was the incremental cost-effectiveness ratio that adding LAM into the diagnostic decision would yield, in terms of cost per DALY averted. Sensitivity and uncertainty analyses were performed on all parameters.

Results

By adding the LAM test, they would be able to diagnose 80 more true cases of TB, at a cost of 25 false-positive TB cases. These false positives occur because the test is only 95% specific, However, it should be noted that specificity is determined in reference to culture as the gold standard for diagnosis — and yet culture misses a substantial proportion of cases, particularly in this population.

All of this comes at an additional incremental cost of $79,000 (mostly the cost of treatment for these cases).

Cost-Effectiveness of Adding Lateral-flow LAM to Standard TB Diagnostics

	Existing diagnostics	Existing diagnostics + Urinary TB-LAM
Cohort size	1000	1000
TB cases	380	380
TB cases treated	262	342
False positives treated	130	155
DALYs	495	437
DALYs averted		58
Cost	$299,000	$378,000
Incremental cost		**$ 79,000**
ICER $/ DALY		**$1370**

The addition of urine lateral-flow LAM averted 58 DALYs at a cost of $1370 per DALY averted (95% uncertainty range: $710-3396). Even if Dr Sun and colleagues had used high values in the sensitivity analysis, the cost per DALY averted is *much* less than the GDP per capita of South Africa of $7275.It should be noted however, that as of yet, there are no empirical evidence from other trials that the addition of urinary LAM improves survival. In addition, the results may not be generalisable to other populations, such as the outpatient setting or in other high-burden settings settings.

However a three-way sensitivity analysis Dr Sun presented suggested that for a test with 95% specificity to be cost effective, if the resulting life expectancy gained from treatment is only 1.5 years, the TB prevalence would need to be at least 5%. If however, the life expectancy is 5 years, TB prevalence must be at least 1%. But if TB treatment prevents TB-related death, and the patient is put on effective antiretroviral therapy, life expectancy would be much greater, making the test begin to look cost effective in advanced people living with HIV even in settings with a substantially lower TB prevalence.

"This illustrates the importance of extending the life expectancy of our population of interest, which can be done by putting them on antiretroviral treatment, which will cause LAM testing to be much more cost-effective," Dr Sun said.

"Cost-effectiveness depends most strongly on LAM specificity, life expectancy, and TB prevalence, and it is highly cost-effective with longer life expectancies," she concluded.

Reference

Sun Di et al. *Cost-effectiveness of a lateral-flow urine lipoarabinomannan test for TB diagnosis in HIV-infected South African adults.* 19th International AIDS Conference, Washington DC, abstract TUAE0101, 2012. (View the abstract of the session on the conference website).

For more information on TB diagnostics, visit the archive of HIV & AIDS treatment in practice at www.aidsmap.com/hatip.

HIV infection does not compromise multidrug-resistant TB treatment outcomes in Botswana

Lesley Odendal

HIV infection did not have an impact on the time it took for multidrug-resistant tuberculosis (MDR-TB) adult to reach culture conversion, according to a study from Botswana presented at the 19th International AIDS Conference (AIDS 2012) in Washington DC. However, high rates of drug toxicity were found overall and were more likely to be associated with HIV co-infection.

In the pre-ARV era, MDR-TB with HIV infection had worse treatment responses and higher mortality compared to HIV-uninfected MDR-TB patients. Few studies of MDR-TB outcomes in HIV-positive people with access to ARVs have been carried out, particularly in sub-Saharan Africa, and there is still limited surveillance information about the prevalence of MDR-TB in people living with HIV, largely because until recently national HIV and TB programmes did not have the laboratory tools to carry out MDR-TB case-finding or comprehensive surveillance.

That information gap may begin to be filled as access to the Gene Xpert MTB/RIF test increases in sub-Saharan Africa from 2013 onwards due to funding from UNITAID, PEPFAR and the Bill and Melinda Gates Foundation. Xpert MTB/RIF is able to detect resistance to rifampicin within hours; if rifampicin resistance is present, samples can be referred for full drug susceptibility testing.

At present much of the knowledge about the prevalence and management of MDR-TB in sub-Saharan Africa is derived from South Africa, where MDR-TB has become recognised as a major public health problem since 2007. The study from Botswana is one of the first reports of MDR-TB management from outside South Africa.

Seventy culture-confirmed MDR-TB patients, who started individualised MDR treatment at two public clinics prior to September 2008 were included in the study. Of the 70, 40 (57%) were HIV infected and 30 (43%) were HIV uninfected. The median baseline CD4 count of the 40 HIV-infected patients was 158 cells/mm^3 (IQR: 88-347). At three months follow-up, the median CD4 count had increased to 262 cells/mm^3 (IQR: 129-382). 28 (69%) of the HIV-infected patients were on ARVs prior to the start of MDR-TB treatment. There were no significant differences in the gender, median age, TB treatment history, or the number of TB drugs patients were resistant to, between the HIV-infected and HIV-uninfected groups.

Eighty-five per cent of the HIV-infected people reached sputum conversion, compared to 83% of those who were HIV-uninfected, a difference which was not found to be statistically significant ($p>0.5$). The study defined sputum culture conversion as two consecutive negative sputum cultures at least one month apart. Overall, 59 of 70 (84%) of the patients reached sputum culture conversion.

There was no statistically significant difference in the median time to sputum culture conversion for those MDR TB patients who were HIV infected (78 days, IQR: 42-186), compared to those who were HIV uninfected (95 days, IQR 70-133), $p>0.5$.

When adjusting for age, gender, TB treatment history, and the number of active agents, HIV-infected patients were 80% as likely to

sputum culture convert as HIV uninfected patients, although this finding was again statistically non-significant (95% CI: 0.4 to 1.4).

"Our data suggest that in resource-limited settings with broad access to ARV and individualised MDR-TB care, short term microbiologic outcomes may be comparable in HIV-infected and uninfected patients," said Dr Jeffrey Hafkin, who authored the study.

Four patients died following during the study period. Two of these deaths occurred following sputum culture conversion, both of whom were HIV infected. The remaining two deaths occurred prior to culture conversion, both of whom were HIV uninfected. Two patients developed extensively drug-resistant TB during follow-up, one of whom was HIV positive. No patients defaulted from care during the study period.

The number of people experiencing drug toxicities was the only significantly different outcome between the HIV-infected and HIV-uninfected groups. 40% of the HIV-infected patients experienced neuropathy compared to 10% of those who were not HIV-infected (p<0.01). Twenty-five per cent of HIV-infected patients experienced nephropathy, compared to only 7% of those who were not HIV infected (p=0.04). However, researchers warned that there may be misclassification bias as there was no characterisation of toxicity done to determine if the toxicity in HIV-infected patients was due to their ARVs.

Reference

Hafkin J et al. *Impact of HIV on early MDR-TB treatment outcomes in Botswana.* 19th International Conference on AIDS, abstract THAB0102, Washington, DC, July 2012. (View the abstract and webcast of the presentation on the conference website).

Co-administration of rifampicin and efavirenz does not reduce efavirenz concentrations or efficacy

Lesley Odendal

Standard dosing of efavirenz, that was not adjusted for patient weight, resulted in therapeutic efavirenz concentrations and excellent virological outcomes in patients coinfected with TB and HIV who were also taking a rifampicin-containing TB treatment, according to results from the ACTG 5221 STRIDE study presented at the at the 19th International AIDS Conference (AIDS 2012) in Washington DC.

These findings have important implications for guidelines on rifampicin and efavirenz co-administration in TB/HIV co-infected patients. Rifampicin is known to cause drug-drug interactions, especially with efavirenz, which is recommended in first-line ARV treatment. Rifampicin co-administration is associated with an approximately 30% decrease in efavirenz trough concentrations (C_{min}). Previous studies have showed that efavirenz dosing should be increased from the standard dose of 600mg to 800mg in TB/HIV patients who weigh more than 50kg when taking rifampicin; a recommendation which the Food and Drug Administration of the United States of America made in January this year.

Efavirenz concentrations were measured using high-performance liquid chromatography where the lower limits of quantification was defined as 1mg/l. C_{min} samples were obtained 20 to 28 hours after efavirenz administration. Efavirenz levels were evaluated at antiretroviral (ARV) treatment weeks 4, 8, 16 and 24 for those patients on rifampicin, and weeks 4 and 8 for those not on rifampicin. Samples were only collected in participants with no self-reported missed efavirenz or rifampicin doses in the previous three days.

According to Dr Annie Luetkemeyer, higher weight did not jeopardise efavirenz efficacy in patients taking rifampicin-containing TB treatment. In 505 patients who were taking both efavirenz and rifampicin, none reached below the minimum recommended plasma concentration of <1 mg/l of efavirenz. The median efavirenz C_{min} was found to be 1.96 mg/l (IQR: 1.24 – 3.7).

Heavier patients did have significantly lower efavirenz concentrations, but only when heavier patients were defined as weighing 60kg or above. The median efavirenz C_{min} in patients weighing below 50kg was 2.08 (IQR:1.33-4.33) compared to 1.86 (IQR:1.18-3.64) in those patients weighing 50kg and above (p=0.09). In contrast, the median efavirenz C_{min} in patients weighing below 60kg was higher at 2.02 (IQR: 1.29-4.09) compared to 1.68 (IQR: 1.07-3.06) in those patients weighing 60kg and above (p=0.02).

When examining the efavirenz C_{min} in patients also taking rifampicin compared to those who were not, there was no significant difference found across patient weight levels, except when disaggregated by race. There was a significant difference in efavirenz C_{min} in black patients taking efavirenz with or without rifampicin. For the black patients taking rifampicin (n=367), the efavirenz C_{min} level was 2.1 compared to those not taking rifampicin (n=269) whose efavirenz C_{min} level was 1.8 (p=0.01). The researchers suggested that this paradoxical finding is likely to be due to genetic distinctions in metabolism in black patients. The study did not include enough members of other races to show significant differences.

Subtherapeutic efavirenz C_{min} of less than 1 mg/l was not associated with rifampicin coadminstration, according to the study results. These showed that 27.3% on rifampicin (versus 26.2% not taking rifampicin) had an efavirenz C_{min} less than 1mg/l and this finding was not found to be statistically significant (p=0.72).

Rates of HIV virological suppression were also found not to be reduced in patients above 50 kg or 60 kg taking efavirenz and rifampicin. The investigators concluded that these data do not support weight-based increase of efavirenz during rifampicin-containing TB treatment.

Efavirenz and rifampicin co-administration in pregnant women

Rifampicin was also shown to have no significant effect of on efavirenz C_{min} levels in pregnant women and their infants, according to the preliminary results from the TSHEPISO efavirenz pharmacokinetic substudy presented at AIDS 2012.

The combined effect of pregnancy and rifampicin-containing TB treatment on efavirenz C_{min}, virologic suppression and prevention of maternal-to-child transmission of HIV (PMTCT) has not been studied before.

TSHEPISO is a prospective cohort study among HIV-infected pregnant women with TB (n=250 cases) and without TB (n=500 controls), currently enrolling in Soweto, South Africa. Women (n=150) with and without TB, on efavirenz-containing ARV will enrol in the substudy, along with their infants.

The preliminary results from 76 women and 70 infants in the substudy to date show that the estimated efavirenz C_{min} among women pre/intrapartum and postpartum were not significantly different. The model, which also took weight and CYP2B6 genotype (the enzyme central to the metabolism of efavirenz) into account, was unable to show a significant effect of rifampicin on efavirenz C_{min} (except among slow efavirenz metabolizers).

The median efavirenz C_{min} of the 40 pre/intrapartum women taking rifampicin was 1.76 (IQR: 0.89-3.13), with 29.6% with an efavirenz C_{min} of less than 1mg/l. In the 46 women not taking

rifampicin six weeks postpartum, the median efavirenz C_{min} was 1.52 (IQR: 1.14-2.02) with 17.1% with an efavirenz C_{min} of less than 1mg/l.

Despite the 29.6% of women on rifampicin with C_{min} less than 1 mg/l, the viral load was suppressed in most women taking efavirenz for three months or more at the time of delivery. There were no cases of mother-to-child transmission of HIV.

The effect of genotype CYP2B6 showed that 56.3% with extensive, 5.7% with intermediate, 16.7% with slow and 0% with very slow efavirenz metabolism had an efavirenz C_{min} of less than 1mg/l.

Difference in weight did not prove a significant factor for EFV C_{min} levels in those taking rifampicin or not taking rifampicin. The median C_{min} levels were both 1.91 for women below and above 60kg in those taking rifampicin, but 20% of those less than 60kg had a C_{min} less than 1mg/l compared to 31.6% in the women weighing more than 60kg. The median C_{min} for women less than 60kg was 1.33 (IQR: 1.12-1.64, 11.1% with a C_{min} less than 1mg/l) and 1.55 (IQR:1.13-2.07,16.7% with a Cmin less than 1mg/l) in women not on rifampicin treatment.

Preliminary results also showed that 70% of TB/HIV co-infected women and 83% of HIV-only infected women had undetectable viral load counts at delivery, although this difference was not statistically significant (p=0.24).Of those taking efavirenz for at least 12 weeks at delivery, 82% of TB/HIV co-infected women and 93% of HIV-only infected women had undetectable viral loads, although this difference was again statistically insignificant (p=0.26).

Blood samples taken from infant umbilical cords in 45 infants showed the median efavirenz C_{min} to be 1.15 (IQR: 0.628-1.91, 8.9% with a C_{min} less than 1mg/l. Cord and maternal pre-partum concentrations were highly correlated (r=0.93). However, the median efavirenz C_{min} in infant blood at seven days after birth was 0.079 (61.4%with a C_{min} less than 1mg/l). However, quantifiable values were related to larger cord-blood concentrations.

Reference

Luetkemeyer A et al. *Relationship between weight, efavirenz (EFV) concentrations and virologic suppression in HIV+ patients on rifampicin (RIF)-based TB treatment in the ACTG 5221 STRIDE study.* 19th International Conference on AIDS, abstract MOAB0301, Washington, DC, July 2012.

View the abstract on the conference website.

View the webcast on the conference website.

McIlleron H et al. *Efavirenz (EFV) concentrations in pregnant women taking EFV-based antiretroviral therapy (ART) with and without rifampicin-containing tuberculosis (TB) treatment: the TSHEPISO Study Team*. 19th International Conference on AIDS, abstract MOAB0303, Washington, DC, July 2012.

View the abstract on the conference website.

View the webcast on the conference website.

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