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ART and TB prevention

By Theo Smart

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We would like to thank the following expert reviewers for their comments on this edition: Prof. Gavin Churchyard, Aurum Institute for Health Research, South Africa; Dr Halima Dawood, Greys Hospital, Pietermaritzburg, South Africa; Dr Haileyesus Getahun, STOP TB department, WHO; Dr Reuben Granich, HIV department, WHO; Prof. Anthony Harries, International Union Against Tuberculosis and Lung Disease; Prof. Diane Havlir, University of California, San Francisco, USA; Dr Stephen Lawn, London School of Hygiene and Tropical Medicine & Desmond Tutu HIV Centre, Cape Town, South Africa; Dr Annelies van Rie, University of North Carolina School of Public Health, USA; Prof. Waafa El-Sadr, Mailman School of Public Health, Columbia University, New York, USA.

Key points

- **Antiretroviral therapy greatly reduces the risk of developing TB in people with HIV who have CD4 cell counts below 350.**
- **Many researchers believe that earlier treatment, at CD4 counts above 350, could be expected to reduce the risk of TB too.**
- **A large international cohort study called CASCADE has found that the risk of TB climbs very sharply in the first year after becoming infected with HIV, even in people with CD4 counts above 500.**
- **In this cohort study, antiretroviral therapy rapidly reduced the risk of TB, but people on ART still had a higher risk of developing TB than the general population. This could be due to a higher risk of re-exposure to TB.**
- **These findings suggest that a central part of any TB prevention strategy in people with HIV should be prevention of immune system damage, using antiretroviral therapy.**
- **However, findings from a randomised trial of earlier treatment in serodiscordant couples as an HIV prevention strategy showed that in people who started treatment at CD4 counts between 350 and 550, antiretroviral therapy did not reduce the risk of developing TB in the lungs (pulmonary). It did reduce the risk of developing TB at other sites in the body (extrapulmonary).**
- **Experts are uncertain about how to explain these findings. More information about TB in the HPTN 052 study is needed.**
- **It remain essential to practise good infection control in facilities where people on ART congregate. ART cannot prevent exposure to infectious TB; good infection control practices can.**
- **Isoniazid preventive therapy can prevent TB in people with high CD4 counts and signs of immune response to TB, as measured by a positive tuberculin skin test.**

This HATIP issue explores what is known about the potential benefits — and the limits — of antiretroviral therapy (ART) for TB prevention and control — and the clinical implications if ART isn't enough to prevent TB.

"I'm more focused on getting people onto ART than interventions like isoniazid preventive therapy (IPT) — if I can keep their CD4 cell count above 500, I'm not worried about their developing tuberculosis," the director of an HIV clinic told HATIP a couple months ago.

His views wouldn't be uncommon in industrialised countries with a low burden of TB, but seemed peculiar given that his clinic was in Cape Town, an area with one of the highest TB burdens in the world. Does having a current CD4 cell count or starting ART and raising the CD4 cell count above 500 CD4 cells really eliminate the risk of TB in people living with HIV (PLHIV) in this setting? We weren't sure we shared his confidence — and after hearing some data presented at the IAS 2011 in Rome, we were sure that we didn't.

Brief background on ART for TB prevention

At the individual level, there is no question that ART dramatically reduces the risk of TB in people living with more advanced disease — though data suggest that PLHIV on ART remain at least twice as high as the general population in Cape Town.[1] (That risk is perhaps higher where the general population is not at such great risk of TB). At the population level, a pivotal study in Haiti had shown that starting treatment when CD4 cells are between 200-350, rather than waiting until they fall below 200, cut the rate of TB in half.[2] A meta-analysis of nine cohort studies in both high-income and resource-limited settings, concluded that ART reduced the risk of TB by 65% (95% Confidence Interval (CI) 55-72%)).[3] The risk reduction was greatest in people with CD4 cell counts below 200, but still significant in three of the nine studies where people started ART with CD4 cell counts above 350, with 57% risk reduction (95% CI 37-70%).

Part of this risk reduction is due to ART slowing the decline of the immune system to the point where TB really becomes much more common. But as early as 1993, a study in the Democratic Republic of Congo (DRC) had demonstrated that TB also occurs at higher CD4 cell counts in PLHIV too, so is it possible that earlier or immediate ART could prevent even more people from developing active TB while they still have high CD4 cell counts?[4]

This was actually suggested by the lead author of the 1993 study. Professor Ya Diul Mukadi, who is now Senior TB Technical Advisor for USAID, during a discussion at the HIV Controversies session, organised by the HIV section of the Union at the 40th Union World Conference on Lung Health in Cancun in 2009, following a presentation by Professor Brian Williams on 'annual HIV testing and immediate ART for all HIV-infected persons' (in other words, 'test-and-treat').

"If we [start ART] earlier, that should prevent the non-AIDS defining complications that some HIV-infected patients are passing away from before they can access ART facilities. And what is important to note at a TB conference, it is going to help us reduce the risk of TB at the individual level. At the public health level, simplifying the management of people living with HIV, will help in the control of tuberculosis," said Prof. Mukadi.

Notably, several years earlier, Prof. Williams and Prof. Christopher Dye had published a modelling study concluding that starting ART at a CD4 cell count above 500 cells (with coverage and adherence, taken together, exceeding 85%) would reduce the lifetime risk for TB in HIV-positive individuals by more than two-fold.[5]

The year after the meeting in Cancun, Prof. Williams and other scientists at the World Health Organisation published a study modelling the impact of testing everyone once a year on average, and starting those who test positive on ART at different times following infection or at different CD4 cell count thresholds.[6] The model drew on real world data on time trends in HIV prevalence and TB notification rates from nine countries in sub-Saharan Africa. The model concluded that with virtually universal annual HIV testing, if PLHIV were to start ART within five years of HIV seroconversion, by 2015, the incidence of HIV-related TB could be reduced by 48% (range: 37–55%). If the time between seroconversion and starting treatment is accurate, by 2050, if treatment is started 5, 2, or 1 years after HIV seroconversion, or as soon as people test positive, the incidence of TB would be reduced by 66% (range: 57–80%), 95% (range: 93–96%), 97.7% (range: 96.9–98.2%) and 98.4% (range: 97.8–98.9%), respectively.

A brilliant review article *'Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it?'* (which covers the available data in much more detail than we can here from biological studies, observational studies, randomised controlled trials, population level studies within communities, as well as modelling studies) was published by Stephen Lawn and colleagues in the *International Journal of Tuberculosis and Lung Disease* in May this year. The authors note that there are limits to the potential benefit of ART for TB prevention, given vagaries of adherence, achievable coverage, poor infection control and so on,[7] but were generally optimistic that earlier ART might even contribute to the control of multi- and extensively drug-resistant TB, M/XDR-TB.

"The overall message is clear. The earlier ART is started, the greater the potential for prevention of HIV-associated TB, including drug-resistant disease," they wrote. "However, unless there is a significant shift towards initiation of ART at much higher CD4 cell counts than is currently happening, much of the potential of ART for TB prevention will be squandered. Much bolder approaches to ART implementation are required."

New data on ART and TB prevention at IAS 2011

However, at the recent IAS 2011 meeting in Rome, while there were data that would seem to support the rationale of earlier ART for TB prevention — the clinical data from a 'test-and-treat' study do not appear to be as supportive as at first glance.

TB incidence data from the Cascade study

One study, which better characterised the risk of TB in people living with HIV at different stages of HIV disease, would seem to support the early ART rationale.

The risk of developing TB disease rockets up *soon* after HIV seroconversion but, again, although ART reduces the risk of TB when it is given late in the course of disease, the risk of TB still remains higher in people living with HIV than in the general population — even in low burden settings according to a study presented by Sara Lodi, a statistician at the National Institutes of Health at Carlos III Hospital in Madrid, Spain.[8]

The findings emerged from an analysis of the evolving risks of TB over time in CASCADE, a major natural history study launched in 1997, that followed a large cohort of HIV-positive people, mostly from Europe, Australia, and Canada, from HIV seroconversion over the course of their lives, and through treatment until death. Even though the data came from mostly upper-income countries with a low burden of TB in the general population, many of the study's findings still have bearing on TB prevention strategies everywhere. In a sense, the picture of TB risk in the CASCADE is conservative. PLHIV in higher TB burden settings would be at a greater absolute (if not relative) risk of TB, because of the greater and ongoing risk of exposure to TB in the community (and possibly, the clinic).

The analysis included 9175 people in the 'pre-ART' cohort at risk of TB. It found that the risk of developing active TB was already dramatically higher during the first year after seroconversion — around 6 cases per 1000 person years, much higher than the annual risk in the general population in the study countries which ranged from 0.05 to 0.2 cases per 1000 person years. (Use of isoniazid preventive therapy was not common in this study.) Then the risk fell, somewhat, to about 3-4 cases per 1000 person years in the third year after seroconversion, but remained many times higher than the general population (not merely two-fold higher as in Cape Town).

After that point, the risk of TB rose with each passing year. The risk of TB grows both with time, and with declining CD4 cell counts. Notably, even at the highest CD4 cell strata assessed (≥500), the risk of TB was dramatically greater than in the general population; it further increased but not profoundly while CD4 cell counts were between 350-500. The risk then doubled in the 200-350 CD4 strata and worsened dramatically once CD4 cell counts fell lower. (This is by far the most definitive study on the subject but number of other smaller studies of specific cohorts (such as gold miners in South Africa) support these findings).[9,10,11,12,13]

The trend and implication is apparent. In late stage HIV disease, the risk of TB is clearly profound — but there is no stage of disease when a person living with HIV is not at higher risk of TB.

"The risk of TB increases over time, from HIV seroconversion on, so prevention interventions should be implemented early in the course of infection," said Dr Lodi. Consequently, these findings provide strong evidence of the importance of early HIV diagnosis for anyone infected with HIV.

These interventions very clearly include ART. Data from over 11,000 individuals who eventually began ART were available for the analysis in the cohort. The effects of ART on TB risk were not apparent in the first few months— possibly due to TB-IRIS or unmasking of TB in the process of becoming active disease. There is a bit of a jump in TB diagnoses shortly after starting ART in people who commonly present late for treatment. Thereafter, however, the risk of TB dropped sharply; and from year 2 onward, the risks were lower than at any point since HIV infection (2 per 1000 person years). Nevertheless, even on ART, in this cohort (which was not as likely to be re-exposed to TB as populations in high TB burden settings), TB incidence still remained significantly higher than in the general population.

As Dr Stephen Lawn said during a Meet the Experts session at the 43rd Union World TB Meeting in Lille, France, a few weeks ago, "ART does not return TB risk to background levels."

It should be mentioned that some of the increased risk in CASCADE could have been due to the fact that some of the cohort were from key populations with a higher risk of TB than the general population (such as people who inject drugs, who have a 3.76 fold greater risk). However, the drug injecting population only made up about 13% of the cohort that initiated ART so it is unlikely to explain the whole effect.

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As for reducing the risk in the cohort on ART, having a higher current CD4 cell count (above 500), and having a lower viral load at the time of ART initiation were both associated with having a lower risk of developing TB (while time-weighted mean CD4 cell count or nadir CD4 cell count were not).

"TB prevention would be improved by antiretroviral policies that minimise the time spent with low CD4 cell counts," said Dr Lodi.

Notably, however, in the CASCADE study, the risk of being diagnosed with TB was significantly higher in someone not on ART than someone on ARTeventhough he or she might have exactly the same current CD4 cell count. Dr Lodi postulated, therefore, that the reduction in the risk of TB after ART may not be entirely due to its effect on CD4 cell counts or immune restoration. It is possible that viral replication or the chronic inflammation that results from viral replication might be part of what increases the risk of TB in PLHIV not on ART.

"Viral load *is* a strong independent risk factor for prevalent TB pre-ART," Dr Lawn told HATIP recently. "In a recent unpublished analysis of long-term follow-up of the Gugulethu cohort (median 5 years), VL >1000 on ART is an independent predictor of TB having adjusted for current CD4 count. Thus I agree that unsuppressed virus is 'bad' with regards to TB risk."

If that is the case, it would lend further support to the argument that ART could have TB preventive effects when initiated at any stage of HIV disease, reducing the risk of developing TB even at high CD4 cell strata — at least in theory**.**

TB in HPTN 052

In practice, there may be some problems with this strategy, as demonstrated by anomalous TB findings in HPTN 052.

The HPTN 052 study is of course, best known for demonstrating that antiretroviral therapy (ART) that effectively suppresses viral load also dramatically reduces the risk of HIV transmission from someone with HIV to their sexual partners (by 96% in that study). But the same study also looked for differences in clinical outcomes between the participants who started ART with CD4 cells between 350 and 550, and those who started later. Consequently, there was considerable excitement at IAS in Rome, when the clinical outcome data from the HPTN 052 study were to be presented — to see whether these clinical data would also support earlier treatment.

And at least initially, they seemed to: the investigators reported that early treatment reduced serious illness by around 40%, but there was no significant difference in deaths, or in the rate of serious bacterial infections. The effect was almost entirely accounted for by fewer cases of extrapulmonary tuberculosis (mostly abdominal and lymph node TB).

The study got a standing ovation but left some people scratching their heads over how to interpret the TB data.

The first problem was that extrapulmonary TB is usually difficult to diagnose and usually not the first manifestation of TB that is seen in PLHIV — in fact, it tends to occur in later stages of HIV disease. The second quandary was that there was no difference in the incidence of pulmonary tuberculosis between the study arms — the manifestation of TB more likely to be seen at higher CD4 cells.

There were thirty cases of pulmonary TB diagnosed, 14 cases in the immediate-treatment arm (0.8 per 100 PY), compared with 16 in the delayed-treatment arm (0.9 per 100 PY). What was also peculiar was that the pulmonary TB was diagnosed at dramatically different CD4 cell counts — these were very high in the immediate treatment arm.

The reduction in extrapulmonary TB in the study really is ***unexplained*** and the lack of effect on pulmonary TB seems to be a failure of the ART for TB prevention approach. Many of the TB researchers we've spoken to thus far remain puzzled.

"This is an interesting observation but it is not clear why extrapulmonary TB should be preferentially reduced," Professor Gavin Churchyard told HATIP when the study results were first presented.

There is also some inconsistency between sites or regions, as NAM's senior editor Keith Alcorn pointed out: "55% of the extrapulmonary TB was diagnosed in India, despite the fact that only 24% of participants were recruited at Indian sites. It would be interesting to see whether the result remains statistically significant if analysed by region."

Abdominal TB may be more frequent in India, or it could be that Indian physicians are simply more adept at diagnosing it.

"Or it could be because the Indians use ultrasound to diagnose extrapulmonary TB," Professor Liz Corbett of the London School told HATIP. "The Indians swear by it."

Indeed, the literature contains numerous references from India to ultrasound-guided extrapulmonary TB diagnosis, sometimes with ultrasound-guided lymph node biopsies and culture confirmation, sometimes without. It may be that this is an early manifestation of TB that has simply been under-explored in other settings.

Dr Annelies Van Rie of University of North Carolina School of Public Health noted, however that "The higher rates of EPTB in India are not just because they may be looking for it more [thoroughly] in India. Higher rates of EPTB are also found among Asian-born individuals living in the US — but because this was an randomised controlled trial (RCT) (though not blinded) the assessment should be the same in both groups."

But the failure to reduce pulmonary TB remains very problematic.

Some reviewers of this article pointed out that perhaps the length of follow-up, at 1.7 years, was too short— and that with longer follow-up there would have been more pulmonary cases in the delayed arm since more of that cohort would have lower CD4 cell counts and thus be at greater risk. Slowing the progression to AIDS, should in the long run, lead to fewer TB events.

But in the short run, ART did not appear to prevent pulmonary TB very well in PLHIV with high CD4 cells. Something most other reports have missed was that much of the TB was being diagnosed at *very* high CD4 counts in the early treatment arm of HPTN 052. The median CD4 count at the time of diagnosis of pulmonary TB in the early treatment arm was 521, compared with 295 cells in the delayed arm.

Interestingly, TB wasn't the only respiratory infection occurring at high CD4 cell counts in the early versus delayed treatment groups. Cases of bacterial pneumonia occurred at a somewhat higher rate in the early treatment arm (see event table), but again at very different median CD4 counts (551 vs. 337 CD4 cells).

There is also a risk that the TB cases are being acquired in the clinic where people are receiving 'early ART' and this may be offsetting any anti-TB benefit that ART might offer in people with higher CD4 cells. If this is the case, it might be remediable by making sure good infection control measures are in place, or by moving away from facility-based management, and trying to treat people in their communities and homes. However, we also need better TB control in the community — one of the other compelling posters at IAS showed that the majority of new TB infections were recently acquired and more than half came from HIV-negative index cases in a periurban Cape Town community.[14]

HPTN 052 Clinical Endpoints*, by Arm – HIV-1 Infected Participants[15]

	Total	Early Arm	Delayed Arm
Total Number of Events [1]	129	53	76
Mycobacterium tuberculosis, pulmonary [2	30	14	16
Bacterial infections, severe	27	16	11
Death	23	10	13
Mycobacterium tuberculosis, extrapulmonary	20	3	17
Herpes simplex, chronic	10	3	7
Bacterial pneumonia, recurrent, severe	4	2	2
Oesophageal candidiasis	4	2	2
Cervical carcinoma, invasive, confirmed by biopsy	2	0	2
Kaposi's sarcoma	2	1	1
Wasting syndrome due to HIV associated with either chronic diarrhea or chronic weakness and documented fever >= 1 month	2	0	2
Cryptococcosis, extrapulmonary including meningitis	1	1	0
Encephalopathy, HIV-related	1	0	1
Lymphoma, Burkitt, immunoblastic, primary central nervous system/cerebral, B cell non Hodgkin	1	0	1
Pneumocystis pneumonia	1	0	1
Septicemia, recurrent, including non-typhoidal Salmonella	1	1	0

*The clinical endpoints include WHO stage 4 events, mycobacterium tuberculosis pulmonary or severe bacterial infections.

[1] A total of 105 participants had at least one clinical event; 15 participants had two or more distinct clinical events. If a participant had multiple events during study follow-up, then all events are counted in this table.

[2] Thirteen (13) people in the early arm had 14 cases of pulmonary TB, and 15 people in the delayed arm had 16 cases of pulmonary TB.

HIV-1 Infected Participants with Two or More Distinct Clinical Events

	Total	Early Arm	Delayed Arm
Combination of Events (Total)	15	7	8
Bacterial infection, severe / TB	3	3	0
Bacterial infection, severe / extrapulmonary TB	1	0	1
Bacterial infection, severe / Bacterial pneumonia, recurrent, severe / TB	1	0	1
Bacterial infection, severe / Bacterial pneumonia, recurrent, severe / Oesophageal candidiasis	1	1	0
Bacterial infection, severe / Septicemia, recurrent	1	1	0
Bacterial infection, severe / Death	2	1	1
Herpes simplex, chronic / TB / Death	1	1	0
Lymphoma, Burkitt, immunoblastic, primary central nervous system/cerebral, B cell non-Hodgkin / extrapulmonary TB	1	0	1
TB / Death	2	0	2
Bacterial pneumonia, recurrent, severe / TB / Death	1	0	1
Encephalopathy, HIV-related / extrapulmonary TB	1	0	1

*See Footnote # 2 in the "Clinical Endpoints by Arm – HIV-1 Infected Participants" table above, indicating that two individuals had two cases of pulmonary TB over time; those cases are not counted in this table as they are the same event.

Dr Van Rie told HATIP she does not believe that this could have been the case in a randomised controlled trial. "People went to the same clinics, and had the same number of clinic visits." Indeed a review of the protocol shows that participants in both arms visited the clinic on a monthly basis.

However, there were differences in those visits depending on whether one was taking ART or not. For instance, those on ART, especially early ART, required toxicity screening and management, and would have made unscheduled visits due to adverse events,

which appeared to have been more common in the early treatment arm. Those taking ART early would have also spent more time in the clinic for adherence training and support. They also would have had to wait in the facilities' pharmacies to pick up their medication. So it is possible that they spent more time in parts of the healthcare facility where there was more risk than those on deferred treatment who only made brief clinic visits for their lab work.

If the high burden of pulmonary TB in the early ART arm was not attributable to poor infection control, then we may need to go back to the basic science drawing board, to develop a better understanding of the deficit of TB immunity in PLHIV — and find a better remedy. Research should investigate whether chronic inflammation due to HIV, or other viral factors, also increases the risk of TB, or whether there is some other specific defect in immunity that could become established during primary HIV infection. If so, it may be worth investigating anti-inflammatory or immune-modulatory factors in people who remain at greater risk of TB despite ART, or who do not yet qualify for ART.

Is there a continued need for IPT in patients on ART?

If they are receiving ART in a clinic setting in a setting with a high burden of TB/HIV, PLHIV may need adjunctive TB preventive therapy even at high CD4 cell count and/or on stable ART to reduce the elevated risk of TB.

Of course, isoniazid preventive therapy (IPT) is the most obvious option, and is recommended by WHO.[16] As another paper by Lawn et al concluded, "We propose that these two interventions [IPT & ART] might best be used as complementary strategies at different stages of HIV progression. At relatively high CD4 cell counts, IPT has been shown to reduce tuberculosis risk 33% (95% CI 13–49%) in patients not stratified by TST status, and by 64% (95% CI 39-78%) in patients with positive tuberculin skin tests, and is the key tuberculosis preventive intervention before patients are eligible for antiretroviral therapy."[17]

WHO guidelines don't require a tuebrculin skin test (TST) given the difficulty of providing it in some settings, and if TSTs are not readily available, WHO strongly recommends people living with HIV in high TB burden settings should take a six-month course of IPT treatment. Indeed, it would seem advisable to take a course of IPT to be on the safe side.

The WHO guidelines also made a conditional recommendation to consider 36 months (or lifelong) IPT for people living with HIV in settings where there is a high risk of TB transmission. But this is how that recommendation is explained in the guidelines: "Given the preliminary and scanty nature of the evidence, feasibility concerns and potential adverse events, the Guidelines Group conditionally recommends 36 months' duration of IPT for people living with HIV in settings with high TB prevalence and transmission, as determined by the local context and national guidelines."

With this less-than-strong endorsement, it is more likely that, before committing to life-long therapy, people living with HIV may want to know that they are TST-positive, and therefore likely to benefit from taking it.

It is worth reviewing the evidence from the two studies that this guidance is based upon. One, the BOTUSA study in Botswana, included participants with a wide range of CD4 cell counts, though the median was 297. TST responses to TB are lost as CD4 cell counts fall, so going by the percentage of TST-positive participants at higher CD4 cell counts, at least a third of this population in the study were probably latently infected with mTB, even if it didn't show up with TST at the lower CD4 cell counts.[18] But the protective effects of IPT were only seen in the TST-positive participants.

There are at least two possible reasons why IPT does not show much effect in TST-negative people. One is that most TST-negative people are not latently infected, and so there is no infection for IPT to prevent from activating. The remaining TST-negative people are anergic — they have been exposed and infected with m.TB, but their TB-specific immune response is too weak to react. Continuous IPT did not help these people in the same way it did for those who were TST-positive. Anergy is generally found in more advanced patients, so the investigators suggest their weak immune systems may have been to blame.

One of BOTUSA's findings was that new cases of TB sprung up very quickly in part of the population that was randomised to stop taking IPT after six months (as opposed to those who took it for 36 months). Investigators suggested that those who stopped taking IPT had high rates of exposure to TB in that setting and that is why they began to develop TB quickly after IPT discontinuation, and that continuous IPT was preventing new infections.

But if that were the case, one would think its effect would have been seen in the TST-negative population — among those with higher CD4 cell counts, most were probably not latently infected — but coming from the same communities, attending the same facilities, they should have had similar risks of becoming exposed to TB. One would have expected to see at least some effect of continuous IPT in this much larger population at risk. The investigators offer only circumstantial evidence in support of their supposition that continuous IPT was preventing new infections, and this is what the recommendation is based upon.

Another possibility is that six months of IPT was simply not enough to clear latent TB in people with advanced immune deficiency, and who may have had issues with food security and malnutrition as well. While the WHO guidelines cited a Cochrane Analysis of all the studies of IPT in people living with HIV, which could find no difference between 6 or 12 months of IPT, adherence problems were rife in many of the early IPT studies, weakening their ability to reach such a conclusion.[19]

Moreover, the Cochrane Analysis simply ignores the large pivotal study in the 1980s of IPT in 28,000 presumably HIV-negative people, who should if anything, *be much easier to treat*. That study suggested that 12 months of IPT is more effective in the on-treatment analysis.[20] Similarly, a review by Professor George Comstock of all the IPT studies in immune-competent individuals concluded that: 1) 6 months of preventive treatment does not give optimal protection; 2) 9-10 months appears to be the optimal duration.[21]

This is clinically relevant information even if it wasn't included in the guidelines decision-making process.

The second study cited in the WHO ICF/IPT guidelines, was performed in South Africa (an equally high-burden setting) in only TST-positive people. The CD4 cell count was significantly higher (median 484) at baseline — much closer to the CD4 cell counts of people going onto early ART in HPTN 052.[22] In this population, Martinson et al didn't find a statistically significant difference between the six-month course and continuous IPT — (though continuous IPT was associated with a lower TB incidence), but the study did report a significantly worse rate of serious adverse events in the continuous IPT arm. Note, this study compared both IPT arms to other combination preventive regimens lasting only three months, and found no statistically significant difference, even though people in those arms would have spent most of their follow-up not on a preventive regimen.

The BOTUSA investigators did offer one interesting theory as to why IPT works in TST-positive patients but doesn't work in anergic people living with HIV: a tuberculosis-specific immune response may be needed to synergise with isoniazid's bacteriostatic effect on TB. People with higher CD4 cell counts still have these responses, and in this population, IPT should be more effective.

But if the BOTUSA investigators are right, and continuous IPT was preventing new TB infections, it is not clear that the risk in a population with advanced HIV is applicable to the population with higher CD4 cell counts. On the other hand, the number of cases of pulmonary TB in HPTN 052, is enough to make one pause.

When asked about his research for a previous edition of HATIP, Dr Neil Martinson told us: "Yes, preventive treatment does protect against TB in a high TB incidence setting. Firstly, multiple clinical trials from sub-Saharan Africa show that without preventive treatment, rates of TB are higher in those who did not receive it. Moreover rates of TB in people in Soweto from an observational study who did not receive IPT are just under double those in people who did get IPT. But ARVs are the key. IPT has no impact on mortality and has a low durability — get people on ARVs!"

At the 2011 Union World Conference on Lung Health in Lille, Dr Lawn stressed that IPT and ART are complementary:

"ART is the key preventive intervention at CD4 counts below 350 cells. IPT is the key intervention at CD4 counts above 350 cells in TST+ individuals. But during long-term ART, IPT is probably needed in addition to ART.

Expert discussion

Given the importance of the issue, HATIP asked our advisory panel and other TB/HIV experts the following questions:

1 Do you believe in that earlier ART or immediate ART may still have a significant role for TB prevention above and beyond treating at the 350 CD4 cell threshold?
2 What should be done to reduce the risk of TB in PLHIV: (a) at higher CD4 cell counts? (b) on ART?
3 Are there other modalities to reduce the risk of TB in PLHIV?
4 Do you have any other explanations for the HPTN 052 findings?

1. Do you believe that earlier ART or immediate ART may still have significant a role for TB prevention above the 350 CD4 cell threshold?

Professor Anthony Harries, International Union against Tuberculosis and Lung Disease:
Yes, although I believe this TB preventive effect of ART diminishes as the CD4 count increases. However, I believe one must dissociate the public health strategy of placing HIV-infected people early on ART from the individual practice of doing this. At the individual level, the TB preventive effect may be modest – however, at the individual level you also have to take into account the other benefits of early ART (reduced HIV transmission to sexual partners and newborn children, treatment for Hepatitis B and so on). At the population level, a strategy of early start of ART will ensure many more people starting ART before catastrophically low CD4 counts develop, and this also gets us away from the undoubted barrier in low-income countries of trying to get CD4 count measurements done to determine eligibility for ART.

Dr Annelies Van Rie, University of North Carolina School of Public Health
: At this point in time, I do not think we have good evidence to support ART > 350 for TB prevention. We need to wait for results of the other ongoing trials.

Dr Halima Dawood, Grey's Hospital, Pietermaritzburg, South Africa:
I think this effect is limited by other factors: exposure to TB and the nature of immune reconstitution, socio-economic factors and nutrition, for example.

Professor Diane Havlir,
University of California, San Francisco: The 052 study is the primary new information to inform your questions. As you know this study was a RCT, the gold standard, conducted in areas of high TB prevalence. In an ITT analysis it showed that ART provides protection against AIDS/TB for persons with CD4 up to 550. Of note, even with the fact that the follow-up was relatively short because of the profound impact that ART had on HIV transmission, the protection afforded by ART was impressive. Multiple cohort studies summarised by Lawn, et al bolster these data and show that ART protects against TB.

TB is a leading killer of persons with HIV—the evidence tells us that ART given to persons up to a threshold of CD4 550 prevents AIDS and TB (including MDRTB) – policy and guidelines should incorporate this evidence now. Of course implementing will be a challenge, but that should not prevent policy from incorporating new evidence.

Professor Gavin Churchyard, Aurum Institute for Health Research:
"I still can't explain why there may be a differential effect on extrapulmonary TB, but I am not sure this was an appropriate analysis strategy. The key message should remain that ART reduces TB risk based on 052 and the observational data."

Dr Annelies Van Rie:
I agree with Diane with respect to activism and engagement. There is lots of data to support early initiation of ART and we should all advocate for that.

The issue to debate is whether we have sufficient data to use prevention of TB as an argument for early ART (meaning ART above 350)? The best data we have is the RCT HPTN 052, which is puzzling. EPTB was prevented, pulmonary TB was not. This is an unexpected finding and hard to explain. I have not yet read any clear hypothesis to explain this finding.

Some have stated that one could use the argument that ART is needed because people with TB transmit, but people with EPTB are less infectious, so to prevent transmission of TB, early ART would need to prevent pulmonary TB, which, based on the only RCT data we have, it does not.

Some have raised the issue of mortality. Data suggest that people with HIV and *diagnosed* TB who receive ART do not have higher mortality rates than those who start ART and do not have TB. The mortality rate of people with TB on ART is driven by *undiagnosed* TB, and among those treated for TB mortality is driven by CD4 count. As such we see strong differences in mortality between major studies of ART in people on TB treatment: SAPIT, STRIDE and CAMELIA. Mortality in people with TB and high CD4 count (> 350) may not be substantially different from HIV-negative individuals with TB, although the data are again limited.

Professor Wafaa El-Sadr,

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Columbia University and the International Center for AIDS Care and Treatment Programs (ICAP): I agree with Diane that HPTN 052 as a randomised clinical trial is the most rigorous source of evidence. However, I have to say that the results of HPTN 052 are very surprising and puzzling to me as they do NOT provide a strong support for the value of early ART on prevention of TB.

Pulmonary TB is a much more common condition than extrapulmonary TB as well as easier to diagnose. Thus, if the hypothesis is that early ART prevents TB, then one would have been much more likely to see a significant effect on pulmonary TB. The lack of such an effect on pulmonary TB (similar number in both arms of HPTN 052) is very puzzling to me and is not consistent with prior findings from observational data (which of course have all the usual limitations and biases).

2. What should be done to reduce the risk of TB in PLHIV at: (a) higher CD4 cell counts? (b) On ART?

Professor Anthony Harries:
I am a believer in early start of ART not only to reduce the risk of TB but for the other reasons mentioned above. If this early ART strategy is not adopted, it makes sense to give IPT but I would only do this within the structure of a pre-ART clinic where the intervention can be monitored. I am totally against giving it out as a free-for-all.

In relation to patients on ART there are three important issues here – a) regular symptomatic screening for TB every time the person attends the clinic with diagnostic action if the symptom screen is positive – in this way active screening and diagnosis and treatment of those with TB; b) good infection control, as the last thing we want is to expose persons on ART to nosocomial TB transmission; c) consideration of IPT. For how long though is a moot point; despite WHO recommending TDF with a phasing out of d4T, this will be very difficult in the current economic climate and the interaction between isoniazid and d4T is significant.

Dr Annelies van Rie:
For patients on ART I think there is a body of evidence for IPT, but I'm not convinced that there is sufficient evidence for people stable on ART with higher CD4 counts. For patients with higher CD4 cell counts I would definitely support IPT for those not yet eligible for ART.

Dr Halima Dawood:
For patients at higher CD4 cell counts, good TB control at a population level. For patients on ART, ensuring adherence to ART and good nutrition.

Dr Stephen Lawn:
Viral load is a strong independent risk factor for prevalent TB pre-ART. In a recent unpublished analysis of long-term follow-up of the Gugulethu cohort (median 5 years), VL >1000 on ART is an independent predictor of TB having adjusted for current CD4. Thus I agree that unsuppressed virus is 'bad' with regards to TB risk.

3. Are there other modalities to reduce the risk of TB in PLHIV?

Professor Anthony Harries:
Of course we need to consider IPT. I still think this will be a major challenge for a number of reasons: a) Where are the structures to deliver this? b) The effect of IPT comes for those who are TST-positive, and getting TST performed and the skin test read in the routine setting is nearly impossible.

HATIP:
The capacity to perform TSTs of course varies by setting; and even those settings which can provide TSTs can have difficulty getting patients to return to the health facility to have their reactions measured. For this reason, WHO guidelines state that TST are not required to provide IPT since it could serve as a barrier to accessing treatment.

Dr Halima Dawood:
"This issue needs to start with prevention of HIV in addition to TB. Once a person is HIV infected, we need to ensure health care is optimised to prevent TB and if TB disease occurs, we provide rapid treatment and containment of disease, along with contact screening. I know it may sound simplistic but we are not doing the basics optimally."

Dr Annelies van Rie:
Investing in basic TB control! We know that a lot of the sources of transmission of TB are HIV-negative individuals with TB in the community and HIV-positive individuals in health care settings, so good TB control with early diagnosis (intensified case finding) and optimal treatment for all individuals with TB (HIV-positive and negative) is essential. In addition, contact tracing at household level, coupled with HIV testing (as done in Zambart [the ZAMSTAR study) is an intervention that could identify people with TB earlier, as well as unknown HIV among contacts with TB who would definitely benefit from IPT(and ART if CD4 < 350).

HATIP:
Indeed, this ties in well with a paper presented by Middelkoop et al at IAS that found that most of the TB in people living with HIV in that peri-urban community near Cape Town was recently acquired, and that the source/index case was most commonly an HIV-negative individual — suggesting that it is in the vested interest of people living with HIV to make certain ALL TB is detected, diagnosed and treated early.

4. Do you have any other explanations for the HPTN 052 findings?

Dr Annelies Van Rie:
I am also puzzled by the HPTN results. The only thing I can think of is differential assessment practices by CD4 count. There was no standard operating procedure for EPTB across sites for assessment of EPTB. If you are more thorough in screening for EPTB in patents with low CD4 counts (a practice that makes sense given the higher risk of EPTB in people with low CD4 count), then you may find more EPTB in those in the delayed arm.

If all cases of EPTB were truly EPTB, then this would not matter, as those who you do not diagnose would develop symptoms over time and be diagnosed later (one would think). No information is given whether cases were confirmed microbacteriologically, which is often the case for lymph node and especially abdominal TB.

My hypothesis is that there was not differential assessment by arm, but by CD4 count, which results in differential assessment by arm over time

So, if there was a bias in assessing for EPTB based on CD4 count (which differed over time between groups and was lower in the delayed group) *and* patients were started on treatment for non-bacteriologically confirmed EPTB *and* not all patients treated empirically actually had EPTB, *then* one could see this difference without there truly being a difference in EPTB rates.

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Professor Wafaa El-Sadr:
Why an effect was noted only for extrapulmonary TB, I do not know. But the absence of an effect on pulmonary TB (as indicated above) makes me worried that the difference noted in extrapulmonary TB was due to chance or ascertainment bias. In addition, my understanding is that none of the extrapulmonary TB cases were microbiologically confirmed. So provider differences in their suspicion level for extrapulmonary TB at the various sites could have influenced this finding. It is also important to keep in mind that HPTN 052 was not a blinded study and of course this can influence provider behavior, and ascertainment practices. For example, were providers were more likely to think of extrapulmonary TB in patients not on ART versus believing that those on ART (in the early ART arm) were "protected" from TB?

The findings from HPTN 052 actually raise questions about the findings shown in the observational studies in terms of effect of early versus delayed ART on TB incidence. While many of these studies were excellent, they suffer from inherent and unavoidable limitations.

Dr. Stephen D. Lawn, London School of Hygiene & Tropical Medicine & Desmond Tutu HIV Centre, Cape Town:
Regarding HPTN 052. I note the scepticism expressed by others regarding the TB end-point. I haven't had chance to look at the study protocol in detail. My impression of the study is that the HIV transmission end-point was very, very rigorously assessed. Well done to them. I strongly suspect that the same rigour did not apply to the TB end-point and that this was probably not standardised across the study sites. HIV acquisition is extremely simple to assess regardless of the study setting; TB is not. I think the takeaway message is that overall TB was reduced by early ART. More detail from the investigators is needed to understand this better.

Professor Anthony Harries:
With regards to HPTN 052 we do not know enough from the paper. If I combine PTB and EPTB then we have 16 TB cases in the early therapy group with 1580 person-years of follow-up (which gives a TB rate of about 1% per annum or 1,000 per 100,000 per year) and we have 32 cases in the delayed therapy group with 1580 person-years of follow up (which gives a TB rate of about 2% per annum or 2,000 per 100,000 per year). **These are huge rates of TB**! I think to understand HPTN 052, we need more data on the TB side.

Conclusion

We presented this discussion in its entirety because there appears to be no consensus on what to make of HPTN 052's TB-related findings at present. Clearly, we need to see more data from this and other studies. based on the data discussed in this article our bias would be that early ART should be beneficial for a variety of reasons, but that it is clearly not enough to prevent TB in a surprisingly large number of patients. The rates of pulmonary TB in the people with high CD4 cell counts on early ART in HPTN 052 are sobering. Taken together, these observations suggest that:

1) In a high burden setting, doctors should perhaps not be complacent about the protection that ART offers, and dismissive of the potential value of IPT. Whether continuous IPT is necessary is debatable, and after an informed consent process, the patient should probably make the choice based upon their informed perception of risk.

2) Infection control in the healthcare setting is essential. People going onto early ART in HPTN 052 may have been at increased risk of exposure in the healthcare setting. In most healthcare facilities in resource-limited settings, each activity (adherence assessments and support, lab work, exams, picking up medications) would be preceded by a significant amount of waiting time. In this study, participants would have had to spend much more time in the facility than would probably occur in practice, and perhaps this explains the high rates of pulmonary TB, if infection control was not optimal. But it also raises the issue of whether early ART, or doing well on stable ART, needs to be taken out of health facilities crowded with sick people and instead delivered to them as far as possible in their homes, via community health workers, expert patient or home based care givers.

3) While universal access to treatment according to current WHO guidelines is still necessary, and will doubtless reduce the burden of TB and TB-related death, we need more data on how much early or immediate ART for everyone diagnosed with HIV with ART may improve TB control. Several other studies are investigating the question, so we should have a clearer answer in a few years. However, we need to make sure the other scheduled studies that look at ART for TB prevention studies, do it properly and do so quickly.

4) Finally, as Dr Dawood and Van Rie said, we need to be doing more of the TB control basics within the community to ultimately reduce the risk of TB for everyone, including people living with HIV.

References

[1] Lawn SD et al. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. AIDS 23: 1717–1725, 2009.
[2] Severe P et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. N Engl J Med 363: 257–265, 2010.
[3] Lawn SD et al. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. Lancet Infect Dis 2010; 10:489–498, 2011.
[4] Mukadi Y, Perriens JH. Spectrum of immunodeficiency in HIV-1-infected patients with pulmonary tuberculosis in Zaire. Lancet, 342:8864, 1993.
[5] Williams BG, Dye C. Antiretroviral drugs for tuberculosis control in the era of HIV/AIDS. Science 301:1535–1537, 2003.
[6] Williams BG et al. Antiretroviral therapy for tuberculosis control in nine African countries. Proc Nat Acad Sci USA 107: 19485–19489, 2010.
[7] Lawn SD et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? Int J Tuberc Lung Dis 15(5):571–581, 2011.
[8] Lodi S et al. Risk of tuberculosis following HIV seroconversion in low-burden tuberculosis countries. IAS 2011, Rome.
[9] Sonnenberg P. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. J Infect Dis 191: 150–158, 2005
[10] Glynn JR. Effects of duration of HIV infection and secondary tuberculosis transmission on tuberculosis incidence in the South African gold mines. AIDS; 22: 1859–1867, 2008.
[11] Holmes CB. CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: implications for prophylaxis and treatment. J Acquir Immune Defi c Syndr 42: 464–469, 2006.
[12] Holmes CB. CD4 decline and incidence of opportunistic infections in Cape Town, Antonucci G. Risk factors for tuberculosis in HIV-infected persons. A prospective cohort study. The Gruppo Italiano di Studio Tubercolosi e AIDS (GISTA). JAMA 274: 143–148, 1995.
[13] Badri M. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. Lancet 359: 2059–2064, 2002.
[14] Middelkoop K et al. Transmission of TB in a high HIV prevalent South African community. IAS 2011, Rome.
[15] Cohen M et al. Prevention of HIV-1 infection with early antiretroviral therapy. New Engl J Med 365:493-505, 2011.

[16] WHO. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, 2011.
[17] Lawn SD et al. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. Lancet Infect Dis. 10(7):489-98, 2010.
[18] Samandari T et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. The Lancet 377: 1588-98, 2011.
[19] Akolo C et al. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database of Systematic Reviews, 1:CD000171, 2010.
[20] International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bull World Health Organ. 60(4): 555–564, 1982.
[21] Comstock GA et al. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults?Int J Tuberc Lung Dis. 3(10):847-50, 1999.
[22] Martinson NA. New Regimens to Prevent Tuberculosis in Adults with HIV Infection. N Engl J Med 365:11-20, 2011

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