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Treatment as prevention works!

By Keith Alcorn

UNAIDS says finding is 'serious game changer' for HIV prevention

A large randomised study of treatment as prevention has closed more than three years early after interim analysis of the data showed that antiretroviral treatment reduced the risk of HIV transmission from treated partner to uninfected partner by 96%.

The magnitude of the reduction in risk is almost the same as that observed in multiple cohort studies in sub-Saharan Africa, and is the strongest effect seen in any trial that has used an antiretroviral-based prevention method.

HPTN 052 is a large, international study which randomised 1736 male-female couples in which one partner was HIV-positive either to begin antiretroviral therapy immediately, or to wait until treatment was clinically indicated (at a CD4 count of 250 cells/mm³).

The study began enrolling participants in 2005 in Botswana, Brazil, India, Kenya, Malawi, South Africa and Zimbabwe, and recruited couples in which the HIV-positive partner had a CD4 cell count between 350 and 550 cells/mm³. The median CD4 count at the time of joining the study was 436 cells/mm³. This level is higher than the threshold at which World Health Organization guidelines currently recommend starting treatment.

The study was due to run until 2015.

The study was halted after an interim review by the Data and Safety Monitoring Board, which found that 39 infections had occurred. Twenty-eight could be genetically linked to the HIV-positive partner, and of these 27 occurred in couples where the HIV-positive partner did not begin antiretroviral therapy immediately. This translates into a 96% reduction in the risk of transmission. This result was highly statistically significant ($P < 0.0001$).

All participants received regular counselling on safer sex, free condoms and treatment for sexually transmitted infections.

The results of HPTN 052 show that treatment of people with relatively high CD4 cell counts results in very substantial reduction in the risk of HIV transmission.

The study also found a statistically significant reduction in the risk of extrapulmonary tuberculosis in the early treatment arm: 17 cases occurred in the deferred treatment arm, compared to 3 cases in the early treatment arm ($p = 0.0013$).

There was not a significant difference in the death rate, however: 13 deaths occurred in the deferred treatment arm and ten in the immediate treatment arm. There were 105 morbidity and mortality events: 65 events in the delayed treatment arm and 40 in the immediate treatment arm.

Reactions

Coming just ahead of the UN General Assembly Special Session on AIDS early next month in New York, these results are likely to give a powerful boost to messages that greater investment in HIV treatment could have a significant impact on the growth of the epidemic.

"This breakthrough is a serious game changer and will drive the prevention revolution forward. It makes HIV treatment a new priority prevention option," said Michel Sidibé, Executive Director of the

Joint United Nations Programme on HIV/AIDS (UNAIDS). "Now we need to make sure that couples have the option to choose Treatment for Prevention and have access to it."

"People living with HIV can now, with dignity and confidence, take additional steps to protect their loved ones from HIV," said Mr Sidibé.

"The upcoming UN High Level Meeting on AIDS should set treatment and prevention targets that take the HPTN 052 results into account," said Mitchell Warren of AVAC, an organisation which advocates for new HIV prevention technologies. "We need to start critical discussions and come to quick decisions about where and how to deploy treatment as prevention in the short-term. Government and international normative agencies now have a critical mass of data to publish guidelines for appropriate implementation of treatment as prevention in concert with other prevention methods."

"Today's result should be viewed in light of other recent findings from trials using ARVs for prevention," said Mitchell Warren. "The recent results from the iPrEx trial showed that PrEP is effective in gay men and transgender women, while the CAPRISA 004 microbicide trial showed that 1% tenofovir gel is effective at reducing HIV risk for women."

"Together, these results allow us to imagine a world in which men and women seek HIV testing with the knowledge and confidence that they will receive a range of highly effective options for staying healthy and protecting themselves and their partners—whatever the test result," Warren added. "The results of the study require us to rethink how we structure the delivery and funding of HIV services overall."

What do treatment as prevention study results mean for treatment?

By Keith Alcorn, Theo Smart

The findings of HPTN 052, the randomised study that recently demonstrated that [providing early antiretroviral therapy \(ART\) to HIV positive individuals reduced transmission of the virus to their partners](#), confirmed what many researchers had long been saying — that treatment of people living with HIV may be one of the most effective ways to reduce the spread of this virus.

Evidence has been accumulating ever since the advent of combination antiretroviral therapy that people with suppressed or undetectable HIV viral loads, especially those on therapy, are a great deal less likely to transmit HIV than untreated persons. But the evidence provided by HPTN is undeniable — early treatment profoundly reduced transmission by 96% and the study had to be terminated early because it was considered unethical to allow the placebo arm to continue.

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has published extensively on the background on the treatment as prevention, including the rationale, cohort studies, modelling and controversies in [a series of linked articles](#). However, there are a number of issues specific to treatment in sub-Saharan Africa and other low-income settings that need to be more fully addressed.

Although the findings of HPTN 052 were hailed as a 'game-changer' for global HIV prevention by UNAIDS, some

advocates are uncomfortable with the phrase. Firstly, people working in the field needed little convincing of the effects of treatment as prevention – but advocates are hoping that this study provides overwhelming evidence to convince funders to step up and provide the resources to reach targets for universal access to HIV prevention, testing, care and treatment (in a considered way that also strengthens global health in general).

The evidence may not be persuasive enough for some. Already some critics have pointed out that the findings only apply to people who have been identified as having HIV and put onto ART, and that, at a population level in sub-Saharan Africa, where most remain untested, and people with early infection remain undetected and highly infectious, the effects of treatment may not be as profound.

Furthermore, it is not a once-off intervention like circumcision, and some economists have suggested that providing life-long ART is too expensive an intervention to consider, when there are many other issues competing for funding in an era of budget cutting. As advocates, we need to be aware of these arguments, and realise there is still much for us to do to push our agenda.

But to the extent that these findings revitalise the fight against HIV, they are a potential ‘game-changer’ for treatment programmes. Indeed, without effective treatment programmes, any ‘game-changing’ effects of HIV treatment on prevention will not materialise.

The preliminary results of the study leave a number of unanswered questions regarding the impact of treatment on both new infections and on the health of people who receive earlier treatment. Indeed, it raises some immediate questions on the effect of early treatment on both the health – and the human rights – of people living with HIV.

What does this study tell us about the possible benefits to people with HIV of early treatment?

For treatment as prevention to work, the people taking the drugs need to be convinced that early treatment is in their interest.

Does this study provide convincing evidence that treatment should begin earlier than current guidelines recommend?

It should be emphasised out that early treatment in this study was defined as having between 350 and 550 CD4 cells, a stage at which other cohort studies have shown some health benefits, such as a delay in the progression to AIDS, but have not been able to conclusively demonstrate a survival benefit. As the first randomised study to study antiretroviral treatment in less advanced HIV infection HPTN 052 is likely to add to the evidence of early ART’s benefits.

HPTN 052 showed a very significant reduction in the risk of extrapulmonary tuberculosis among those who received earlier treatment, and also a trend towards less morbidity and mortality in the early treatment arm. Until these results are analysed in more detail we do not know whether the trend in morbidity events alone was significant, or what volume of health service utilisation was avoided by earlier treatment. These data may become available by the time of the International AIDS Society conference in Rome in July, or in a paper now being prepared for journal publication.

Nevertheless, the TB finding alone is likely to strengthen arguments for prioritising early treatment for HIV-positive people in order to prevent new TB cases. The finding that TB was significantly less frequent in people who were treated earlier extends [the finding of the CIPRA HT 001 study](#), which also found a reduced rate of tuberculosis among people who started treatment at a CD4 count between 200 and 350, when compared to treatment deferred until later. This finding adds further weight to the view that earlier

antiretroviral therapy is a very powerful means of TB control in settings where the burden of both HIV and TB is high.

It has also been argued that earlier treatment will reduce the risk of developing non-AIDS defining serious events such as cancers, heart disease or liver failure.

[A recently published study](#) comparing rates of non-AIDS defining serious events in the United States and Botswana found that the rate of such events was around twice as high in the Botswana cohort, with the difference driven chiefly by cardiovascular events and by non-AIDS-defining malignancies. This finding could be interpreted as illustrating the consequences of late treatment initiation, but further confirmatory studies are needed from other resource-limited settings before we fully understand the burden of non-AIDS defining serious events and the most important correlates.

It is unclear if HPTN 052 will be able to provide detailed information about the impact of earlier treatment on these outcomes in low and middle-income settings. Although the study collected data on these outcomes from 2007, it may not have sufficient statistical power because the study closed much earlier than expected. This may also have limited its power to detect differences in mortality and in morbidity. More information about the impact of earlier treatment on these outcomes will come from the Strategic Timing of Antiretroviral Therapy (START) study, which is comparing treatment initiation at CD4 counts above 500, or at 350.

We also need to know more about long-term toxicity of antiretroviral therapy in people with higher CD4 cell counts. HPTN 052 began recruiting participants in 2005, and initially used AZT/3TC plus nevirapine, efavirenz or atazanavir in the first-line regimen. HPTN 052 will be able to provide more information about drug toxicity in people with higher CD4 counts than most other major clinical trials, and will thus be a valuable source of information about the safety of earlier treatment in non-Caucasian populations.

The questions about the risks and benefit of early treatment also need to be considered in the context of the rights and needs of people with HIV. Although many people with HIV would agree that preventing transmission to sexual partners is an important reason for taking HIV treatment, there is a risk that urging earlier treatment onto people with HIV places the responsibility for transmission squarely on people living with HIV, rather than recognising that their sexual partners have an equal responsibility to protect themselves. This is particularly problematic in countries where there is growing willingness to use the criminal law to prosecute people with HIV for transmitting HIV – or even for failing to disclose their HIV status. How long will it be before legislators – or judges – conclude that failing to take available treatment should be considered as contributory negligence in cases of HIV transmission?

Challenges in translation

Any attempt to expand treatment still faces a number of bottlenecks, many of which are attributable to a lack of trained staff and a lack of health systems information. All of these are likely to be well known to readers of HATIP.

Performance at each of these stages needs to be maximised in order to achieve anything approaching the 96% reduction in transmission rates seen in HPTN 052.

- **Improving rates of diagnosis without coercion:** Even though awareness of the benefits of antiretroviral therapy is spreading in the worst-affected countries, reluctance to test for HIV is still widespread, and the median CD4 count at the time of diagnosis

remains very low. Improving the acceptability of testing for HIV, dispelling the stigma associated with HIV and informing people about the effectiveness of treatment will be critical steps in scaling up treatment so that it has an impact on new infections as well as illness and death. Models of community-wide testing that respect the rights of people not to test, and which ensure confidentiality, will be critical in achieving widespread uptake of testing.

- **Linkage to care and retaining people in care prior to ART:** referral from testing facilities and [retention in care of untreated people](#) continue to pose challenges for many treatment programmes. In some settings barriers such as co-payments for treatment and transport to clinics will pose problems.
- **Capacity to initiate patients onto treatment:** Even if rates of testing and diagnosis are high, this will have little or no effect in prevention terms unless people who are eligible begin treatment promptly. This is critically dependent on the capacity of the health system to start patients on treatment, and is likely to require task-shifting in order to expand the number of health care workers who can initiate and / or monitor treatment. Efforts to delegate prescribing or monitoring of antiretroviral treatment to nurses and other non-physician health care staff are at variable stages across sub-Saharan Africa, and will need much greater emphasis if health systems are to reach ambitious targets for treatment enrolment.
- **Proportion of eligible persons on therapy:** a [survey of cohorts in 8 PEPFAR focus countries](#) in sub-Saharan Africa showed that between 2005 and 2008 the median CD4 count at treatment initiation was 135 cells/mm³, indicating that any preventive benefit of ART would occur only after a long period of undiagnosed infection had elapsed. The proportion of persons on treatment will obviously depend on the CD4 threshold for starting treatment, and who is eligible to start treatment at what CD4 level.
- **Proportion of patients retained in care:** Some treatment programmes report high rates of loss to follow-up in patients who have already started treatment. In some cases patients are lost because they started treatment too late to save their lives, but in many cases [features of the treatment programme](#) are to blame.
- **Proportion failing therapy:** Although treatment failure and the risk of drug resistance has been held up as the great flaw in the 'treatment as prevention' model, treatment failure in people who remain engaged in care is likely to be less of a problem than loss to follow-up. Nevertheless, a better understanding of [which adherence interventions are most effective](#), and in which settings, will be critical in limiting rates of treatment failure. Earlier treatment carries with it the risk that if people fail treatment, they will require more costly second or third-line regimens. Early treatment without strong adherence support programmes and follow-up mechanisms poses the risk of earlier treatment failure and correspondingly greater costs in the future.

For all these reasons UNAIDS last year launched a new concept for thinking about treatment scale-up and the role of treatment as a prevention tool – Treatment 2.0. This has five components, or 'pillars':

- Creating a better pill and diagnostics: a fixed dose combination that has a low risk of toxicity, low monitoring requirements and a low risk of resistance would aid expansion of treatment, as would diagnostics that could be used anywhere to reduce the burden on health systems.

- Treatment as prevention as part of a combination prevention strategy.
- Stop cost being an obstacle by driving down the cost of treatment and monitoring
- Improve uptake of HIV testing and linkage to care
- Strengthen community mobilisation in order to improve the engagement in care of populations at high risk of HIV infection.

Treatment 2.0 provides an important aspirational goal for advocates, scientists, donors and policymakers, but the more immediate questions of how to address the bottlenecks that keep people off treatment and untested need to be resolved.

In a report to the South African parliament this week, Health Minister Aaron Motsoaledi showed that addressing the bottlenecks is, first of all, a matter of political will.

Although things are far from perfect in South Africa, the country has made dramatic progress in the past year towards scaling up treatment. As a result of a national campaign that has begun to treat the epidemics of HIV and TB as the country's number one health problem after years of political denial and bureaucratic torpor, South Africa has made dramatic progress in less than a year.

SOUTH AFRICA'S PROGRESS TOWARDS UNIVERSAL ACCESS

	Before June 2010	February 2011	Target
Numbers tested	2 million tests annually	11.9 million since June 2010	Further expansion of testing at village level, from June 2011
Health centres accredited to provide ART	490	2205	All 4000 health outlets by Dec 2011
Nurses accredited to prescribe ART	250	2000	4000 by Dec 2011
People receiving ART	923,000	1.4 million	3 million by 2015

For treatment to have any impact as a prevention method, this is the minimum level of political commitment and organisational response that will be necessary to achieve high levels of diagnosis and treatment coverage.

A more comprehensive approach that aims to test and treat an even larger proportion of the population will be tested in a number of field implementation trials now being planned, with the intention of evaluating the impact of early and widespread treatment on new infections, behaviour and HIV-related morbidity and mortality. The studies will also evaluate the cost-effectiveness of offering wider treatment, and the acceptability of offering the HIV test on a universal basis.

These include studies in Uganda and KwaZulu-Natal, together with studies that embed antiretroviral therapy within more comprehensive packages of 'combination prevention'. ([See list here](#)).

One challenge for future studies will be defining the components of a package of combination prevention. Contrary to the assumptions of many policymakers and donors, we still have remarkably little idea of the effectiveness of non-biomedical prevention measures in varying settings, or of how to tailor packages of combination prevention to local epidemic settings.

To take just one example, what should be the balance between investment in biomedical approaches such as circumcision and structural approaches such as empowering women and girls, and does this vary according to HIV prevalence? Although circumcision may result in a rapid reduction in risk of infection for men because it is a one-off procedure, it will not reduce the risk of infection for women and girls until it has delivered a long-term reduction in HIV prevalence for men.

Conversely, although economic empowerment for women and girls might reduce vulnerability to HIV infection by a variety of mechanisms, this is likely to be a long-run approach that cannot deliver rapid reductions in new infections.

Understanding how to strike this balance is part of the very complex research agenda that we face in learning how to develop combination prevention, and requires attention not just to the local epidemic – what UNAIDS describes as ‘know your epidemic’ – but also attention to the local context, which means everything from understanding what influences people to change their behaviour, to the ways in which gender roles are understood and talked about in a specific society.

Another important research issue is understanding how scaled-up community-based campaigns to offer counselling and testing for HIV can be integrated with activities that improve TB case-finding across the whole community, expand the provision of insecticide-treated bednets and effective treatment for malaria, and improve the diagnosis and treatment of other common infections and diseases. The community mobilisation necessary for treatment as prevention to succeed also offers huge opportunities for other health gains to be achieved. We hope to look in more detail at some examples of these approaches later in the year.

Cost

A shift towards earlier treatment – and more widespread treatment – would obviously have enormous cost implications.

However there are signs that a possible policy shift is not being dismissed on grounds of cost. Despite the pressure on US foreign aid budgets, the US Global Health Initiative is already looking at how it might assess the cost-effectiveness of treatment's prevention impact.

“We are in the midst of beginning a rigorous internal USG [U.S. government] discussion on just that question,” said US Global AIDS Ambassador Goosby said ([see report](#)). “What I’m now committed to doing is shepherding the dialogue within USG quickly so we will know what we are up against. I think this is a study that reaches the level [that] it needs to be fully looked at, needs to challenge the way we are doing business.”

In an interview with the Science Speaks TB/HIV blog Anthony Fauci, *Director of the United States National Institute of Allergy and Infectious Diseases at the National Institutes of Health*, said:

“If you don’t put in the money now, sooner or later you are going to have to pay at the end of the spectrum. And if you do that, at the end of the day, the amount of money spent is going to be much more. I am totally sensitive to the financial constraints we have, but I believe in the big picture of things, investing more money now is the way to go.”

A shorter TB preventive therapy regimen that’s not ready for primetime yet

By Theo Smart

As reported [here](#) on **aidsmap**, a major clinical trial has now shown that a 12-week course of rifapentine (900 mg) plus isoniazid (900 mg) once weekly treatment for latent tuberculosis is just as effective as a 9-month course of daily isoniazid—in countries with a low to moderate burden of TB. The regimen has additional advantage in that it only needs to be dosed once a week.

The Prevent TB study included close to 8000 participants and took ten years to complete. The results were reported last month at the American Thoracic Society’s International Conference in Denver—and have been lauded as being a major advance by the press, global health advocates, and public health officials.

“New, simpler ways to prevent TB disease are urgently needed, and this breakthrough represents one of the biggest developments in TB treatment in decades,” said Dr Thomas Friedman, who is the Director of the US Centers for Disease Control.

Indeed, a short three-month regimen that could cure latent TB would be welcome news— particularly in countries where TB is epidemic and/or wherever there is a high burden of HIV — given that HIV dramatically increases the risk of latent TB becoming active disease.

Unfortunately, there’s a hitch. At this point, this ‘breakthrough’ is not recommended, and may not be appropriate in the very settings or populations that most urgently need new and simpler ways to prevent TB disease.

The spin on this study could have unintended consequences in many settings with a high burden of HIV-related TB, where many programme managers and communities are considering, or now embarking upon the roll-out of isoniazid preventive therapy (IPT) for people living with HIV.

In some settings, according to recent WHO guidelines, IPT may even need to be given continuously when the risk of exposure to TB is especially great. There’s a danger the buzz about a shorter combination regimen may make some consider putting existing IPT plans on hold, even though the new regimen has not been adequately tested in their settings.

This dilemma was noted at the end of the press release put out by the CDC, which said that the researchers had cautioned, “that these results are only directly applicable to countries with low-to-medium incidence of TB.”

During a teleconference last week to discuss the study findings, Dr Kenneth Castro, Director of the CDC’s Division of TB Elimination expanded on these concerns.

“It’s important to note that the study was conducted in countries which carry a low to medium incidence of tuberculosis. That is primarily in the United States and Canada, and the results can therefore only be applied to these settings. The trial did not include countries with high tuberculosis incidence where the increased risk of re-infection could affect the effectiveness of this regimen,” he said (more on this below).

In fact, 89% of the participants were from the US and Canada (both very low burden countries), with a small number of patients coming from Spain (which also has a low burden of TB) and Brazil

(medium burden). Furthermore, there were very few people with HIV included in the trial — an important omission given that HIV is the key driver for the TB epidemic in most of the world.

In its press release, the CDC stressed that additional studies “will likely be needed before this new regimen can be recommended in countries with a high incidence of TB, especially those with high HIV prevalence and where the risk of TB re-infection is greater.”

Yet the wording makes it sound as though this ‘breakthrough’ could still be just around the corner for the rest of the world — once just a little more research is conducted. But the inevitability of this advance in resource-limited settings is far from guaranteed. In fact, until studies demonstrate otherwise, particularly where resistance to TB drugs is increasing, there is a chance the approach could even be dangerous.

At the same time, however, some of the concerns about the regimen’s potential limitations in high-burden settings may not be entirely warranted.

This article attempts to put the results from the Prevent TB study in context of other recent data on TB preventive regimens, including but not limited to IPT, in order to determine just how promising shorter TB preventive regimens might be in resource-limited settings.

Unpublished trial results are preliminary and often incomplete data

First and foremost, it should be stressed that there has only been one short report on the study findings, a conference call to discuss these data and a press release that was rather scanty on details. Clinical trial results presented at conferences are preliminary until they are peer reviewed for publication, but this may be more true than usual in this particular case partly because, despite the large number of participants in the study, there were rather few study endpoints reached.

To review, the study endpoints in this case were culture-confirmed TB cases in adults (and clinically confirmed TB in younger participants), seven in the combination arm and 15 on the isoniazid arm in a modified intent-to-treat analysis (which can be inferred to mean that the analysis included virtually all of those enrolled in the trial). The study was designed to show the combination was ‘non-inferior’ to the 9-month isoniazid arm. This condition appeared to be easily met, with a high statistical significance. While the combination arm may look superior, the study was not designed or powered in such a way to draw this conclusion.

Other details about when and where the TB cases occurred have yet to be released. However, Jennifer Horvath of the CDC’s news media team told HATIP that there were no TB cases during treatment in the arm that received the combination regimen — which suggests that some of the cases did occur during the first nine months of the isoniazid monotherapy arm. However, in an intent-to-treat analysis, this could include TB cases that occurred in participants who may have discontinued treatment, for instance, due to toxicity.

Differences in endpoints by site were not presented, but when there are such a small number of events, it is possible that small differences in baseline characteristics and other variables could influence interpretation of the results.

Notably, the per protocol analysis (which excludes patients known to have discontinued study treatment for a number of possible reasons) only included 5,858 of the 8053 participants recruited to the study. Of those who remained, there were eight

cases of active disease diagnosed in those taking isoniazid monotherapy and four on combination treatment. These are small numbers, but what is perhaps more important is that this means that overall ~45% of the reported active TB cases occurred in people who prematurely discontinued treatment, perhaps due to toxicity, or due to other protocol violations, such as missing data.

Easier adherence — but can isoniazid adherence be improved?

Another critical variable is adherence to treatment—in other words, were there differences between the study arms in how well participants took their pills? In the Prevent TB study, differences in adherence support were built into the protocol.

This was, of course, half the point of the study — adherence was expected to be better on the much shorter, once-weekly, supervised combination arm than a pill that had to be taken daily for nine months. Dr Timothy Sterling of Vanderbilt University, who presented the Prevent TB results in Denver, said that around 82% stayed on treatment and made their study visits through to 33 months of follow-up in the combination arm compared to 69% study completion on the isoniazid arm.

But with better adherence support the isoniazid monotherapy arm might have been significantly more effective. According to the recently published results from the BOTUSA study comparing 6 months of IPT to 36 months of IPT, the largest decrease in tuberculosis was seen in TST-positive participants with the “strongest adherence to continued isoniazid treatment.”¹

On the conference call, though, Dr Castro stressed that adherence has long been a key weakness of IPT.

“Even among those who do begin treatment, up to 60% never complete their treatment,” he said. “In study conditions, people are usually at their best performance — and I would argue that the 69% completion that we saw for nine months of isoniazid is as good as it gets. Without the study conditions, I would expect much fewer individuals to complete treatment during nine-month regimens.”

Indeed, this has historically been the case.^{2, 3, 4} However, since the Prevent TB study started, adherence support interventions for IPT have improved as experience of using IPT in people living with HIV has grown. In particular, lessons learned from supporting people taking antiretroviral therapy have increased confidence in supporting people through a long course of IPT.

In clinical trials, at least, the idea that 69% adherence to IPT is as good as it gets could be a bit outdated. For instance, in the Thibela TB study, which includes over 27,000 South Africans working in the mining industry, retention was initially fairly low, but it has steadily improved to around 75% in the latest clusters of participants to be enrolled.⁵

In another recent study by the Tuberculosis Research Centre (TRC) in Chennai, rates of adherence were also very high. Of those randomised to IPT (36 months) 93% were judged to be taking at least 80% of their pills, as gauged by unannounced home visit pill counts.⁶ Researchers at the TRC stressed that people living with HIV liked the quality of care they received at the site, and continued coming to them even after the study had completed. Adherence in the other arm of that study, ethambutol plus isoniazid for six months, was similar.

Meanwhile, in the BOTUSA study, adherence, or retention in care, was defined as ‘making 80% or more of their clinic visits’.⁷ A number of participants dropped out during the initial six months when everyone received IPT, but after that, during the blinded part of the study, adherence remained rather good: falling from a high of

85% to 78% in those who continued making more than 80% of their clinic visits. A subset analysis looking at the level of isoniazid in spot urine tests in 200 randomly selected subjects suggest that 80% actually continued taking the medication for seven months to one year, and 74% were still taking it between months 25-30.

Note this was in marked contrast to the IPT programme in Botswana, where large numbers of patients were lost to follow-up at least partly because the population is highly mobile there.⁸ However, as described in [HATIP #175](#), people living with HIV and civil society organisations in the southern Africa region have since been taking up the challenge to better educate and support people in the community to adhere to IPT.

Would the combination regimen in the study have performed as well without each dose being directly observed? Perhaps not, so a subsequent study is being performed to answer the question.

Side-effects - now or later?

When the endpoints being averted are so rare (in low TB burden countries at least), one has to ask whether the benefits of treatment outweigh its risks.

In the case of some preventive regimens such as rifampin/pyrazinamide, the answer has been no (see below). Rifapentine/isoniazid performs better, but it was not necessarily better than IPT. Data on adverse events in the study were mixed — there were significantly more mild adverse events reported on the isoniazid arm, which was not surprising given that the longer course of treatment provided more opportunities for complaints to arise. However, the trend was reversed for more serious events. 4.7% of those in the rifapentine-containing regimen permanently discontinued treatment due to an adverse event versus 3.6 percent in the isoniazid arm. There was no significant difference between the arms in terms of serious grade 3 or 4 adverse events or death. However, the side effects on the combination regimen occurred over a short course of time — so the toxicity on the regimen is more, up front.

Of note, the only major study so far to look at the rifapentine/isoniazid preventive regimen in people living with HIV in a high burden setting also suggested it was fairly well tolerated.⁹ The Soweto study compared four arms, 1) the three-month rifapentine/isoniazid regimen to 2) rifampin 600 mg plus isoniazid 900 mg twice weekly for 12 weeks, to 3) daily isoniazid 300 mg for 6 months, and finally a smaller number were randomised to 4) continuous isoniazid for the course of the study. Over the course of follow-up, there were no significant differences in adverse events between the rifapentine regimens, except for a significantly higher rate of adverse events on the continuous isoniazid arm. However, this markedly higher rate of adverse events on continuous isoniazid was not observed in either the BOTUSA study, or the study in Chennai.

Shorter TB preventive regimens: not new, but still not widespread

Though the Prevent TB study was by far the largest to address the question, it is not the first study to report that other TB preventive regimens are as effective as isoniazid. A few of these alternative regimens, **rifampin plus pyrazinamide**, **rifampin plus isoniazid**, and **rifampin or rifabutin alone** were described as early as 1997, by one of the champions of IPT, Dr Richard Chaisson and his colleague Dr William Bishai of Johns Hopkins University.¹⁰ In addition to the perceived problems with toxicity and adherence on isoniazid, Bishai

and Chaisson wrote that “bacteriologic models suggest that, in their persistent form, tubercle bacilli are relatively resistant to isoniazid but become more sensitive to other drugs.” In other words, isoniazid was simply not the most effective TB drug to use to clear latent TB (although studies have clearly shown *that IPT works*, particularly, in this writer’s opinion, if you give it long enough). Rifampin, on the other hand, has much greater sterilising activity and could theoretically clear an infection faster.¹¹

But in the fourteen years that have passed since that paper was published, and despite numerous studies, uptake of these alternative regimens has been limited for several reasons.

The first was toxicity, particularly with the rifampin plus pyrazinamide regimen that proved to be profoundly disappointing. Initially there was great excitement about this even shorter course regimen of rifampin plus pyrazinamide (taken for two months) after it was found to be as — if not more — effective than IPT (for up to 12 months).¹² Most of the early studies had been conducted in people living with HIV, who seemed to tolerate the regimen adequately. In people without HIV however, the results ‘were radically different,’ according to a recent review of the different treatments of latent TB infection by Lobue and Menzies.¹³ [Much of this section is drawn from this review (which is exhaustive); citations for the key studies of these regimens can be found in their paper]. Rates of grade III/IV liver toxicity were dramatically higher than on nine months of isoniazid.¹⁴

Other options seem much safer. For instance, several randomised trials have reported that the rifampin/isoniazid regimen, taken twice weekly for three to four months, has similar completion rates, comparable toxicity and effectiveness as six or more months of IPT (again, the adverse events may be more common while taking the combination treatment). In many ways, the rifapentine plus isoniazid regimen is a variation on this theme, since rifapentine is essentially a rifamycin, like rifampin but with a five-fold longer half-life. However, because of the difference in dosing, half-life and adherence, the drug exposure achieved by the two regimens is not necessarily equivalent. (And there are questions about the adequacy of once weekly rifapentine/isoniazid in other contexts (see below).

A couple of studies have previously looked at rifapentine/isoniazid to prevent TB. One was a Brazilian study in HIV-negative individuals that found it to be somewhat less effective than rifampin/pyrazinamide — though given the low event rate the study was underpowered for this finding to reach significance.¹⁵ What was clear was that rifapentine was associated with far fewer adverse events.

The other study was the SOWETO study, which stands out for being conducted in a high burden setting and in people with HIV. The study involved 1150 participants and found no differences in efficacy across the four arms. “The proportion who had active TB (or died) was the same in all,” SOWETO’s chief investigator, Dr Neil Martinson told HATIP.

(Another preventive option, six months of ethambutol/isoniazid, is discussed later in the article).

Studies also suggest four to six months of rifampin monotherapy is better tolerated, easier to adhere to, and case series suggest it is highly effective.^{16, 17} A large-scale international trial to assess the effectiveness of 4 months rifampin compared to nine months of IPT is underway. Notably the only study to compare the combination of isoniazid plus rifampin to rifampin alone suggested that the combination actually performed worse (perhaps because of tolerability or pill-burden related adherence problems).¹⁸

But there are some downsides of rifamycin-containing TB preventive regimens.

Drug interactions

One of the other problems with preventive regimens containing rifampin or rifapentine is that they are metabolised by the same hepatic enzyme pathway that metabolises the non-nucleoside reverse transcriptase inhibitors and protease inhibitors that anchor antiretroviral therapy (ART). Even efavirenz, which is the preferred option to use in people on ART who must take TB treatment, is somewhat affected — to the extent that you probably wouldn't want to use rifampin or rifapentine for a preventive regimen. People on ART were excluded from the Prevent TB study.

Rifabutin, which is less likely to interfere with antiretrovirals, might be an alternative in preventive regimens, but hasn't been studied much for latent TB, though at least one small study suggests it is relatively safe when used in combination with isoniazid (dosed twice weekly).¹⁹ Rifabutin is now on the WHO's essential medicine list so it should be easier to explore these options in resource-limited settings.

Resistance (drug and programmatic)

Given their importance to treatment of active disease, many TB specialists and national TB programmes insist that any regimen that uses a rifamycin should be directly observed or there should be some comparable adherence support given the importance of those drugs for treatment and the fear of encouraging the development of resistance.

It took years to convince national TB programmes to begin to relinquish control of isoniazid in order to allow HIV programmes to begin offering IPT to people living with HIV (some are still 'resisting'). While Lorub & Menzie suggest that they believe rifampin resistance to be less likely to spontaneously evolve (if active TB has been excluded), this may not reassure those who fear that screening programmes may miss active cases and put them on suboptimal therapy.

One of the reassuring aspects of following the recent WHO guidelines on intensified case finding and IPT is that, if there is a breakthrough case of active TB on IPT, it ought to be quickly detected by monthly screening. Furthermore, data suggest that breakthrough cases on IPT are generally only mildly resistant to isoniazid, and should remain highly treatable with standard TB treatment (although increasing the dose of isoniazid used for treatment may be advisable). The same cannot be said, however, for rifamycin-resistant TB that could develop if active cases are not caught soon enough. In other word, even if less common, the consequences of developing rifamycin resistance are much greater.

One option is to make sure that isoniazid is also part of the regimen as this "does offer theoretical protection against development of resistance if a person with undiagnosed active TB is inadvertently treated for latent TB infection," according to Lorub and Menzies.

But is this necessarily true if isoniazid is only administered once a week, as is the case with rifapentine/isoniazid?

In the Soweto study, there were a few cases of resistance detected — and more of these were on the weekly rifapentine arm. When initially reported, the study investigators concluded "the development of RIF-resistance and MDR TB in patients in the weekly RPT/INH arm is of concern."

Today, Dr Martinson is less worried.

"There is always a concern about resistance but we found no real cause for alarm," he told HATIP, noting they had also found rifamycin resistance in the six-month isoniazid arm. When the researchers looked at the people who had active TB at baseline and were excluded from the study "out of 90 cases there were two with rifamycin resistance. Not that it is 'scientifically' significant (given low rates and [the fact that this is] comparing incidence with prevalence). But it suggests that there is circulating rifamycin resistance."

In other words there is a chance that the resistance was acquired in a reinfection rather than being selected, but Dr Martinson concedes they did not do contact tracing (and *phylo* typing) to make certain of this.

But the concern might persist particularly in a programmatic setting, where early cases of active TB are more likely to be missed, especially in people living with HIV.

In another context where rifapentine/isoniazid has been used in HIV-positive people, this time in people with active TB — though on maintenance therapy — once-weekly dosing was clearly associated with the emergence of resistance.

This was observed in US Public Health Service Study 22, which included mostly HIV-negative and a smaller number of HIV-positive participants.²⁰ In order to reduce the burden of directly observing doses, the study compared the once-weekly regimen of rifapentine/isoniazid with twice weekly rifampin/isoniazid during the 4-month continuation phase of treatment for pulmonary tuberculosis (after the first two months of intensive treatment which should generally make someone AFB-smear negative).

In the HIV-positive people with TB, slightly more people who were randomised to rifapentine/isoniazid relapsed than those on rifampin/isoniazid though this was not statistically significant given the small size of the subset. What was significant, and frightening however, was that four out of five of those who relapsed on the once-weekly regimen had developed rifamycin-resistant TB — compared to none on the twice-weekly rifampin regimen ($p=0.05$). In contrast, there was no rifamycin-resistant relapse among the HIV-seronegative patients on rifapentine.²¹

A subsequent analysis concluded that this was not the fault of rifapentine, at least not directly. Instead, it was the low isoniazid concentrations achieved with once-weekly dosing that were associated with failure/relapse.²²

"Because low isoniazid concentrations were associated with failure/relapse, a drug with consistently greater area under the concentration-time curve than isoniazid may be needed to achieve highly active once-weekly therapy with rifapentine," the authors of that analysis concluded. In other words, weekly dosing really requires a drug with a longer half-life.

The risk of resistance developing in people living with HIV on a once weekly TB preventive therapy in programmatic settings is one reason why further research of this combination could be necessary.

Reinfection

Another reason, as Dr Castro mentioned, is the potential for reinfection, particularly for people who are more susceptible to TB (due to poor health, nutrition and HIV), in places where they are more likely to be repeatedly re-exposed to TB. In such settings, anything short of continuous therapy might appear to be wrong-headed.

Or is it?

Although clearly people do become reinfected, even in high-burden settings, the risk varies from setting to setting, person to person, difference in CD4 cell count and tuberculin skin test status. Data to support the benefits of *continuous* IPT as being worth the costs (side effects, financial and other health system resources) are, at present, far from unequivocal.

Only a few studies have looked at the durability of TB preventive therapy, with variable results. Most of the older IPT studies in high TB burden countries suggest that HIV-positive people who are put on six months of IPT continue to have a reduced incidence of TB compared to those who were untreated for awhile after discontinuing treatment, though the effect diminishes gradually over time.²³ One study in Zambia suggested that the protective effect could last up to three years.²⁴ while a study from Uganda found the effect only lasted one year.²⁵ These studies have to be interpreted with caution however as there was substantial loss to follow-up.²⁶

On the basis of these data, one of the 'old questions' about IPT was how often HIV-positive people in regions with a higher risk of TB exposure should have to repeat a course.

This changed somewhat when the BOTUSA study results came out. Again, everyone in that study got six months of IPT and was then randomised to either placebo (stopping IPT) or continuing IPT out to 36 months. Much to their surprise, the investigators found that the protection provided by the short course of IPT in their study wore off more quickly than they expected in those randomised to placebo – within six months of completing treatment. The researchers theorised this was probably because people were at such a high risk of re-exposure to, and reinfection with, TB in Botswana. They may be right, or at least partly right, but there are a number of possible explanations. For instance, in the one of the studies mentioned above. Quigley et al wrote that “the diminishing effect of preventive therapy over time in HIV-infected Zambian adults may be explained by the high risk of new infection or by *inadequate sterilization of dormant tubercle bacilli in the absence of immunity.*”

It is odd that the BOTUSA investigators don't consider that this last idea, that six months of IPT doesn't entirely clear the infection in all individuals, is at least part of the explanation for what happened in their study. After all, most studies and a meta-analysis suggest that in tuberculin skin test positive patients, six months of IPT reduces the risk of TB by only around 60%. The remaining cases will still happen – without more preventive therapy.

Instead, the BOTUSA investigators give two primary reasons why they think reinfection is what is occurring. One, they note that there have been high rates of clustering and reinfection of successfully treated cases of tuberculosis reported in Botswana – and there is no denying this. Then they claim that short-courses of isoniazid preventive treatment have a durable protective effect for people with HIV and positive tuberculin skin tests in areas of low tuberculosis incidence.” But the study that they cite to support their argument involved 12 months of isoniazid – not six months – and 12 months of IPT may have a better chance of clearing the bacilli if there is good adherence.

This was very clearly suggested in an on-treatment analysis of the pivotal IPT study conducted by the International Union Against Tuberculosis Committee on Prophylaxis including over 28,000 people in the late 1970s.²⁷ The preventive effect became evident after the first 12 weeks on treatment with a 31% reduction in incidence of active disease, but the effect increased to 69% after 24 weeks of IPT. But in adherent patients, the benefit increased to over 93% at 52 weeks.

People may be putting too much faith in early studies of IPT in people living with HIV that found there were no differences in efficacy between six versus 12 months in HIV-positive patients (in intent to treat analyses). This could be due to the rampant adherence problems or other issues. It is difficult for this writer to ignore the weight of the Union's study. Furthermore, it seems rather paradoxical that the WHO guidelines review committee concluded that twelve months isn't more effective than 6 months, and yet gave a conditional recommendation of continuous IPT, on the basis of a study that reported the loss of benefit so shortly after discontinuing six months of IPT.

One of the BOTUSA study's findings undermines their argument somewhat: continued IPT only reduced TB incidence in people who, when they first entered the study, were TST positive (the clearest measure of having a pre-existing latent TB infection). Note, that only 23% of the study participants were TST positive and therefore showing clear evidence of previous exposure to TB.

If ongoing exposure to TB is so widespread, why didn't the study see a big increase in the number of TB cases in the rest of the study population on placebo? One would have expected to see *some* slight trend of difference in the remaining participants, who made up roughly 77% of the study population. The fact that breakthrough cases only occurred in someone who was TST positive at baseline is suggestive of an infection that wasn't cleared, although it is possible that people who were already latently infected (as the TST shows) are somehow more susceptible to becoming infected again.

But there is limited evidence, such as the study previously mentioned in Uganda –that the benefit of 6 months of IPT is relatively short-lived. However, in the same study, the benefit of shorter more potent combination regimens is sustained out to three years.²⁸ Similarly, in the TRC study in Chennai, there did not appear to be any statistically significant rebound of TB after the six-month ethambutol/isoniazid regimen concluded, (though the event rate was higher than in those randomised to three years of IPT).

If it does take a longer course of isoniazid to clear the infection (if indeed it is possible some of the more advanced people living with HIV), then it may be possible that a more potent regimen may better clear latent TB in less time. If this is true, then there will be less loss of effect – a longer window period free from the risk of TB – even in the higher burden settings. This will need to be demonstrated by further clinical research but it is certainly worth investigating.

If rifapentine/isoniazid, or another short course regimen is effective and safe, then the question of when to give people living with HIV a repeat course may become pertinent again. Dr Martinson doesn't believe it will be necessary.

“In HIV-positive people the ‘real sterilising’ effect is getting ARVs and restoring immunity soon after receipt of preventive treatment,” he said. “I think few people would be diagnosed soon enough, with a high CD4 count, to receive a short course twice prior to ART initiation. ARVs are the key. IPT has no impact on mortality and has a low durability – get people on ARVs!”

Cost and access issues

But another very simple reason why the Prevent TB study probably won't soon affect policy in resource-limited settings is that rifapentine is not widely available or on the market in much of the world.

In addition, at current prices, the cost of the rifapentine/isoniazid regimen is \$160 per patient – versus roughly \$6 for nine months of isoniazid. If that were the price of preventive therapy, it will be a pretty big ask to put every single person with HIV on it, as current

WHO guidelines recommend, particularly in programmes that are already financially strained.

However, it is possible that lower prices can be negotiated, and during the conference call, Dr Castro reminded the participants that there were other costs in a preventive programme besides the cost of the drug.

"We are developing some updated estimates. However, I can refer to a cost-efficacy study published by Dr. David Holland and colleagues recently. For the nine months of isoniazid, it's estimated that it would cost about \$237 to implement, whereas the three months of isoniazid and rifapentine would cost about \$503. Rifapentine is much costlier than isoniazid." However, he pointed out, there are other cost considerations, including the number of visits and the laboratory tests that would be required to monitor individuals and evaluate safety.

This would be true in resource-limited settings as well. While community-based mechanisms of adherence support — where they exist — may be able to provide adherence support, it is not clear that overburdened HIV clinics that do not have community-based service providers will be able to cope with the repeat ICF screening, and toxicity screening on a monthly basis to roll TB preventive therapy out to all people living with HIV. Shortening the regimen may significantly reduce the burden on the health system.

In the meantime, however, it is important that the buzz about a potential breakthrough treatment not be allowed to confuse and weaken the resolve to implement an existing intervention that we know will reduce the burden of TB among people living with HIV. The efforts to build demand for IPT are not helped when CDC officials describe the regimen as being 'lengthy and cumbersome' — after all, people living with HIV take ART medications every day, and must do so indefinitely. Finally, considering how connected the world is, and how the greatest need for TB advances is *not* in the US or Canada, it is perhaps important not to promote something as a 'TB breakthrough' until it has been shown to work in the people and settings where people are most at risk.

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