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News from the Union World Conference on Lung Health

TB still killing 4,000 people with HIV each day, WHO reports

By Keith Alcorn

Tuberculosis is still killing more than 4,000 people with HIV every day worldwide, the World Health Organization reported this week. Despite progress over the past few years, more needs to be done to identify and treat HIV in TB patients, and to prevent TB in people with HIV.

The [new tuberculosis control data from the World Health Organization](#) show that despite modest progress in 2009, the majority of people with HIV and TB worldwide are still not receiving antiretroviral therapy or isoniazid preventive therapy.

Nevertheless the findings, released this week ahead of the 41st Union World Lung Health conference in Berlin, do show substantial improvement in rates of HIV testing among TB patients.

The survey, compiled by WHO from official returns submitted by all national TB control programmes, shows that in 16 countries in sub-Saharan Africa, three-quarters of people diagnosed with TB were tested for HIV in 2009, including many of those countries worst affected by HIV.

Across sub-Saharan Africa, just over half (53%) of TB cases were tested for HIV in 2009. This compares to 22% in 2006 and 38% in 2007, suggesting that vigorous efforts to promote integration of HIV and TB activities is beginning to have a substantial impact in sub-Saharan Africa.

Forty-six per cent of TB patients tested for HIV had a positive result in 2009 in sub-Saharan Africa.

However a number of important interventions that have the potential to improve the health of people with HIV and TB, or to prevent the development of TB in people with HIV, still have limited coverage.

Cotrimoxazole as an adjunct to TB treatment reduces the risk of death in people with HIV. It is recommended in WHO and national guidelines as a prophylactic measure against opportunistic infections in people with HIV, but the TB control survey shows that one-quarter of people with HIV and TB did not receive cotrimoxazole in 2009.

The proportion who received cotrimoxazole in sub-Saharan Africa (76%) has remained almost unchanged since 2006.

Antiretroviral therapy, recommended in [WHO guidelines issued at the end of 2009](#) for all people with TB/HIV coinfection regardless of CD4 count, was received by only 36% of people with coinfection in sub-Saharan Africa in 2009, and by 37% worldwide. The finding indicates not only a shortcoming in TB/HIV integration, but also the huge gap that remains between available treatment and the number of people in need.

A course of isoniazid preventive therapy (IPT), although not recommended universally in national guidelines, is proven to reduce the risk of developing TB in people with HIV. Sixty thousand people in Africa (15% of those eligible) and a further 25,000 people in other regions of the world received IPT in 2009, up from 50,000 in 2008. Almost all the increase was accounted for by patients with HIV who received IPT in sub-Saharan Africa and Europe.

In South-East Asia just 467 people with HIV were reported to have received IPT in 2009 – around 1% of all TB cases diagnosed with HIV.

The Global Plan to Stop TB aims to achieve 100% access to each of these interventions by 2015.

Progress towards TB targets shows improvement

Global progress towards overall TB control targets was positive in 2009.

The global incidence of TB fell slightly in 2009, to 137 cases per 100,000 people, indicating that the peak of global TB incidence was probably reached in 2004 at 142 cases per 100,000 people. There were around 9.4 million cases of TB worldwide in 2009, WHO estimates.

Approximately 11-13% of incident TB cases occurred in people with HIV, WHO estimates. Eighty per cent of these cases occurred in Africa.

The global death rate from TB has fallen by 35% since 1990. In 2009 1.7 million people died from TB worldwide, including 380,000 people with HIV.

Global treatment success rates have also reached their highest level. Eight-six per cent of people treated for TB were cured in 2009, and two countries with a high burden of HIV and TB coinfection, Tanzania and Kenya, achieved an 85% cure rate in their national TB programmes in 2009, indicating that even with the additional burden of HIV-related TB, a high level of performance is possible.

Across Africa as a whole the treatment success rate was 80%.

WHO says that 13 of the 22 countries with the highest burden of TB are on track to reach the 2015 Millennium Development Goal target of halting and reversing the rise in TB incidence, and 12 countries are likely to halve the incidence of TB by 2015.

TMC207 leading the pack of TB drugs moving towards market

By Theo Smart

The addition of a new anti-tuberculosis (TB) drug, Tibotec's TMC207, to a five-drug regimen for multidrug resistant TB (MDR-TB) was significantly more effective (in a number of measures) than the five-drug regimen alone according to a report presented at the Union World Conference on Lung Health held November 12-15 in Berlin.

Adding the new drug to the regimen resulted in a significantly faster culture conversion within 24 weeks ($p=0.003$), with a median time to culture conversion of 12 versus 18 weeks on the five-drug regimen alone; and in a significantly higher sputum conversion rate at 24 weeks, 79% versus 58% ($p=0.008$).

These are the first efficacy data from a multicentre randomised trial for TMC207, and if results in the phase III studies, slated to begin next year, are consistent with these findings, this could be the first new TB drug in a generation. But this may only be the start of the good news because TMC207 is but the first of a number of new anti-TB compounds in development, which, should they prove safe and effective, together could render MDR-TB and even extensively drug-resistant TB much easier to treat, and possibly reduce the time it takes to treat any form of TB.

TMC-207 background

TMC-207 is a member of the diarylquinoline class of drugs with a unique mechanism of action. It targets ATP synthase of mycobacteria specifically (and thus represents the first drug to

interfere with mycobacterial energy production). It kills both replicating and non-replicating bacilli. It has shown great potential for bactericidal and sterilising activity both in vitro and in vivo studies and has potential to shorten treatment of MDR-TB. For instance, in mice studies, it shortened TB treatment duration from 6 months to four months, for drug sensitive TB, and from 24 months to 6 months for MDR-TB.

Close to 600 people have been dosed with TMC-207 in clinical trials so far. Early pharmacokinetic studies found some important food and drug interactions. The drug has a very long half-life, and steady state levels take more than 14 days to achieve. Administration with food increases exposure to TMC-207 by two-fold. TMC-207 is metabolised through the CYP3A4 liver isoenzyme system – and the co-administration of rifampicin lowers TMC207 levels by 50%. There are only modest interactions with *Kaletra* (an increase of TMC207 levels by 22%) and nevirapine – so there shouldn't be any problems coadministering the drug with antiretrovirals.

In an early one-week proof of principle study, the drug showed early bactericidal activity; then, in a subsequent open-label study in South Africa, TMC-207 demonstrated a conversion rate of around 40% in MDR-TB patients at 8 weeks of administration.

The TMC207 study

The results presented in Berlin came from the second stage of that study, with sites in Brazil, India, Latvia, Peru, Philippines, Russia, South Africa and Thailand. The study enrolled 161 subjects, with newly diagnosed sputum smear-positive pulmonary MDR-TB infection that was either diagnosed with culture-based methods or in later stages with molecular methods like the Hain line probe assay (LPA). Before starting study drug, patients had one week of rifampicin wash-out to get rid of that interaction potential, and were stratified for sites and for the degree of lung cavitation. Participants were randomized to receive either placebo or TMC207, given at 400 mg per day for 14 days, and then three times a week at 200 mg until the end of 24 weeks, added to a background regimen, which was given as per the local national treatment programmes.

The primary analysis was the time to sputum culture conversion and sputum culture conversion was defined as 2 consecutive negative MGIT cultures collected at least 25 days apart and not followed by a confirmed positive culture. Subjects who dropped out during these 24 weeks were considered to have failed, irrespective of their culture status at the time of drop-out. The secondary analysis was culture conversion rates at week 24.

Twenty-nine subjects were excluded from the analysis, either because they could not be confirmed as MDR-TB cases, or because they were found to have XDR-TB, leaving 66 in each arm for the modified intent-to-treat analysis. There were four discontinuations in the placebo arm and three on TMC207. Adverse events were evenly distributed across treatment groups and there were no serious adverse events related to study drug. There were some degree of QTcF prolongation (changes in the heart's electrical cycle) seen on TMC207, the relevance of which was unclear and it is under investigation. According to the study presenters, it was not a large prolongation, no adverse events were associated with these QT changes and no pathologically prolonged QT intervals were observed.

As already noted, outcomes on TMC207 were significantly better than placebo, with a higher rate of, and shorter time to, culture conversion. According to the Kaplan-Meier analysis, the curves began to diverge as early as week two. The divergence seems to flatten out a bit towards the end (as the background regimen begins

to achieve more culture conversion over time) but does not converge.

Further studies to move TMC207 closer to the market

So the next question is how to move TMC207's clinical development along as quickly – but responsibly – as possible. In order to collect further evidence on the drug's safety, the TMC/Tibotec-207 team is conducting what is being called the "Breathe" study, which is an open label study for 231 patients receiving optimised background therapy plus TMC-207 for 6 months.

But there are many other questions about how to proceed with the development of the new drug. One concern is to avoid creating resistance to the new compound, according to Dr David McNeely of Tibotec. "The XDR situation keeps us very concerned about the appropriate use of the drug in the future because we don't want to be administering the drug as virtual monotherapy at one point and having resistance developing very quickly and then ruin the drug for the future," he said.

"We hope TMC-207 could [both] in the future be involved in a simplified regimen – maybe one could get rid of some of the more toxic drugs that are used – and to shorten treatment, in drug-susceptible and in drug-resistant TB. Of course a lot of this depends on the companion drugs that we should be giving it with and it's unfortunate for MDR-TB that people have been treated for generations with drugs that people don't even know if they work. So we're looking at all of those in all of these directions and pursuing the various avenues as we have timely resources and energy to do that," said Dr McNeely

But he was reluctant to discuss the design of future TMC207 studies.

One possibility is that the phase III study could combine TMC207 with one or more of the other new TB drugs at similar stages of clinical development, such as OPC-67683 – should that drug demonstrate efficacy in its just completed phase II study.

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New drugs for TB – suddenly, an abundance

By Theo Smart

With the release of the TMC207 efficacy data, and with data due soon from a number of other new compounds together with other drugs which are being 'repurposed' for TB, the TB drug pipeline has never looked more promising. There were at least 5 separate symposia at the Union World Conference on Lung Health in Berlin that focused either on advances in treatment, new drugs, optimising classes of drugs (fluoroquinolones or rifamycins) or on the substantial challenges of their clinical development.

Indeed, evaluating multiple new TB drugs and getting the ones that work to the market as quickly and carefully as possible poses a number of unprecedented and formidable logistical, ethical and technical challenges for the TB research establishment.

Drug companies and research programmes are considering novel clinical trial designs, carefully considering the most appropriate clinical endpoints, and whether surrogate markers for TB drug effectiveness might expedite the process – and asking how to package the drugs (individually or in fixed dose combinations). How will so many new drugs be tested? Which combinations of drugs should be prioritised?

Some of these drugs will almost certainly qualify for accelerated approval – and there will be a need to provide compassionate use to the potentially life-saving drugs for people with few other options – and to gather more safety data through parallel track expanded access programmes. How can this be done responsibly – while limiting the opportunities for the development of resistance to the new compounds – will be of paramount importance.

The inadequacy of existing MDR-TB regimens

Several sessions of the conference starkly illustrated the need for new drugs to treat drug sensitive and resistant TB. Dr Christian Lienhardt of WHO detailed the principles (and drawbacks) of existing regimens for MDR-TB. According to current WHO guidance, the regimen must include at least 4 drugs with 'almost certain effectiveness, based on drug sensitivity testing (DST) and/or the patient's drug history.'

But more than four drugs may be needed if the susceptibility pattern is unknown, if one or more of the agents being used is of questionable effectiveness, or if there is extensive, bilateral pulmonary disease.

At least one of the drugs should be an injectable agent (an aminoglycoside or capreomycin) that is used for a minimum of 6 months. The other drugs need to be administered six days a week, using directly observed therapy (DOT) throughout treatment for a minimum duration of 18 months – and most of the time 24 months – beyond culture conversion.

The shortcomings of the existing approach to MDR-TB treatment are many, starting with the fact that the drugs are extremely expensive and not easily available everywhere they are needed. Moreover, the long duration of treatment, together with the toxicity of drugs and problems with drug interactions, lead to high rates of default, poor treatment outcomes and increasing drug resistance.

This was clearly illustrated in preliminary data from the PETT study, presented by Dr Peter Cegielski of the US Center for Disease Control (CDC). The study found the emergence of additional drug resistance on MDR-TB treatment, even in projects approved by the Green Light Committee (established to improve the quality of MDR-TB care and increase access to appropriate second line therapy for people with MDR-TB). The purpose of the study was actually to see whether the Green Light Committee projects result in less resistance – and indeed so far this seems to be the case, though Dr Cegielski cautioned that the data analysis is incomplete – currently based upon final drug sensitivity testing (DST) of only 561, or two thirds, of the participant's paired isolates (isolates taken at baseline and later over the course of follow-up).

However, over time, there was a steady increase in resistance from the pattern at baseline. Between 9.4% (GLC arm) and 15.1% (non-GLC arm) acquired resistance to fluoroquinolones within a mean of 9.6 and 7.4 months on treatment respectively; and resistance to the second line injectable drugs was found after a mean of a little over 7 months on treatment, in 6.6% in the GLC arm and 10.7% in the non-GLC arm. A small proportion of participants had isolates that, at baseline, were not only MDR, but also resistant to either the fluoroquinolones or the second-line injectables. Of these, about a quarter who were at the GLC sites went on to develop

XDR-TB within a mean of 9.9 months; while the non-GLC sites, 46.9% of these 'pre-XDR-TB' cases became XDR-TB, within a mean of 5.7 months. Otherwise, the development of XDR-TB from MDR-TB was relatively rare (in 0.94% of GLC and 4.4% of the non-GLC participants).

Another presentation in the same session focused on the adverse events associated with MDR-TB treatment. Dr Gunta Dravniece, who works with KNCV, described how over 70% of people on second-line treatment experience at least one adverse event, the median number is closer to three, and many patients experience several more. The most common are nausea and vomiting – which, as one audience member suggested must have a negative effect on drug exposure in the patient, and could potentially increase the risk of further resistance developing.

Clearly, there is a need for new drugs that can make these second line TB treatment regimens more effective, less toxic and, one hopes, much shorter than the current 18-24 months. While the session was supposed to present new data from studies on two such drugs, TMC-207 and OPC-67683, only the analysis of the first drug was ready in time for the conference.

TB Drugs in development

	Preclinical	Phase I	Phase II	Phase III
Existing drugs 'repurposed' for TB		Meropenem/clavulanate Linezolid	Rifapentine	Gatifloxacin Moxifloxacin
New Drugs	TBK-613, AZD-5847, CPZEN-45 BTZ-043	SQ109 PNU100480	OPC67863 PA-824 TMC207	

Fluoroquinolones

The repurposed drugs that are furthest along are the fluoroquinolones, such as gatifloxacin and, especially, moxifloxacin. The fluoroquinolones are already recommended by WHO as an essential components in MDR-TB treatment. But they are not all created equal.

Moxifloxacin is the most potent fluoroquinolone against TB, based on in vitro activity and animal studies, followed by gatifloxacin, levofloxacin and ofloxacin. An entire symposium was devoted to whether the fluoroquinolones are still useful after the emergence of XDR-TB. The short answer is yes, as the more potent fluoroquinolones still appear to be active against strains that may be resistant to ofloxacin.

However, a number of studies are underway or are being completed to characterise just how gatifloxacin or moxifloxacin will best be used in TB.

The Union is conducting one of these, the Standardized Treatment Regimen of Anti-tuberculosis drugs for patients with Multi-drug resistant tuberculosis or STREAM study. It is based on an observational study in Bangladesh in which 9-month regimen (using gatifloxacin) achieved a relapse-free cure rate of 87.9 percent (95 percent CI 82.7, 92.6) among 206 MDR-TB patients (Van Deun, AJRCCM 2010). The STREAM study will compare outcomes among around 400 patients with MDR-TB randomised on a 2:1 ratio to receive a nine-month treatment regimen containing moxifloxacin compared to the standardised GLC regimen (of 18 to 24 months of

treatment). All patients are supposed to be followed-up for 27 months post-randomisation. The end-point will be a favourable outcome, considered as culture negative at the end of follow up (27 months); and unfavorable outcomes will be either death or treatment failure at 6 months; relapse; change of treatment with a culture positive when last seen.

Other studies are looking to see whether gatifloxacin or moxifloxacin can be substituted for one of the drugs in the standard regimen to shorten duration of the first-line regimen by a couple of months (from six months to four months). In the OFLUTUB study, patients are randomised to a standard regimen or a regimen in which gatifloxacin is being substituted for ethambutol, and those results should be available this coming June. Meanwhile, the REMox study, which so far has enrolled over 700 patients in a number of resource-constrained sites, compares the standard first-line regimen to two moxifloxacin-based regimens (one in which it has been substituted for isoniazid, and the other in which it has been substituted for ethambutol).

Optimised rifamycins

With the benefit of hindsight, it now appears that the development of the last major anti-TB drug, rifampicin, was somewhat botched. In a conference session on the rifamycin class of drugs, Dr Eric Nuermberger of Johns Hopkins University described how, when rifampicin was approved in the mid-1960s, it was only at the minimally effective dose. He shared data from mouse studies showing that with increasing concentrations of rifampicin, there is a steep decline in bacterial loads.

“What’s very clear is a very steep and deep dose response. It is very clear that increasing exposures is associated with increasing activity, and the extent of this activity is very large. So the higher the rifamycin exposure the better, and toxicity is probably the limiting factor in how high we can go with rifamycin-based therapy. But the exposures achieved with our current dosing strategies put us at the very low end of the dose response curve. If one looks at the AUC/MIC in humans, we aren’t nearly getting what we could out of the rifamycins and increases with exposure could be associated with great increases in activity,” said Dr Nuermberger.

Accordingly, a host of studies are underway which are now looking for the maximum tolerated dose of either rifampin or the related rifapentine and looking to see whether use of these doses can shorten the time to cure. Rifapentine is a drug which was once considered for intermittent dosing (once-weekly) because of its longer half-life, but it seemed to have a higher rate of relapse than standard treatment in people with HIV. However, the current studies are looking at higher doses, or even at daily or nearly daily dosing. More frequent dosing achieves drug exposures three times higher than achieved with rifampicin. In mouse studies, these doses cut the time to cure in half.

There are multiple studies ongoing. One compares standard TB treatment with two doses of rifapentine/moxifloxacin (given either once or twice weekly but for only four months) and it is specifically assessing whether there may be a problem with relapse in people with HIV. The Pan African Consortium for the Evaluation of anti-tuberculosis Antibiotics (PANACEA) is conducting dose-ranging studies with standard rifampicin, aiming for a dose of 20 mg/kg. If that dose is tolerated, they will conduct a study combining it with moxifloxacin.

Dr Susan Dornan of Johns Hopkins University described a host of other studies looking at maximising the use of rifapentine. There are two studies looking at daily rifapentine (being substituted for rifampicin), another study in Brazil is looking at substituting daily

rifapentine for rifampicin and moxifloxacin for ethambutol in the standard regimen. Another study in healthy individuals will look for rifapentine’s maximal tolerated dose, and then another study will look at the antimicrobial effect and safety of doses higher than 10 mg/kg per day substituted for rifampicin as part of the standard intensive phase regimens. Each of these studies will be looking for differences in cure at 8 weeks.

“It all comes down to toxicity,” claimed Dr Martin Boeree of PANACEA, but studies from the past have not found significantly increased toxicity. In fact, one of the reasons, the dose wasn’t pushed was because of the cost of rifampicin, which was quite high when it was first developed.

Linezolid

A member of the oxazolidinone class of drugs, linezolid is an antibiotic used for very difficult infections caused by vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* (MRSA). The drug has shown activity against MDR-TB, but has a fairly significant drawback – its toxicity. It can cause severe toxicities such as polyneuropathy, bone marrow depression and optic neuropathy.

In a retrospective analysis of German patients with M/XDR-TB that was presented at the meeting, the drug looked somewhat underwhelming. “Clear efficacy on treatment outcome could not be demonstrated,” said Dr Christoph Lange, who presented the findings, although he said there was an indication of better efficacy in a very small subset of people who were resistant to more than seven TB drugs. However, major adverse events were very common, so “treatment with linezolid against MDR/XDR-TB should be considered for the most difficult to treat patients only.”

Dr Dravnic agreed with the assessment of linezolid’s safety. “It can cause severe adverse events. Is it the most “dangerous” and difficult drug from MDR/XDR-TB treatment? Probably. At least in my experience, I’m quite scared of linezolid,” she said.

However, there appear to be much safer oxazolidinones (PNU100480 and AZD-5847) with better activity against TB that are now moving into clinical development for TB (see below). In the meantime, linezolid may represent an option for people with life-threatening X or pre-XDR-TB.

Meropenem/clavulanate

(sensitizing MTB to beta-lactams and possible other antibiotics)

Many antibiotics such as beta-lactams (which include penicillin) have little or no activity against MTB because the organism has an enzyme called β -lactamase that blocks their activity. However, almost two years ago, [scientists at the Albert Einstein College of Medicine published a paper showing that by combining a \$\beta\$ -lactamase inhibitor, clavulanic acid, with meropenem, a beta-lactam antibiotic, it was possible to sterilise cultures containing various TB strains, including XDR-TB.](#)

And during a late-breaker at this year’s ICAAC, researchers in Belgium reported on the treatment of four XDR-TB patients from Chechnya with meropenem/clavulanate and linezolid. Two responded rather promptly at one month, and three out of four survived with good responses, with culture conversion by week 20 and relapse free from 7 to fourteen months so far.

According to a presentation by Dr William Bishai of Johns Hopkins University and K-Rith (a new TB research group associated with the Nelson Mandela School of Medicine), this may just be the tip of the ice-berg for this type of approach. He presented preclinical data showing that it may be possible to develop inhibitors of other mTB enzymes that make TB resistant to other antibiotics as well.

New compounds

As already noted in a related article, a randomised trial has now shown that TMC-207 improves outcomes when added to standard MDR-TB treatment – the next question is how best it should be optimised in clinical practice.

OPC-67683 is a member of the nitroimidazole class of compounds that is being developed by Otsuka pharmaceutical company. This drug has been assessed in a phase 2 trial in 430 people with pulmonary MDR-TB (in cases of HIV co-infection, persons with a CD4 cell count of more than 350). Two different doses were added to optimised background therapy (OBT) and compared to placebo plus OBT. The primary outcomes, which are currently being analysed, are the proportion of patients with sputum conversion at 8 weeks and time to culture conversion.

PA-824 is also a member of the nitroimidazole class of compounds which is currently being evaluated in dose ranging and early bactericidal activity studies (in combination with other agents, see below).

Pfizer is developing PNU-100480, an oxazolidinone which shows substantially improved activity over linezolid in mouse models of tuberculosis. A phase I dose ranging study has been completed, with no hematologic or other typical oxazolidinone safety signals, according to Dr Leinhardt. At 600 mg BID, plasma concentrations remain below the IC₅₀ for inhibition of mitochondrial protein synthesis (one of the mechanisms for linezolid's bone marrow toxicity).

SQ109 (ethylenediamine) is a novel structure related to ethambutol with very high potency and long half-life. The first studies of this drug are as first line, because of its high synergy with rifampicin. However, the drug is also synergistic with TMC-207. Early bacterial dose-ranging studies are to be followed by a study in which SQ109 will be substituted for ethambutol in the standard regimen.

Challenges of clinical development

Dr Leinhardt pointed out that moving ahead with the clinical development of so many different compounds and approaches will be complicated. "We need to identify the best combination of drugs to improve efficacy, decrease treatment duration, improve adherence, decrease toxicity, simplify delivery and which is suitable in combination with ART," he said. Potentially though, it may be possible to develop a new combination that works 'for all comers' whether drug sensitive or resistant.

According to Dr Zhenkun Ma of the Global Alliance for TB Drug Development, one challenge is which combinations to prioritise for testing. At present, he said, there are roughly 10 separate types of oral anti-TB drugs, including the current TB drug classes and clofazimine, plus five broad new classes in development (potent fluoroquinolones, TMC207, SQ109, OPC67863 and PA-824 (both nitroimidazoles), and the oxazolidinones (PNU100480 and AZD-5847). Based upon that there could be 120 potential 3-drug combinations and 210 potential four-drug combinations. "Clearly, it is not feasible to test so many potential combinations in clinical trials, so we need a way to prioritise selection of regimens," he said.

He described a mouse model that GATDD is developing, looking at which combinations of agents are most synergistic. For instance, he said that there were very good data with PA-824 when it is combined with moxifloxacin and pyrazinamide. So this will be tested in the clinic soon, to see if it validates the method of preclinical selection for combinations to test.

Other questions concern whether there really is the capacity and funding to develop so many compounds, and whether there isn't a way to make the pathway to approval shorter.

"We need to shorten the pathway to development - that is absolutely agreed," said Dr Leinhardt. "But we have to find the best way to shorten this pathway and find an optimal way to assess combinations. For instance, we need suitable surrogate markers of drug activity to shorten the duration of phase 3 trials. We need increased trials capacity [with good quality assurance, TB infrastructure for DOT, and infection control, good lab/drug sensitivity testing capacity etc]. There is also a need for collaboration and there is a need to reassess the roles of respective concerned players. It is now clear that the pharmaceutical industry can carry new agents through phase 1-2 trials but the question is who will carry out the late stage phase 2 trials? This is a case where there is a need for collaboration. The TB Alliance can complete the path to drug registration. Public sector agencies (NIH, CDC, EDCTP, MRC) can help in completing the development of new regimens both for drug-sensitive and drug-resistant TB, Public sector regulatory agencies can also provide contexts to assure protection of new agents from rapid development of resistance," Dr Leinhardt concluded.

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Lung disease common in adolescents with HIV in Zimbabwe

By Keith Alcorn

Health care workers treating older children and adolescents with HIV in sub-Saharan Africa should be alert for early symptoms of chronic lung disease in their patients, and do their best to identify and treat HIV infection before it has a significant impact on those who survive beyond the first year of life.

The lung disease, which is not related to tuberculosis, is severely debilitating.

Without antiretroviral treatment around two-thirds of infants perinatally infected with HIV will die before reaching the age of one year, but evidence from southern Africa shows that among the remainder, survival into adolescence is common.

Twenty-eight per cent of infants infected with HIV around the time of birth or during breastfeeding will survive to the age of ten, and those who survive the first year of life have a median survival of 16 years.

Among this group of survivors, late presentation with HIV disease is common. Children often show severe stunting, delayed puberty and severe cutaneous problems before developing opportunistic infections.

"Although the number of younger children with HIV in our hospitals is melting away due to antiretroviral therapy, the number of older children we are seeing is growing," said Dr Rashida Ferrand, presenting findings from a study conducted in Zimbabwe to the 41st Union World Conference on Lung Health.

A large proportion of older children and adolescents presenting for care to health services in Zimbabwe are infected with HIV, Dr Ferrand told the conference. Among adolescents receiving care at hospitals in Zimbabwe HIV prevalence of 28% has been recorded, while 17% of 10-18 year olds attending primary care were HIV-positive in one cross-sectional study.

A survey of all children enrolled in the first year of primary education in one district of Zimbabwe found an HIV prevalence of 2.8%.

In a country like Zimbabwe with a population of 12 million and high HIV prevalence this means there could be around 30,000 older children and adolescents with undiagnosed HIV infection.

But Dr Ferrand said that among patients of this age group in Zimbabwe, one of the most common problems was chronic and progressive lung disease that frequently leaves patients almost unable to function normally.

She carried out a study in order to understand why so many adolescents without significant evidence of lung damage on chest X-ray were so debilitated, using CT scans to look in more detail at their lungs.

She presented results of a cross-sectional survey of 116 consecutive older children and adolescents with HIV presenting for care at two HIV clinics in Zimbabwe. The mean age was 14, and 69% were receiving antiretroviral therapy; the mean CD4 count was 380.

Among these patients 66% had chronic cough, 21% had a restricted ability to exercise as a result of reduced lung function (NYHA scale 2-4). Forty per cent had hypoxia and 44% had a reduced lung function defined as FEV1 <80% of predicted value. Seven per cent had pulmonary hypertension.

High resolution CAT scan showed that in 50% of patients, there was mosaic attenuation ([see link for definition and images](#)), which is strongly correlated with bronchiectasis and airflow obstruction – a condition called obliterative bronchiectasis (OB). It is also characterized by daily production of very large amounts of sputum, coughed up from the airways.

The condition is highly prevalent in Zimbabwean adolescents; a survey showed 44% with CD4 counts above 350 had some evidence of chronic lung disease.

The condition is probably not very responsive to ART, said Dr Ferrand, since there was no significant relationship between the duration of ART exposure and the severity of the condition, suggesting that the condition may be irreversible once established.

Dr Ferrand speculated that OB in children with HIV becomes progressive as a result of a cycle of viral and bacterial infections of the respiratory tract, leading to chronic inflammation, small airway damage and an increased risk of mycobacterial infection. Many of the children in the cohort had received multiple courses of presumptive treatment for tuberculosis as a result of their chronic cough.

Dr Ferrand said early diagnosis of HIV infection and prompt initiation of HIV treatment appeared to be the best way of preventing development of the condition, but further research was needed to determine the extent to which ART can prevent or relieve the condition.

Chronic cough in older children should be the trigger for more thorough investigation, said Dr Ferrand, rather than an immediate presumption of TB. "There's a need to stress that it's not always TB just because it's cough and the chest X-ray looks a bit dodgy," she said.

Although CT scans are not available in many countries outside private hospitals, Dr Liz Corbett of the London School of Hygiene and Tropical Medicine told **aidsmap**: "Once you know what [OB] is, and what to look for, the tests are straightforward"

"Measuring oxygen saturation is not difficult, and even measuring lung function, although it's technically challenging, is not a high cost intervention," said Dr Ferrand.

Very basic complaints about inability to exercise should trigger suspicion. "Being unable to sing because of the coughing is a common sign; it's a big social handicap in Zimbabwe," said Dr Corbett.

Dr Ferrand recommended the investigation of aggressive management of intercurrent respiratory infections in children with HIV, together with the use of prophylactic antibiotics. Use of a combination of antiretroviral therapy, bronchodilators and corticosteroids might relieve the condition or prevent progression, but this approach needs to be tested, especially given the risk of predisposing patients to TB by corticosteroid use, she said.

Reference

Ferrand R. *TB-HIV in adolescents – an emerging challenge*. 41st Union World Conference on Lung Health, Berlin, November 11-15, 2010.

Is self-testing for HIV on the way in Africa?

By Keith Alcorn

Self-testing for HIV using oral tests could radically increase HIV testing rates in tuberculosis programmes, TB researchers argued this weekend at the 41st Union World Conference on Lung Health in Berlin.

Similarly, community sputum collection points where individuals can go to provide a sputum sample for TB detection, without having to wait to see a nurse or doctor, have proved very popular in Zambia.

Rates of diagnosis for both TB and HIV remain very low, and even when a person is diagnosed with one infection, screening for the other infection may not take place.

Furthermore, even if people have symptoms that might indicate active TB, their likelihood of having those symptoms fully investigated is low. A community survey in Zambia in 2006 among 9,000 people who identified themselves as suffering from persistent cough found that only half had attended a health facility as a result, said Dr Helen Ayles of the London School of Hygiene and Tropical Medicine.

Just less than half who attended a health facility were asked to produce sputum in order to test for TB, and just 5% of all those questioned eventually started TB treatment, despite a local TB prevalence of 960 cases per 100,000 and a local HIV prevalence of 26%.

Given these barriers, TB specialists working in countries with a high burden of both TB and HIV have been asking how rates of diagnosis and access to care can be improved, as a first step towards reducing the burden of TB in these settings.

In Zambia the [ZAMSTAR study](#), led by Dr Helen Ayles, is currently comparing approaches to TB case-finding and TB/HIV service delivery. As part of its enhanced community case-finding strategy, the study is running community sputum collection points, as well as open access sputum collection points at health facilities. These require no appointment and no nurse time and will provide a result to patients within 48 hours.

A big advantage of these schemes, said Dr Ayles, is that they avoid concentrating patients with potentially infectious TB in crowded waiting rooms for long periods. People with suspected TB are very happy with the speed of the process, and keen to be tested when the barrier of extended waiting time is removed. Nearly 40% of the sputum samples being processed in the laboratories used by ZAMSTAR now come from community collection points, showing how much the innovative method is extending the reach of TB case-finding efforts.

Community sputum collection is also having other unforeseen benefits.

“Almost as soon as we set it up the community sputum collectors decided that the sputum collection points were going to be condom distribution points too,” said Dr Ayles.

From condom distribution it should be only a short step to offering HIV testing, but at the moment programmes predominantly offer conventional voluntary counselling and testing, or door-to-door testing. Significant resistance remains to voluntary counselling and testing, for a host of reasons, including the difficulty of attending the facility, fears about confidentiality and the quality of the counselling.

In Malawi, for example, research led by Dr Liz Corbett of the London School of Hygiene and Tropical Medicine has found that when compared with door-to-door VCT conducted by health care workers, the possibility of self-testing was much more attractive.

Self-testing using an oral saliva test has already been piloted in Malawi, and proved highly acceptable, said Dr Corbett. Ninety-one per cent of a sample of 260 randomly selected Malawians offered the opportunity to carry out the oral test themselves took the test, and 99.2% got the result right first time.

“Withholding a fabulous diagnostic from the population because of concerns about their ability to handle it seems lunacy to me,” said Dr Corbett.

“The commonest feedback we had was ‘why don’t we know about these tests and why isn’t the government in Malawi distributing these tests to everyone each year?’”

Some people are more cautious about the use of self-testing. Jeremiah Chakaya, head of Kenya’s National TB Control Programme pointed to [the recent case of a Kenyan policeman](#) who went on a rampage and shot ten people after learning that he was HIV-positive.

“HIV and sexually transmitted infections will remain stigmatised for a long time to come. There are absolutely no issues with the accuracy of the test but we shouldn’t promote self-testing without dealing with stigma.

“Disclosure is a big problem, as we can see from the preference for self-testing in Malawi. Will people go to their doctor and say ‘I

did a self-test yesterday and I am HIV-positive’, or will they go into themselves and get depressed and get angry?” he asked.

There’s also concern about forcible testing; some people raised concerns at the conference about the potential use of the tests to forcibly test partners or family members.

“If you can’t even negotiate condom use, how are you going to deal with it when your husband brings an HIV test kit home?” asked one delegate from South Africa during a debate on self-testing.

“One of the big things about self-testing is that couples really like it,” said Dr Liz Corbett. “Women are being tested through the PMTCT programme and men are using their status as a surrogate for their own status. Women told us ‘if we take the test kits home our men will test with us.’”

Concerns also exist about the effect of self-testing on sexual behaviour in those who test negative. There is some evidence from studies of voluntary counselling and testing that a negative test is not associated with a subsequent reduction in unprotected sex.

Self-testing already happening

Self-testing may now be an unstoppable development, and one that the health care sector and community organisations will have to learn to deal with. The implications of self-testing go far beyond TB programmes.

“I think this is coming whether people like it or not, and it’s already happening on quite a scale in South Africa,” said Dr Helen Ayles.

The first over-the-counter oral HIV test that can be conducted entirely at home is likely to be approved in the United States soon, opening the door to approval in many other countries.

Anecdotal evidence suggests that individuals are already gaining access to self-testing kits in South Africa, and the use of rapid antibody tests for self-testing by health care workers in Africa is widespread, acknowledged Dr Liz Corbett.

Dr Renee Ridzon of the Bill and Melinda Gates Foundation warns that self-testing is going to be necessary if antiretroviral-based prevention methods such as microbicides and pre-exposure prophylaxis become available, simply to accommodate the volume of regular testing that will be necessary to use these methods safely.

She expressed concern about the diversity of rapid tests currently available, and the potential for confusion about how to use tests accurately if multiple tests with different operating procedures are in circulation.

“Some test kits remain positive for ten minutes, others for 20 minutes. There’s a need for standardisation of the test specifications,” she said.

In a [recent article in the South African Medical Journal](#) Marlise Richter of Ghent University, Francois Venter of the Reproductive Health and HIV Research Unit at University of Witwatersrand and Andy Gray of the University of Kwazulu Natal argued that the way in which HIV tests kits are regulated in South Africa is yet another example of ‘AIDS exceptionalism’.

They say that self-testing should be enabled by a new regulatory regime in South Africa that would allow anyone to buy a test kit, supplied with written information about the test and the window period, together with a clear warning that testing another person without their consent is illegal. The test should be backed up by a toll-free hotline.

“Self testing changes the paradigm from ‘people with a disease’ to people taking responsibility for their health, but it will require empowerment,” said Dr Rony Zachariah of Médecins sans Frontières.

Nevirapine / rifampicin interaction linked to higher recurrence of TB in people on ART

By Keith Alcorn

People with HIV and tuberculosis who took a once-daily nevirapine regimen alongside TB treatment containing rifampicin were significantly more likely to develop a recurrence of TB than people taking efavirenz in a randomised trial, Indian researchers reported today at the 41st Union World Conference on Lung Health in Berlin.

TB and HIV treatment are complicated by the fact that one of the key drugs used in TB treatment, rifampicin, reduces blood levels of nevirapine by 30-55% and also reduces levels of most protease inhibitors.

A further complicating factor is that nevirapine must be given at a lower dose for the first two weeks of treatment in order to reduce the risk of toxicities, further increasing the risk of sub-therapeutic drug levels when dosed with rifampicin.

For these reasons treatment guidelines now recommend the use of an efavirenz-based antiretroviral regimen.

However nevirapine is widely used in antiretroviral therapy in resource-limited settings due to its low cost and availability in a wide range of fixed-dose combinations.

The alternative, efavirenz, is not currently recommended for pregnant women, particularly in the first trimester, due to evidence of a higher risk of birth defects in animal studies. (However a [recently published meta-analysis](#) found no elevated risk of birth defects in the offspring of women exposed to efavirenz in the first trimester.)

Indian researchers at the Tuberculosis Research Centre in Chennai designed a randomised study to investigate the extent to which responses to HIV treatment and TB treatment are compromised by drug interactions.

Virological responses to treatment in the study have already been presented ([see report here](#), including more detailed discussion of studies examining the response to nevirapine in people receiving rifampicin), and showed that patients receiving nevirapine were significantly more likely to experience virological failure, or a lack of virological response, when compared to those who received efavirenz.

Dr Soumya Swaminathan presented a follow-up analysis of the study looking at the incidence of TB according to antiretroviral regimen.

The trial randomised 116 patients with culture-confirmed TB and HIV infection between 2002 and 2006 to a once-daily regimen of ddI/3TC and either efavirenz or nevirapine, given as directly observed therapy each morning alongside the TB regimen. All patients received the recommended Indian regimen for TB treatment.

The primary outcomes evaluated in this analysis were the proportion of patients in each arm who were culture-negative for TB after 6 months of treatment in cases of pulmonary TB, and the proportion of patients who experienced improvement in lesions or symptoms of extrapulmonary TB, with radiological evaluation where appropriate.

The study found a significantly higher rate of TB recurrence in the nevirapine arm (3 of 54 patients in the efavirenz arm compared to 9 of 46 patients in the nevirapine arm, $p=0.03$) during long-term follow-up to month 18, and this difference appeared to be driven by the higher rate of virological failure of antiretroviral treatment.

Although there was a trend towards a higher rate of treatment failure at month 6 in the nevirapine group (92% vs 81%, $p=0.09$), this difference was not significant.

The findings are further evidence of the difficulties of using nevirapine in antiretroviral treatment for people with TB, and of the need for affordable alternatives to efavirenz when use of that drug is considered unsuitable, particularly in pregnant women.

Reference

Swaminathan S et al. *Tuberculosis treatment outcomes among patients treated with a short-course intermittent anti-TB regimen and either once-daily nevirapine or efavirenz-based antiretroviral therapy: a randomized trial*. 41st Union World Conference on Lung Health, Berlin, abstract LB3, 2010.

Immediate HIV treatment has biggest impact in TB patients with CD4 counts below 100

By Keith Alcorn

Minimising the gap between the start of TB treatment and the start of antiretroviral treatment had the biggest impact on death rates in people with very low CD4 counts, but made much less difference in patients with higher CD4 counts, observational cohort data from Rwanda show.

The findings, presented at the 41st Union World Conference on Lung Health in Berlin, also demonstrated a very similar reduction in the risk of death in patients treated early to that observed in the CAMELIA study, a randomised comparison of immediate versus delayed antiretroviral treatment in TB patients conducted in Cambodia.

The question of when to start antiretroviral treatment in people already receiving TB treatment has been the focus of considerable attention among researchers due to concerns about drug interactions between rifampicin and some antiretroviral drugs.

There has also been concern about the possible development of immune reconstitution inflammatory syndrome in people who have not cleared TB, and of a potential risk of death due to severe cases of IRIS.

For all these reasons there has been a tendency to delay the start of antiretroviral treatment until at least two months after starting TB treatment. Some physicians have preferred to delay antiretroviral treatment until after the completion of TB treatment, particularly in those with less advanced HIV disease and higher CD4 counts.

However a large study in South Africa, the SAPIT trial, reported in 2008 that delaying antiretroviral treatment until after the completion of TB treatment was associated with a significantly higher risk of death.

World Health Organization guidelines have subsequently been updated to recommend that antiretroviral treatment should be commenced in all HIV-positive patients receiving TB treatment, regardless of CD4 count.

What's remains unclear is just how soon after starting TB treatment it is necessary to start antiretroviral therapy in order to minimise the risk of death.

The SAPIT study is continuing with a comparison of starting antiretroviral treatment no more than two months after TB treatment, or starting within two weeks of starting TB treatment.

A US AIDS Clinical Trials Group (ACTG) study, ACTG 5221, is also comparing the effects of initiating antiretroviral therapy either two or eight weeks after starting TB treatment.

A study conducted in Cambodia, [the CAMELIA trial, recently reported](#) that among a group of patients with very advanced HIV disease, starting antiretroviral treatment within two weeks of TB treatment was associated with a significantly reduced risk of death. Intriguingly, the reduction in risk became more pronounced over time, and was not confined to the early period of TB treatment.

However, the results of the CAMELIA study may not be applicable to all settings, or to patients with higher CD4 counts, so in advance of results from further studies, researchers from Harvard Medical School and Partners in Health used routinely collected observational data from Rwanda to examine whether a similar pattern held true in their cohort.

In particular they wanted to examine whether the results of the CAMELIA study were generalisable to settings where it is not possible to carry out microbiological confirmation of TB (microbiologically confirmed TB was an entry criterion for the CAMELIA study).

Their study reviewed data from medical records of 308 patients with CD4 counts below 350 who had started TB treatment and subsequently started HIV treatment.

The researchers evaluated the two-year survival rate based on the delay between starting TB and HIV treatment regimens – 15, 30, 60 or 180 days.

They controlled for baseline confounding factors (CD4 count, age, gender, rural or urban care, inpatient or outpatient care), and for time-variant confounding factors (current CD4 count and hospitalisation).

In this population only 17% of patients had smear-positive pulmonary TB. Twenty-five per cent had smear-negative pulmonary TB; the remainder had extrapulmonary TB.

The median interval between starting TB treatment and starting ART was 72 days. Starting antiretroviral treatment within 15 days of TB treatment had a significant protective effect compared with any greater delay only in those with baseline CD4 counts below 100.

When the investigators compared the survival probability according to baseline CD4 count in the Rwanda cohort among those who started ART no more than 15 days after beginning TB treatment, they found a very close fit with the survival probabilities observed in the CAMELIA study among patients with very low CD4 counts.

Starting ART by day 15 was associated with 2-year survival probabilities of 0.82 [0.76 – 0.89] and 0.86 [0.80 – 0.92] in persons with baseline CD4 counts below 50 and 100 respectively in the Rwanda cohort.

In comparison the 2-year survival probability observed in the CAMELIA trial among those who initiated treatment within 15 days was 0.82 (0.78-0.86). In that study the median Cd4 count of participants was 25 cells/mm³.

Although the authors of the study are careful not to over-state the significance of the findings, they point out that observational databases such as the Rwanda cohort have a valuable role to play in informing future practice, and in providing information that may be lacking in clinical trials.

“Failure to draw on the experience of national treatment programs may come at a formidable cost to clinicians, patients and their families as they await results from randomized trials,” the researchers warned.

Reference

Franke MF et al. *Effectiveness of early antiretroviral initiation among HIV-infected adults with tuberculosis disease*. 41st Union World Conference on Lung Health, late breaker session, Berlin, 2010.

TB REACH call for proposals

TB REACH is accepting proposals for the second wave of funding for projects that promote early and increased case detection of tuberculosis (TB) cases and ensure their timely treatment, while maintaining high cure rates within National TB Programmes.

TB REACH encourages the development and application of innovative, ground-breaking and efficient interventions and activities that result in increased TB case detection, reduced transmission and prevention of the emergence of drug-resistant forms of TB. As suggested by its name, TB REACH focuses on reaching vulnerable people, people from poverty areas and/or people who have limited or no access to TB services.

Eligibility criteria, the application form, instructions for applicants, examples of suitable interventions and technical guidance, are available on the **TB REACH web site - Wave 2** <http://www.stoptb.org/global/awards/tbreach/wave2.asp>

The deadline for submitting proposals for Wave 2 is 28 February 2011.

Eligible applications will be reviewed by the Proposal Review Committee - an independent group of experts - during March 2011. All proposals recommended for funding will be presented for approval to the Stop TB Partnership Coordinating Board at its next meeting. The final results of the review are likely to be made available to all applicants by May 2011.

TB REACH was launched officially on 25 January 2010. Thirty projects in 19 eligible countries, which aim to detect and treat additional 40 000 new smear-positive TB cases, received funding under Wave 1.

The TB REACH initiative receives support from the Canadian International Development Agency (CIDA).

We encourage all organizations engaged in TB care to develop innovative approaches to TB detection and care - and to apply for funding to TB REACH Wave 2.

If you need further information, do not hesitate to contact the TB REACH Secretariat at tbreach@who.int

Prevention trial news

By Gus Cairns

Anti-HIV drugs prevent HIV infection, trial shows – if you take them

A randomised controlled trial has found that the HIV infection rate in HIV-negative gay men who were given a daily preventative pill containing two HIV drugs was reduced by 44%, compared with men given a placebo.

The efficacy in subjects who, by self-report and pill count, took the drugs more than 90% of the time was 73%.

The other big finding of the [iPrEx](#) (Pre-exposure Prophylaxis Initiative) trial was that while 93% of trial subjects reported taking the pills correctly, on the basis of drug level monitoring in blood tests, only 51% actually did so.

The investigators calculate that if participants had taken their pills every time, the efficacy of the drug regimen would have been at least 92%, compared with placebo.

The trial

The iPrEx trial gave identical pills containing either the antiretroviral (ARV) drugs tenofovir (*Viread*) plus FTC (emtricitabine, *Emtriva*), or a dummy placebo pill, to 2499 initially HIV-negative men who have sex with men at high risk of HIV infection, in nine cities in four continents. The men were told to take the pills once a day.

The trial subjects were told there was a 50% chance they might be taking a placebo and were therefore 'instructed' to maintain safer sex. The men paid study visits every four weeks during the two-year study. At every study visit they were tested for HIV, asked about their risk behaviour, given adherence and safer-sex counselling, and provided with condoms.

The subjects were followed for an average of 14 months between July 2007 and December 2009: 31% were followed for two years or more.

Who took part

Over 4900 subjects were screened, of whom 2406 were ineligible or never joined the study, 410 (8.5%) because they turned out already to have HIV. Patients with high liver enzyme or creatinine levels, indicating liver or kidney damage, were excluded.

The average age of the men enrolled was 27 and three-quarters classed themselves as Hispanic and/or of mixed race (participants could choose more than one category). Nineteen subjects (1%) classed themselves as female transgenders. Sixty-eight per cent came from Lima or Iquitos in Peru or Guayaquil in Ecuador: iPrEx was initially launched in these two countries and other study sites added later.

At screening the average number of sexual partners reported by trial subjects in the past three months was 18. Sixty per cent reported unprotected anal intercourse (UAI) in the last three months, 77.5% reported UAI with a partner of unknown HIV status in the last six months and 2.5% with a partner known to have HIV. Thirteen per cent tested positive for syphilis and 35% for genital herpes (HSV-2), for which they received treatment, as did all subjects with STIs. A third had already had hepatitis B and were immune and two-thirds were offered hepatitis B vaccine.

One notable finding was a high level of alcohol use in the trial subjects: over half (54%) had more than five alcoholic drinks per day.

Safety

Few side-effects attributable to the study drug were observed. There was a higher level of nausea (9% versus 5%) in the first month in patients who took tenofovir/FTC, and the investigators advance this as a possible contributing factor to low adherence. Trial subjects gained weight, on average (due to maturing age in this young cohort), but in subjects on tenofovir/FTC the weight gain was delayed by three months relative to subjects on placebo. Nausea of grade 2 level or above (stronger or more long-lasting feelings of nausea) was experienced by 2% of the tenofovir/FTC group compared to 1% of the placebo group.

There were twice as many reports of raised creatinine levels in patients taking tenofovir, which is associated with kidney damage in a minority, though reports were rare: 25 (2%) in patients on tenofovir/FTC versus 14 (1%) on placebo. Five patients were taken off tenofovir/FTC due to raised creatinine levels but four of these re-started and creatinine levels did not rise again.

Resistance

During follow-up 110 men tested HIV antibody positive. It was subsequently found, by doing viral load tests on stored blood, that ten of these subjects actually had acute HIV infection at the time of recruitment, which was not detected using HIV antibody tests.

Doctors' notes showed that at least seven of these ten subjects had symptoms suggestive of acute HIV infection.

Of the ten participants who had acute HIV infection at baseline, three (one taking placebo) had HIV that was resistant to FTC when they were tested at week four of the study. The one taking placebo clearly had transmitted drug resistance (he had AZT and NNRTI resistance too): one appears to have acquired FTC resistance due to taking the PrEP drugs with a lot of HIV in his body (he had a viral load of 10 million at baseline); and one had a very low viral load at enrolment and could not be given a resistance test, so we cannot say if he developed resistance in response to PrEP.

No-one in the trial developed resistance to tenofovir and none of the 100 people who became HIV-positive during the trial developed any drug resistance.

Efficacy

Of the 100 infected during follow-up, 36 infections occurred in men given tenofovir/FTC and 64 in men given placebo, yielding an overall efficacy of 44% (95% confidence interval, 15% to 63%; $p = 0.005$).

No HIV drug resistance was found in any subject who acquired HIV during follow-up.

On the basis of pill counts and self-reports, study subjects would have been judged as taking their pills at least 86% of the time and on average over 95% of the time.

In subjects reporting greater than 50% adherence, the efficacy of tenofovir/FTC was 50%. Efficacy in subjects reporting unprotected receptive anal intercourse at screening was 58%; in subjects reporting no receptive sex, efficacy was actually negative, indicating that PrEP may only make a significant difference to infection risk in the highest-risk men, namely ones who take the receptive role in unsafe sex.

Efficacy was also significantly greater than placebo in men reporting over 90% adherence (73% efficacy); aged over 25 (59%); with at least secondary education (54%); who took fewer than five alcoholic drinks a day (57%); who were circumcised (77%); and who did not have HSV-2 (54%).

Adherence and drug levels

A surprise awaited researchers when they tested for drug levels. They did not do this with every trial subject but tested every subject who became infected with HIV and compared them with two uninfected, matched controls.

They found that drug levels were detectable in either the blood or cells of only 9% of subjects who became infected. But they also found that drug levels were detectable in only 51% of the HIV-negative controls, including 54% who reported over 50% adherence.

The drug level assays used could detect drug in the cells up to two weeks after a dose, indicating not only that far fewer subjects than reported were actually taking their pills, but that this was a long-term pattern and not caused by sporadically missing doses.

The investigators calculate on the basis of these figures that if all subjects had taken the study drug exactly as prescribed, the efficacy would be at least 92% and possibly up to 95%.

Why not only the poor efficacy, but the concealment of it? [Other HIV prevention trials have shown that trial subjects adhere to their](#)

[medication considerably less than they report](#). This may be influenced, the iPrEx investigators speculate, by knowledge that they may be on placebo or by side-effects. However qualitative surveys found that some of the participants found the style of adherence counselling “overbearing”, according to Principal Investigator Bob Grant, and a new non-directive style of adherence counselling will continue into the rollover study.

In pre-exposure prophylaxis, poor adherence is of concern because it might give rise to HIV drug resistance, although in this trial it appears that adherence in those who did acquire HIV was so low this did not happen.

Conclusion

This is the first study to definitively prove that pre-exposure prophylaxis, as a concept, works. Under study conditions, it protected nearly half of a group of high-risk gay men who would otherwise have caught HIV. With good adherence, its likely efficacy would be considerably greater.

As such, especially in conjunction with the result of the [CAPRISA 004 microbicide trial](#), is a major advance in the study of HIV prevention methods and potentially adds new prevention options.

Bob Grant commented: “I hope this will inspire and galvanise an active discussion in people who care about HIV prevention.

“We now have four positive signals on new methods of HIV prevention - circumcision, a vaccine, microbicides and now PrEP; we have the possibility of constructing an active portfolio of prevention methods for individuals, with the support of an engaged community.

“These were mainly young guys in the trials who were finding out who they were. These are the people PrEP will be useful for. We can say ‘We want you to develop your own ways to protect yourself, but meanwhile, here’s a pill that can maybe protect you while you’re doing that.’”

An open-label rollover study, with all participants in the original study who wish to continue PrEP, will start in early 2011 and will report in 2013.

Reference

Grant RM et al. *Preexposure chemoprophylaxis for HIV prevention in men*. *New Engl Jour Med* early online edition, 23 November 2010.

PrEP, the big issues: iPrEx study directors discuss unanswered questions

The success of [the iPrEx study of pre-exposure prophylaxis](#) (PrEP) in gay men opens up as many urgent questions as it has answered. This became clear as the results of the study were discussed by Anthony Fauci, head of the US National Institute of Allergies and Infectious Diseases (NIAID), who were the biggest funders of the trial, and Bob Grant, the iPrEx study’s Principal Investigator.

To summarise, the iPrEx study gave half of a group of men who have sex with men (MSM) who were at high risk of HIV infection one *Truvada* (tenofovir+FTC) pill a day and the other half a placebo. After an average 14 months on the regimen there were 44% fewer infections in men taking *Truvada* than in men taking placebo.

How do we support adherence to PrEP?

The other interesting finding was that adherence in the study was not only lower than expected, it was also a lot lower in reality than it was on the basis of participants’ own reports or by counting the number of pills dispensed. Participants claimed at least 90%

adherence but a substudy, in which drug levels in participants’ blood and immune cells were measured, suggested that in reality it was about 50%.

Subanalyses were done suggesting that, based on pill counts and self-reports, the efficacy of PrEP in people who took more than half their doses was 50% and in people who took 90% of their doses was 74%. However the significantly lower ‘real’ adherence levels make analyses based on pill counts unreliable, as they assumed all pills dispensed were taken.

We can’t really say, therefore, that PrEP will definitely work if you have perfect adherence, nor can we say (as one agency concluded) that PrEP definitely *won’t* work if your adherence is less than 90%.

“All we can say,” Susan Buchbinder, one of the iPrEx investigators told Aidsmap, “is that it does look like people who were able to take their drug more regularly were more likely to be protected.”

This on the one hand is discouraging as it suggests adherence will be a big challenge in making PrEP work; on the other hand it suggests that the potential efficacy of PrEP is very high – as efficacious as condoms if not more so – and if we can help patients achieve high adherence it could offer significant protection against infection.

Bob Grant, the study’s global Principal Investigator, said: “Although daily use of a pill to prevent something is challenging, it is feasible. We know from the use of statins to prevent high cholesterol and, perhaps more relevantly, oral contraceptives to prevent pregnancy, that people will adhere to preventative regimens if they see enough benefit in them.”

He said that the iPrEx researchers would be looking into the adherence and efficacy question much more deeply, and would be checking thousands of other stored samples for drug levels to get a much more accurate idea of the true adherence levels in the trial. These investigations would not only help establish a truer picture of efficacy but also look at whether people gave up taking their pills at characteristic times: if those who stopped taking *Truvada* did so very soon after starting, for instance, it might suggest that the reason was side-effects.

He emphasised that one of the most promising aspects of the trial was that efficacy was highest in the highest-risk people: the men who had significant levels of unprotected anal sex as the passive partner. In fact there was little measurable efficacy in men who denied being receptive in anal sex.

“It became apparent early in the trial,” he said, “that iPrEx was attracting the highest risk individuals. Many had never had an HIV test before or come forward for help with prevention, yet here they were volunteering to be part of a prevention initiative. It was also just as effective in the youngest men in the study as in anyone else.”

A rollover study offering every participant in the study open-label *Truvada* will start in early 2011. This study, which will last till 2013, will allow the investigators to monitor for longer-term side effects and long-term changes in behaviour.

Importantly the study will also use a completely different style of adherence counselling, which was piloted in the last few months of iPrEx. Feedback from interviews with participants showed that they found being reminded about adherence by the same people who were giving them blood tests was not conducive to being honest about adherence problems. The rollover study will therefore feature adherence counsellors who are completely separate from the staff doing monitoring tests, and who will not be informed of patients’ adherence levels as assessed by blood tests: all patients will be treated equally and asked about what factors are making it easy or hard to take the pills.

Should PrEP become standard of care in prevention trials?

One thorny question resulting from iPrEx is whether, given that the intervention appears to be potentially very effective, forthcoming or ongoing prevention trials should now start using *Truvada* as their control arm instead of an inactive placebo.

Anthony Fauci said that this was a difficult question and the answer would depend on the trial. iPrEx had only established the efficacy of PrEP in one population and it might be very different in others: if studies started using *Truvada* instead of placebo they might have to become unrealistically large, and we might fail to demonstrate whether PrEP had universal efficacy. He said that NIAID would approach this question on a case-by-case basis, going through every trial protocol to decide if a placebo arm was still ethical.

Possible answers to this included re-consenting trial participants so that they were informed of the iPrEx results and asked if they still wished to remain in the trial, or adding a third arm comparing oral *Truvada* to whatever other intervention was being studied, but he could not predict what was going to happen without an investigation of all studies.

Community recommendations

The same cautions also applied to what messages to send out to affected communities and the people who care for them.

Anthony Fauci said that, on the one hand, because *Truvada* was already available, the formulation of new guidelines was urgently needed so that potential providers, from individual physicians to insurers, understood what iPrEx told us and, more importantly, did not tell us about PrEP in case patients asked for it.

The US Centers for Disease Control (CDC) moved particularly fast to counsel caution about immediately assuming we had a new prevention tool for gay men.

Pointing out that one implication of the findings was that anything under 90% adherence *might* be ineffective, the CDC said: "PrEP should never be seen as the first line of defence against HIV. It was only proven to be partially effective when used in combination with regular HIV testing, condoms and other proven prevention methods, and it does not protect against other sexually transmitted infections".

It emphasised that the cornerstones of HIV prevention for gay men remained using condoms consistently and correctly, getting tested to know their status, getting treated for STIs, getting support to reduce drug use and sexual risk behaviour, and trying to reduce the number of sexual partners.

Fauci said that the CDC should now get together with other stakeholders to produce a unified set of recommendations for prevention in light of these new findings. "Is [taking PrEP] something we want people to do," he asked, "given that we don't know anything about its effects in women or men, and we know nothing about its long-term implications?"

In terms of moving forward to licensing *Truvada* as a preventative drug, Bob Grant said that because tenofovir and FTC had been used as treatment for eight or nine years and their safety profile well-known, a completely new marketing authorisation would not be necessary and all that was needed would be a change of indication on the label. It would, however, probably take at least one more convincing trial result in a different population before this could be considered.

Resistance and acute infection

One of the acknowledged problems with PrEP is that it is almost impossible to eliminate the possibility that some people might come forward for it who already have HIV, especially acute HIV infection that does not yet show up on antibody tests. This happened to ten people in the study, and one or two of them appear to have developed drug resistance as a result. Routine HIV RNA testing to detect viral load in people yet to form antibodies would be prohibitively expensive.

Bob Grant said that there were cheaper alternatives such as p24 antigen testing, already used in the UK, but noted that at least seven out of the ten participants who had acute HIV infection had symptoms that were severe enough for them to seek medical attention. Although it would not eliminate all acute infections, he said, a guideline should be adopted that said that PrEP should under no circumstances be started if people have flu-like symptoms, a rash, a sore throat or any other symptoms suggestive of a viral infection.

Cost and practicality

The list price for *Truvada* in the US is \$14,000 a year and even in heavily-discounted public schemes still costs thousands. Fauci and Grant were asked how using a 'chemical condom' that cost \$38 a day could be justified when condoms themselves cost a few cents each.

Fauci said that he thought that the iPrEx results might change the pricing structure of the drugs. "We might start seeing a whole range of prices," he said, "and we have to remember that generics are available in many countries." He was, however, concerned whether downward pressure on the prices of tenofovir and FTC might increase disparity between different countries.

At this point Javier Lama, the local principal investigator for Peru, said that, ironically, neither generic nor branded *Truvada* was yet available for HIV treatment in Peru, though he hoped it would be next month, and the separate drugs were available.

In the developed-world context, further cost-effectiveness analyses, such as computing the cost of the intervention per infection averted, would be needed to convince insurers [and, in the case of countries like the UK with universal-access healthcare, evaluation agencies like NICE], that paying for PrEP was worthwhile.

The biggest question around cost and practicality is the concern that providing antiretrovirals for HIV prevention could be seen as a distraction or as competing for scarce resources in a world where, as Anthony Fauci re-emphasised, only 36% of people with HIV have access to ARVs to save their lives.

Bob Grant said that he could see increasing "synergy" between HIV treatment and prevention approaching. "We have to have something to slow the spread of HIV in these communities," he said, "and only treating the already-infected does not seem to be slowing the rate of new infections enough." He foresaw antiretrovirals being provided in integrated prevention-and-treatment programmes that would also feature testing, prevention advice and so on. "Might using these drugs for prevention also encourage people to test, reduce stigma, and encourage treatment uptake?" he asked.

Fauci also thought that PrEP might only be necessary for short periods of people's lives. "We think it may become a bridge to other protective behaviours," he said.

HIV treatment advocates also expressed caution about the implications of iPrEx for people with HIV, but also emphasised that the treatment experience of people with HIV might be crucial in helping people come forward for testing.

Kevin Moody, Chief Executive Officer of the Global Network of People Living with HIV (GNP+) said: "As treatment and prevention come together, it is important to involve HIV-positive people in discussions about how PrEP can and should be made available in the future.

"People living with HIV have a crucially important role to play in HIV prevention, both for the development of new HIV prevention tools and in advocating for improved access to existing prevention options."

Further information

See also [Anti-HIV drugs prevent HIV infection, trial shows - if you take them](#). (23 November 2010).

We have previously reported research from the iPrEx trials on adherence to PrEP, presented at the Fifth International Conference of HIV Treatment Adherence in Miami. See [Adherence to ARV prevention methods is challenging, partly because they don't treat illness](#) (27 May 2010).

For more information on pre-exposure prophylaxis (PrEP), visit the [PrEP pages of our website](#).

For more information on the iPrEx trial, visit the iPrEx website: www.globaliprex.com

Other news

By Keith Alcorn

Mobile phone messages improve adherence and HIV control in Kenyan trial

A text message from a clinic each week resulted in better adherence and a higher level of viral load suppression among people with HIV after starting antiretroviral treatment in Kenya, a randomised controlled trial has shown.

The results were published in the Online First section of *The Lancet* this week. The trial was sponsored by the US President's Emergency Plan for AIDS Relief (PEPFAR).

The intervention cost around 20 cents per patient each month, and would potentially allow one nurse to monitor adherence and other issues in 1000 patients each month, the researchers calculated.

Mobile phones are emerging as a new tool in health care. In sub-Saharan Africa mobile phone networks have expanded to cover much of the continent, and phone ownership is growing exponentially.

The Kenyan study is the first randomised study to test whether sending a reminder message sent to patients taking antiretroviral drugs in sub-Saharan Africa not only improves adherence, but also has a long-term effect on responses to treatment.

The study was conducted at two clinics in Nairobi (one serving a very low income area and one a more prosperous district) and at one clinic in a rural district.

It recruited patients starting ART for the first time who owned a mobile phone (88%) or who had access to a shared phone (12%). Patients paid for their own air time and text messages.

The study recruited 538 participants eligible for antiretroviral therapy under Kenyan national guidelines in 2007 and 2008, and participants were randomised either to the text message group (n=273) or the standard care group (n=265).

Patients received structured adherence counselling prior to starting treatment, and those in the message group were told to

report if they had any problems with adherence in responses to their weekly text message from the clinic.

Typically, the slogan "Mambo?" was sent, which is Kiswahili for "How are you?" The health workers used multiple recipient (bulk) messaging functions to improve efficiency. Patients in the intervention group were instructed to respond within 48 hours that either they were doing well ("Sawa") or that they had a problem ("Shida"). The clinician then called patients who said they had a problem or who failed to respond within two days.

The primary outcomes measured in this study were self-reported ART adherence (>95% of prescribed doses in the past 30 days at both 6 and 12 month follow-up visits) and viral load suppression below 400 copies/ml at 12 months.

During the study 114 patients dropped out, including 44 patients lost to follow-up and 55 who died. There was no significant difference in loss-to-follow-up rates between the two groups.

Intent to treat analysis, which evaluated outcomes in everyone recruited to the study, with lost patients counted as failures, showed that optimal adherence to ART was reported in 168 of 273 (62%) patients receiving the message intervention compared with 132 of 265 (50%) in the control group. Suppressed viral loads were reported in 156 of 273 patients (57%) in the message group and 128 of 265 (48%) in the control group.

On treatment analysis, which counted only those who remained in the study until the end, showed no significant difference in adherence (91%) but a significantly higher rate of viral suppression in the message group (75% vs 66%, p=0.047).

After adjustment for baseline factors such as age, CD4 count, gender, literacy and income, adherence in the message group remained significantly better (odds ratio 0.57, 95% confidence interval .040 – 0.83, p=0.0028). The relationship between message receipt and viral load suppression was less strong in the adjusted analysis, and was on the borderline of statistical significance (odds ratio 0.70, CI 0.50 – 1.01, p=0.058).

Overall, an average of 3.3% of patients sent messages indicating that they needed help each week, and this proportion declined from 6% in the first three months to 2% afterwards (p<0.0001).

No breaches of confidentiality as a result of text messaging occurred during the study, and patients were highly satisfied with the service. 98% said they would recommend it to a friend, and all but three patients receiving the service at the end of the study said they wanted it to continue. Many patients said they valued the service because they felt "like someone cares".

The study had a very low impact on health care staff; it required no advance training to deliver the service, and the researchers estimated that one nurse could manage 1000 patients and expect to call only 33 patients each week.

The researchers say that one extra patient would achieve adherence for every nine patients using the SMS service; while one extra person would achieve viral suppression for every 12 treated in the SMS group.

In conclusion, say the authors, the study has a number of important implications.

It is the first to show that an adherence intervention has an effect on virological failure rates, and it is a very low-cost intervention. If it was applied to everyone receiving ART in Kenya through PEPFAR funding (297,000 in 2009), they calculate, it would result in an additional 26,354 people with suppressed viral load.

The authors also note that increasing viral suppression in the population is likely to have a knock-on benefit for HIV prevention.

In an accompanying editorial comment, Jeffrey Stringer and Benjamin Chi of the Centre for Infectious Disease Research in

Zambia say that policy makers should now consider bringing the intervention to scale, but say a number of questions still need to be investigated before copying the intervention.

At the moment, they say, it's not clear how the once-weekly message affected adherence. Also, it's not clear how it would work in other countries, particularly where fewer people own phones. Would it be necessary to provide phones or subsidise airtime?

They also say think that cost-effectiveness needs to be studied, since if it was applied across the whole national treatment programme in Kenya, it would take up 1% of the current budget at a

cost of around \$2.6 million. But this might be cost-effective given the cost of second-line treatment, they say.

Reference

Lester RT et al. *Effects of a mobile phone short messaging service on antiretroviral treatment adherence in Kenya (WeTel Kenya1): a randomised trial*. The Lancet, advance online publication, November 9, 2010.

about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

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

For further information please visit the HATIP section of aidsmap.com