

## Treatment of tuberculosis: present status and future prospects

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**Abstract** Over recent years, tuberculosis (TB) and disease caused by human immunodeficiency virus (HIV) have merged in a synergistic pandemic. The number of new cases of TB is stabilizing and declining, except in countries with a high prevalence of HIV infection. In these countries, where HIV is driving an increase in the TB burden, the capacity of the current tools and strategies to reduce the burden has been exceeded. This paper summarizes the current status of TB management and describes recent thinking and strategy adjustments required for the control of TB in settings of high HIV prevalence. We review the information on anti-TB drugs that is available in the public domain and highlight the need for continued and concerted efforts (including financial, human and infrastructural investments) for the development of new strategies and anti-TB agents.

**Keywords** Tuberculosis, Multidrug-resistant/drug therapy; Antitubercular agents/administration and dosage/adverse effects; Directly observed therapy; Drug therapy/trends; Drug combinations; Quinolones; Quinolone; Nitroimidazoles; Quinolizines; HIV infections/drug therapy; Evaluation studies (source: MeSH, NLM).

**Mots clés** Tuberculose résistante à la polychimiothérapie /chimiothérapie; Antituberculeux/administration et posologie/effets indésirables; Thérapie sous observation directe; Chimiothérapie/orientations; Association médicamenteuse; Quinolones; Quinolines; Nitroimidazoles; Quinolizines; Infection à VIH/chimiothérapie; Etude évaluation (source: MeSH, INSERM).

**Palabras clave** Tuberculosis resistente a multidrogas/quimioterapia; Agentes antituberculosos/administración y dosificación/efectos adversos; Terapia por observación directa; Quimioterapia/tendencias; Combinación de medicamentos; Quinolonas; Quinolinas; Rifamicinas; Nitroimidazoles; Quinolizinas; Infecciones por VIH/quimioterapia; Estudios de evaluación (fuente: DeCS, BIREME).

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### Introduction

The expanding HIV pandemic has had a profound adverse effect on tuberculosis (TB), resulting in a general increase in the burden of TB, increasing the risk of active disease, the risk for reactivation of latent TB and TB case fatality. About one-third of people infected with HIV are also infected with TB and 70% of these people live in sub-Saharan Africa (1). The incidence of TB is declining in all countries except those with a high prevalence of HIV, where it is on the increase (2). When fuelled by HIV infection, the increase in the incidence of TB outstrips the capacity of current strategies to handle the burden.

Modern evidence-based short-course regimens for the treatment of TB have been among the most effective, and cost-effective, ways of securing healthy human life, especially

when administered under DOTS,<sup>a</sup> the global strategy for TB control as developed by the Stop TB partnership and WHO (3). However, problems include early case finding, ensuring patient adherence to 6 months of treatment, the occurrence of adverse drug reactions and interactions (especially among HIV-positive patients), and the emergence of multidrug-resistant TB (MDR-TB), which, by definition, is resistant to isoniazid and rifampicin, but may or may not be resistant to other agents.

With the magnitude of the TB problem increasing as a result of the synergistic HIV pandemic, the new WHO framework for the control of TB in high-HIV settings advocates significant expansion in the scope of the DOTS strategy, beyond effective case finding and cure (4). This expansion includes intensified case finding and cure, preventive treatment for

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<sup>a</sup> The name 'DOTS' is derived from 'directly observed therapy, short-course' but is no longer an acronym and is used to describe a broader WHO public health strategy for TB control.

TB, and interventions aimed at preventing and treating HIV, thereby directly and indirectly reducing the burden of TB. It is increasingly recognized that, over the long term, new anti-TB agents will need to be effective and safe for use not only in patients with this disease, which has been a scourge of the human race for millennia, but also in patients who are infected with HIV, some of whom will be receiving treatment with antiretroviral agents. In the short term, the role and relevance of existing strategies for the control of TB, for the same reason, will need to be continuously reassessed. New diagnostic tests, drugs, drug combinations or regimens are needed to address the problems of early TB and MDR-TB case finding, addressing latent infection with TB, treating co-infection with TB and HIV, and treating drug-resistant TB, including MDR-TB. The duration of therapy needs to be shortened, agents that have been lost because of the development of resistance need to be replaced, the safety and convenience of regimens require improvement, and fresh assessments of current strategies — dosing intervals of intermittent treatment, and identification of optimal regimens and timing of treatment for people infected with HIV — are called for.

## The evolution of present-day anti-TB drug regimens

After the discovery in 1944 of the first effective anti-TB agent, streptomycin, clinical studies revealed that resistance to this agent developed readily. Although this problem was solved by the use of combination therapy with other agents discovered at around this time (notably, isoniazid and *para*-aminosalicylic acid), other problems were encountered. Foremost among these was the difficulty in ensuring patient adherence to a lengthy course of therapy associated with painful injections and toxic adverse effects.

A major advance occurred in the late 1960s with the discovery of rifampicin, which enabled the development of orally administered regimens that ultimately reduced the length of therapy from 18–24 months to a mere 6 months. The aim of therapy is not just to cure the patients and to prevent their relapse, but also to render them rapidly non-infectious and to prevent the emergence of drug resistance. Anti-TB agents are therefore selected to rapidly kill actively metabolizing bacilli in the lung cavities, to destroy less actively replicating bacilli in acidic and anoxic closed lesions and to kill near-dormant bacilli that might otherwise cause a relapse of the disease (5). In this context, a distinction is drawn between agents that will kill bacilli *in vitro* (bactericidal agents) and those that will sterilize lesions *in vivo*.

The most effective agents for the destruction of tubercle bacilli in the three categories described above are, respectively, isoniazid, pyrazinamide and rifampicin. Accordingly, these three agents form the basis of modern regimens, which are divided into an initial 2-month intensive phase in which all three agents are administered together with, in most regimens, a fourth agent, usually ethambutol (6). These agents destroy almost all bacilli in the three physiological categories during the initial intensive phase of treatment. This phase is followed by a continuation phase, usually a 4-month course of rifampicin and isoniazid. The former kills any residual dormant bacilli and the latter kills any rifampicin-resistant mutants that commence replication.

The regimens recommended by WHO for four categories of patient are listed in Table 1. In practice, most patients

would be placed in category I. The 6-month regimens with rifampicin throughout are preferable, since rifampicin is the most potent sterilizing drug available for use in treating TB. The first-line anti-TB agents and their properties are briefly summarized in Table 2.

## Regimens for drug-resistant and MDR-TB

Resistance to one or more anti-TB agents is a worldwide problem and the distribution of various forms of resistance, which varies considerably from region to region, has been determined by means of a number of surveys (7). TB that is resistant to a single agent (most often, isoniazid) is not uncommon and most patients respond to the standard regimens. There is a theoretical risk that patients who are resistant to isoniazid will be at an increased risk of developing resistance to rifampicin during the continuation phase of treatment as they will then, effectively, be receiving rifampicin monotherapy. At present, however, this possibility is not supported by clinical evidence (8).

Cases of MDR-TB are much more difficult to treat, the therapy being based on agents that are often more toxic, more expensive and less active than the standard first-line drugs. Furthermore, the therapy is of longer duration than that of standard regimens, being continued for 9 months to 1 year after the sputum becomes bacteriologically negative, and careful supervision of medication is required to prevent relapse with disease that has become resistant to even more drugs.

Treatment is based on the use of any of the first-line drugs (such as pyrazinamide, to which the strains are still susceptible) and on alternative or second-line drugs (9). These include older agents such as ethionamide and the closely related prothionamide and, rarely, cycloserine, capreomycin, *para*-aminosalicylic acid, and also some more recently discovered classes of drugs, notably the fluoroquinolones (e.g. ofloxacin, moxifloxacin). There is limited evidence that the antileprosy drug clofazimine, newer macrolides (clarithromycin, azithromycin) and combinations of penicillins or cephalosporins and  $\beta$ -lactamase inhibitors, such as amoxicillin-sulbactam and cefazolin-clavulanic acid combinations, are also of use (10). The second-line anti-TB agents and their properties are briefly summarized in Table 3.

With careful management, many patients with MDR-TB may be cured, although mortality in those who also have HIV disease remains high. The strategy for managing MDR-TB has been named “DOTS-Plus” (11), and WHO has published treatment guidelines and convened a “Green Light Committee” for establishing, assessing and evaluating pilot projects under this strategy (12).

Ideally, treatment regimens are determined for each patient on the basis of tests for drug susceptibility, but where this cannot be achieved empirical treatment is given on the basis of the predominant patterns of drug resistance in a given region.

## Drug formulations

Combination preparations containing two, three or four first-line drugs facilitate patient compliance and ensure that patients receive all the drugs, thereby lowering (but not completely avoiding) the risk of development of drug resistance (13). Only combination preparations that have been evaluated by WHO-approved laboratories should be used, since the production of such preparations requires skill and experience (14). Combination preparations may be obtained, at low cost, from the Global Drug Facility of the WHO Stop TB Partnership (15).

Table 1. Short-course anti-TB<sup>a</sup> drug regimens recommended by WHO for different diagnostic categories of patients (6)

TB diagnostic category	TB patients	Initial phase <sup>b</sup> (daily or, in some regimens, three times per week)	Continuation phase <sup>b</sup>
I	New smear-positive patients; new smear-negative PTB <sup>c</sup> with extensive parenchymal involvement; concomitant HIV disease or severe forms of extrapulmonary TB	<b>Preferred</b> 2 HRZE <sup>d,e</sup>	<b>Preferred</b> 4 HR 4 (HR) <sup>3</sup> 6 HE
		<b>Optional</b> 2 (HRZE) <sup>3</sup> or 2 HRZE	<b>Optional</b> 4 (HR) <sup>3</sup> or 6 HE
II	Previously treated sputum smear-positive PTB: - relapse; - treatment after default	<b>Preferred</b> 2 HRZES <sup>f</sup> / 1 HRZE <sup>g</sup>	<b>Preferred</b> 5 HRE <sup>g</sup>
	Treatment failure of category I in settings with: - adequate programme performance; - representative DRS <sup>h</sup> data showing high rates of MDR-TB and/or capacity for DST <sup>i</sup> of cases, and - availability of category IV regimens	<b>Optional</b> 2 (HRZES) <sup>3</sup> / 1 HRZE <sup>3</sup>	<b>Optional</b> 5 (HRE) <sup>3</sup>
	In settings where - representative DRS data show low rates of MDR-TB or individualized DST shows drug-susceptible disease	<b>Preferred</b> 2 HRZES / 1 HRZE	<b>Preferred</b> 5 HRE
	or in settings of - poor programme performance, - absence of representative DRS data, - insufficient resources to implement category IV treatment	<b>Optional</b> 2 (HRZES) <sup>3</sup> / 1 HRZE <sup>3</sup>	<b>Optional</b> 5 (HRE) <sup>3</sup>
III	New smear-negative PTB (other than in category I) and less severe forms of extra-pulmonary TB	<b>Preferred</b> 2 HRZE <sup>j</sup>	<b>Preferred</b> 4 HR 4 (HR) <sup>3</sup>
		<b>Optional</b> 2 (HRZE) <sup>3</sup> or 2 HRZE	<b>Optional</b> 4 (HR) <sup>3</sup> or 6 HE
IV	Chronic (still sputum-positive after supervised re-treatment); proven or susceptibility MDR-TB cases <sup>k</sup>	Specially designed standardized or individualized regimens	

<sup>a</sup> TB = tuberculosis.

<sup>b</sup> The number before the initials of the drug names indicates the duration of the treatment phases in months. Subscript numbers after the initials indicate the number of times per week that the drugs are given. The absence of a subscript number indicates that the drugs are given daily.

<sup>c</sup> PTB = pulmonary TB

<sup>d</sup> E = ethambutol; H = isoniazid; R = rifampicin; Z = pyrazinamide.

<sup>e</sup> Streptomycin may be used instead of ethambutol. In tuberculous meningitis, ethambutol should be replaced by streptomycin.

<sup>f</sup> S = streptomycin.

<sup>g</sup> Daily treatment is preferred. However, thrice weekly treatment during the continuation phase or during both phases is an acceptable option.

<sup>h</sup> DRS = drug resistance surveillance.

<sup>i</sup> DRT = drug resistance testing.

<sup>j</sup> Ethambutol in the initial phase may be omitted for patients with limited, non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients with less severe forms of extra-pulmonary TB, and young children with primary TB.

<sup>k</sup> Drug susceptibility testing is recommended for patients who are contacts of MDR-TB patients.

Table 2. Properties of first-line anti-TB<sup>a</sup> agents

Agent	Description	Adverse effects
Isoniazid	Highly active against replicating but not dormant or near-dormant tubercle bacilli. No cross-resistance with other anti-TB agents. Converted to an inactive form by acetylation, the rate of which is genetically determined; people are either rapid or slow acetylators. The rate of acetylation does not affect the efficiency of standard short-course anti-TB therapy, but slow acetylators are more prone to adverse drug reactions and interactions.	Uncommon and mostly involve the nervous system, manifesting as restlessness, insomnia, muscle twitching and psychiatric disorders. Risk is greatly reduced by prescription of pyridoxine (vitamin B6) at 10 mg/day. Occasionally causes hypersensitivity skin reactions, notably in patients with disease caused by HIV.
Rifampicin (rifampin)	A member of the rifamycin group of antibiotics and the most powerful anti-TB agent currently available; effective concentrations are obtained in all tissues. No cross-resistance with other anti-TB agents, except for other rifamycins. Its red colour is imparted to urine, tears and sweat.	Include mild itching and erythema (usually self-limiting), gastrointestinal upsets and impaired liver function in alcoholics and those with liver diseases. A few patients develop the “flu syndrome”, with fever, chills, headache, bone pain and, rarely, a mild thrombocytopenic purpura. The flu syndrome occurs more often in those on intermittent than on daily treatment. Rare serious complications, also more frequent in those on intermittent therapy, include respiratory collapse, low platelet counts leading to purpura and haemorrhages, haemolytic anaemia and renal failure.
Ethambutol	Active during the early, intensive, phase of treatment and may enhance the activity of other anti-TB agents by increasing the permeability of the mycobacterial cell wall.	Include peripheral neuritis, joint pain, low platelet counts, jaundice and optic neuritis. The latter is very uncommon (especially if the maximum recommended dose is not exceeded and the drug is only given in the 2-month intensive phase), but is very serious as it may cause irreversible blindness. National codes of practice for detection and prevention of this adverse effect should therefore be strictly adhered to.
Pyrazinamide	Active against tubercle bacilli in acidic inflammatory lesions but not in the neutral or slightly alkaline cavity wall.	Uncommon and include gastrointestinal upsets and anorexia, photosensitization of the skin, arthralgia and gout. Hepatic toxicity is rare, except in patients with pre-existing liver disease.
Streptomycin	A member of the aminoglycoside group of antibiotics. In contrast to pyrazinamide, it is active in neutral or alkaline conditions. It must be given by intramuscular injection, with the risk of transmission of HIV and other viruses.	Include renal and inner ear damage, the latter leading to vertigo and deafness which may be permanent if treatment is not stopped.

<sup>a</sup> TB = tuberculosis.

## Adverse drug reactions and interactions

Although adverse reactions have been reported for all anti-TB agents (16–18), only a small minority of patients experience such reactions when treated using modern short-course regimens (19). Adverse reactions are more common with the second-line agents used to treat drug-resistant TB. They are also more often seen in patients aged > 60 years and in those co-infected with HIV.

The most frequent adverse reactions to these drugs are dermal hypersensitivity reactions, hepatic toxicity and neurological complications. Rifampicin causes an influenza-like condition — the so-called “flu syndrome” — that, paradoxically, occurs more frequently in those receiving the drug twice or three times per week than in those receiving it daily.

Dermal hypersensitivity reactions are usually mild, but severe and potentially fatal forms (including the Stevens–Johnson syndrome) occur, especially in those with HIV and particularly so in those treated with thiacetazone. Hepatic toxicity is induced by all the first-line drugs and is usually mild, but very severe and sometimes fatal hepatitis is a rare complication of therapy. Opinions differ on the need for regular tests of liver function during the course of therapy for TB (20). Neurological

complications are principally associated with isoniazid and are largely preventable by prescribing pyridoxine (vitamin B6).

Some anti-TB agents inhibit or enhance the effects of other drugs and this may have serious clinical implications (21). Drug interactions pose a particular problem for patients co-infected with HIV, especially as some may be treated with antiretroviral agents or drugs for various bacterial, viral and fungal infections (22).

Most of the reported drug interactions involve rifampicin and other rifamycins, as these induce hepatic cytochrome enzymes that are involved in the metabolism of many drugs, thereby reducing their active levels. The principal drugs affected are listed in Table 4. Particular problems are posed by the use of rifamycins in patients receiving antiretroviral therapy and, as regimens for the latter are often revised, current guidelines issued by the United States Centers for Disease Control, Atlanta, GA, should be consulted (23).

## Prospects for novel anti-TB agents and regimens

Until very recently, no new class of antibacterial agent suitable for the treatment of TB had emerged for 30 years. One reason

Table 3. Properties of second-line anti-TB<sup>a</sup> agents

Agent	Description	Adverse effects
Fluoroquinolones	Include ofloxacin, moxifloxacin, gatifloxacin and levofloxacin, which are being evaluated for the treatment of drug-resistant TB.	
Ethionamide and prothionamide	Closely related to each other and also to isoniazid, although there is no cross-resistance with the latter. They are weak drugs and are bacteriostatic rather than bactericidal agents.	Distressing gastric irritation is common.
Other aminoglycosides, e.g. kanamycin and amikacin		Like streptomycin, they are given by intramuscular injection and they have similar adverse effects.
Capreomycin and viomycin	Of restricted availability and rarely used. Although unrelated structurally to the aminoglycosides, partial cross-resistance occurs.	Must be given by intramuscular injection and their adverse effects are similar to those of the aminoglycosides.
<i>para</i> -Aminosalicylic acid (PAS)	Of limited availability and very rarely used nowadays. Has only limited bacteriostatic activity.	Gastrointestinal upsets are common.
Thiacetazone	A weak drug that should be dropped from the list of agents used to treat TB.	A cause of an unacceptably high incidence of severe and life-threatening skin reactions, particularly in those with disease caused by HIV.
Cycloserine	A weak bacteriostatic drug.	Use is limited by the high incidence of neurological and psychiatric adverse effects including headache, dizziness, depression and confusion.
Other agents	Other members of the rifamycin group of antibiotics, notably rifabutin and rifapentine, are used as alternatives to rifampicin under some circumstances. Rifabutin is used as an alternative to rifampicin in HIV-infected patients receiving antiretroviral therapy, as adverse drug interactions are less frequent. Other agents, with some evidence of efficacy, include newer macrolides (azithromycin, clarithromycin, the antileprosy drug clofazimine (Lamprene) and $\beta$ -lactam/ $\beta$ -lactamase inhibitors.	

<sup>a</sup> TB = tuberculosis.

is the reluctance of the pharmaceutical industry to invest in the development of drugs that are unlikely to generate enough revenue to cover the costs of development. This regrettable situation is, however, changing (24). Although traditionally such agents have been found by empirical screening of antibiotics and synthetic chemicals, the sequencing of the genome of *Mycobacterium tuberculosis* and more refined techniques for elucidating metabolic pathways, particularly those involved in the synthesis of the complex mycobacterial cell wall, have opened up exciting new avenues of research (25–27). Some of these are summarized in Table 5.

A review of currently available treatment alternatives shows that there has been some initial progress towards major strategic goals, i.e. shortening and simplification of regimens for the treatment of TB, improved treatment for MDR-TB and management of TB/HIV co-infection with reasonable safety profiles and patterns of drug interactions. As these areas are cross-cutting in nature, new developments have the potential to influence more than one area. At present, it seems clear that the fluoroquinolones and the new diarylquinoline (R207910) under development by Johnson & Johnson also hold promise for the management of TB, MDR-TB and safe co-administration with antiretroviral agents (28).

Although today there are about 26 products listed in the portfolio of drug development of the Global Alliance for TB

with 11 of these being in preclinical or clinical testing (29, 30), there is a major bottleneck in the speed with which these agents can be advanced through early-phase testing in humans so that promising products are brought through to Phase III testing. The main reason is the high financial risk associated with drug development and market uncertainty. Candidate drugs that are advanced in the investigational pipeline are described below.

## Drugs in clinical development

### Quinolones

Fluoroquinolones (ofloxacin, moxifloxacin, gatifloxacin and levofloxacin) are currently the only potential anti-TB agents that have entered advanced Phase II and III evaluation (31–35). Registered for use for the treatment of infections of the skin and respiratory tract, fluoroquinolones have shown high levels of activity against TB in murine models in vitro. A trial of shorter treatment regimens conducted in Chennai, India, affirmed the potential of ofloxacin in a 4-month regimen (33). In this study, patients treated daily with isoniazid, rifampicin, pyrazinamide and ofloxacin for 3 months, and then twice per week with isoniazid and rifampicin for 1 or 2 months, had cure rates of 92–98% and low relapse rates (2–4%). Confidence limits on the relapse rates were, however, wide and there was no 4-month control regimen of standard treatment without

ofloxacin. In experimental murine TB, moxifloxacin has shown sterilizing activity (34), while ofloxacin has not (35). The patent on ofloxacin will soon expire, and it is likely to be available cheaply. The L-isomer of ofloxacin, levofloxacin, may act in the same manner (36).

Gatifloxacin (37) is being tested in a multicentre Phase III trial and moxifloxacin is currently being evaluated in a Phase II trial (Centers for Disease Control TB Trials Consortium) and in a multicentre Phase III trial (WHO and the European Community).

### Diarylquinolines (DARQs)

Structurally and functionally, DARQs are different from both fluoroquinolones and quinolones. One DARQ under development (R207910) is active against a new target on the proton-pump of ATP-synthase in *M. tuberculosis*, and thus has an activity that is different from that of current drugs (28). Promising characteristics of this candidate drug include low minimum inhibitory concentration (MIC) values, early and late bactericidal activity, efficacy against MDR strains in studies in vitro, good tolerability and an “effective” half-life that exceeds 24 hours. Bactericidal activity exceeding that of rifampicin and isoniazid, and accelerated activity leading to complete culture conversion after 2 months of combination therapy, as reported for the murine model, is yet to be confirmed in human trials. Phase I trials in healthy human volunteers have been completed with a reportedly good safety profile (28).

### Rifamycins

Rifamycins with a longer duration of action (rifabutin, rifapentine and rifalazil) have the potential for use in more widely spaced, intermittent treatment regimens and hold promise for avoiding cross-resistance to other rifamycins and interactions with antiretroviral agents. Disappointing results were seen in a Phase III study evaluating a once-weekly regimen of rifapentine and isoniazid during the continuation phase of standard chemotherapy (38). A high rate of drug-susceptible relapse was identified among HIV-negative individuals, which seemed to correlate with lower plasma concentrations of isoniazid. The new longer-acting quinolones (in particular, moxifloxacin) have been proposed as alternative companion drugs for the intermittent regimens with rifapentine (25, 39). The safety and bactericidal activity of rifalazil have been investigated in one Phase II study (40). The drug was found to be well tolerated and similar reductions in sputum bacillary load were found in patients treated with two doses of rifalazil (10 mg or 40 mg) plus isoniazid for 2 weeks, isoniazid alone or isoniazid plus rifampicin.

### Drugs in preclinical development

#### Nitroimidazoles

PA-824 is the first product of public-private collaboration and is under joint development by Chiron and the Global Alliance for TB Drug Development. PA-824 has shown promising preclinical bactericidal and sterilizing activity against drug-sensitive TB and MDR-TB via a novel dual mechanism of action involving disruption of protein synthesis and inhibition of the ability of the pathogen to make fatty acids needed for cell wall synthesis (41). An encouraging aspect of the now nearly complete preclinical evaluation is its lack of significant inhibition of the cytochrome P450 isozymes, rendering this

Table 4. Principal drugs whose effects are opposed by rifampicin

• Antiretroviral agents	• Opioids
• Azathioprine	• Oral contraceptives
• Corticosteroids	• Phenytoin
• Cyclosporin	• Propranolol
• Diazepam	• Quinidine
• Digoxin	• Theophylline
• Haloperidol	• Tolbutamide
• Imidazoles	• Warfarin

drug potentially suitable for co-administration with antiretroviral agents. Non-clinical studies have indicated a reasonable toxicity profile. The drug entered Phase I clinical trial evaluation in June 2005.

### Quinolizines and pyridones

KRQ-10018, a quinolizine synthesized at the Korean Research Institute of Chemical Technology, Republic of Korea, underwent preclinical efficacy testing at Yonsei University, Seoul City. Researchers at Lupin Pharmaceuticals in India report promising preclinical results for agent LL3858, used as a potent treatment-shortening drug to replace the more toxic isoniazid. This appears to be the most promising of three of their compounds currently being investigated at the preclinical stage. A non-fluorinated quinolone is also under development by Procter & Gamble. All these compounds are being evaluated in conjunction with the Global Alliance for TB Drug Development (42). Since this paper was reviewed, clinical trial evaluation of Lupin's pyrrole LL3858 has begun (29).

### Ethambutol analogues

The efficacy of SQ109, a diamine selected from a library of more than 63 000 analogues based on ethambutol, was demonstrated in a murine model of TB (42). This compound is now at the preclinical stage of evaluation by Sequella Inc. in collaboration with the Global Alliance (30).

### Treatment of latent TB

A number of placebo-controlled trials in HIV-negative people with latent TB infection have shown that giving isoniazid daily for 6–12 months substantially reduces the subsequent risk of developing active TB (43). In HIV-infected persons, however, a variety of factors may have an adverse impact on the efficacy of such therapy. There is evidence that absorption of anti-TB agents may be hampered in patients with acquired immunodeficiency syndrome (AIDS) (44). Moreover, as patients with HIV disease may be taking antiretroviral therapy, as well as other medications for the treatment of AIDS-related diseases, drug interactions can occur (21, 45). Furthermore, compliance with prescribed regimens may be limited in dually infected patients owing to associated morbidity, multiple medication and adverse drug reactions, thus increasing the likelihood of MDR-TB (23). Assumptions about the effective protective potential of therapy to prevent TB in HIV-positive people may therefore be premature, as the extent, duration and magnitude of protection associated with preventive therapy in those infected with HIV remains to be adequately quantified, especially within programme settings.

Table 5. New approaches to the development of therapy for TB<sup>a</sup>

- Modification of existing classes of agents to give greater specific activity or superior pharmacokinetics, e.g. new rifamycins, quinolones, macrolides and  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations, pyrazinamide analogues.
- Evaluation of new classes of antibacterial agents, e.g. nitroimidazoles.
- Novel modes of drug delivery, e.g. depot preparations, liposome encapsulations.
- "Designer" agents that inhibit specific mycobacterial metabolic pathways including those involved in synthesis of determinants of virulence.
- Agents that increase mycobacterial cell wall permeability.
- Agents that "resensitize" drug-resistant bacteria.
- Cytokines or adjuvants that enhance protective immune responses and/or downregulate tissue-destroying hypersensitivity reactions.

<sup>a</sup> TB = tuberculosis.

Eleven trials with a total of 8130 randomized participants were analysed in a recently updated Cochrane Review (46). The administration of preventive therapy was associated with a lower incidence of active TB compared with placebo (RR, 0.64; 95% CI, 0.51–0.81). This benefit was more pronounced in individuals with positive tuberculin skin tests (RR, 0.38; 95% CI, 0.25–0.57) than in those with negative test results (RR, 0.83; 95% CI, 0.58–1.18). Efficacy was similar for all regimens, regardless of drug type, frequency or duration of treatment. Compared with isoniazid monotherapy, short-course multi-drug regimens were much more likely to require discontinuation of treatment due to adverse effects. Overall, there was no evidence that preventive therapy reduced all-cause mortality when compared with placebo, although a favourable trend was found in patients with a positive result for the tuberculin test (RR, 0.80; 95% CI, 0.63–1.02). Despite evidence for the efficacy of preventive therapy, further research is required, not only to quantify its impact in reducing the incidence of TB at the population level and the duration of its protective effect, but also to convince policy-makers that its use nationally will not result in an increase in resistance. Further work needs to be done to evaluate the effect of combined preventive therapy with antiretroviral therapy versus the latter alone in preventing TB among people with HIV/AIDS.

## Combined treatment for TB and HIV

Evidence on strategies to optimize the clinical management of patients dually infected with TB and HIV is required. A multicentre, WHO-sponsored clinical trial designed to provide evidence for the efficacy, safety and feasibility of the concomitant use of drugs to treat TB and HIV in co-infected patients under programme conditions in four African countries is in preparation. This placebo-controlled trial will provide evidence on the benefits and risks of initiating concomitant antiretroviral treatment in patients with TB who are undergoing treatment with anti-TB drugs and who are co-infected with HIV, and will establish whether there are significant benefits for patients not currently eligible for concomitant treatment, i.e. those with CD4 T-cell counts of > 200–349 or 350–500 cells/mm<sup>3</sup>. The trial will also provide information on drug interactions and the potential influence of levels of immune suppression on absorption in different genetic populations.

## The way forward

Treatment of TB with chemotherapeutic agents remains the cornerstone of patient management and is likely to remain so for the foreseeable future. The critical challenge is the delivery of high quality therapy to all patients with TB. The success of

drug-based treatment is dependent on the speed with which cases are identified and treatment initiated. The current Global TB Strategy, DOTS, relies on the identification of active smear microscopy-positive cases of TB, considered to be about 44% of all cases (47). With the increasing prevalence of HIV infection and the attendant increases in smear-negative TB in the same populations, it is unlikely that the present DOTS strategy alone will reduce the overall burden of TB, especially in countries in sub-Saharan Africa, where the incidence of TB is rising in populations with a high prevalence of HIV (48). The way forward may not lie in a uniform global strategy, but in approaches that respond to specific local epidemiological features of TB, especially in the context of HIV and drug resistance.

Furthermore, facilities treating patients with TB and HIV/AIDS — often the same patients — should aim at managing the patient and not two separate diseases. Currently, drug resistance is often inferred from the lack of response to treatment after 6 months. Iseman (49) argues that the timing of assessment is too late and may worsen lung damage leading to death, or to transmission of drug-resistant organisms, implying the need for early testing for drug susceptibility in settings in which resources are limited. It is likely that improvement in treatment outcomes will be facilitated by early detection of drug-resistant cases, and especially within centres and facilities for HIV testing.

Although much can be done with the current drugs, if properly used, there is an urgent need for new drugs with novel modes of action. In this context, emphasis should be placed on improving early bactericidal activity (EBA) or late sterilizing activity with the goal of shortening treatment (49). Studies on strategies that potentially improve patient management should be conducted; for example, evaluation of the efficacy and safety of adjunctive immunomodulation with current chemotherapy, and treatment of latent TB. In view of the rising incidence of TB, urgent attention needs to be paid to the development of new and inexpensive diagnostic tests for smear-negative TB and latent infection with TB and their evaluation within national TB control programmes.

Thus far, progress in TB research and development has been painfully slow. The investment of financial capital by the Global Alliance needs to be matched with similar investments in human capital and infrastructure to build the capacity to conduct the necessary trials efficiently and speedily. The creation of the European Developing Countries Clinical Trial Partnership (EDCTP) is an attempt at this approach. Two treatment trials investigating, firstly, moxifloxacin in a Phase III treatment-shortening regimen and, secondly, the effect on mortality of treating TB and HIV infection early and simultaneously under TB control programme conditions in Africa are planned,

with potential support from the EDTCP. Complementary basic research identifying surrogate markers of TB cure is also necessary and has been approved for funding by EDCTP. The aim is to find a new therapeutic option by 2010. The current rate of research and development makes this a potentially achievable goal. ■

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## Résumé

### Traitement de la tuberculose : situation actuelle et perspectives d'avenir

Ces dernières années, on a observé une grande synergie entre la tuberculose (TB) et la maladie provoquée par le virus de l'immunodéficience humaine (VIH), conduisant à une pandémie de co-infection VIH/TB. Le nombre de nouveaux cas de TB est en cours de stabilisation ou de déclin, sauf dans les pays subissant une forte prévalence des infections à VIH. Dans ces pays, où la propagation du VIH est le moteur d'une augmentation de la morbidité tuberculeuse, la capacité des outils et des stratégies actuellement disponibles pour réduire la charge de morbidité due à cette maladie est dépassée. Le présent article récapitule la

situation actuelle en matière de prise en charge de la TB et expose les nouveaux ajustements intellectuels et stratégiques nécessaires pour lutter contre la tuberculose dans les pays à forte prévalence du VIH. Il examine les données relatives aux antituberculeux disponibles dans le domaine public et souligne la nécessité d'efforts ininterrompus et concertés (y compris des investissements dans les domaines financiers et humains et dans les infrastructures) pour mettre au point de nouvelles stratégies et de nouveaux agents antituberculeux.

## Resumen

### Tratamiento de la tuberculosis: situación actual y perspectivas

A lo largo de los últimos años, la tuberculosis y la enfermedad causada por el virus de la inmunodeficiencia humana (VIH) se han fusionado en una pandemia sinérgica. El número de casos nuevos de tuberculosis se está estabilizando o disminuyendo, excepto en los países con alta prevalencia de infección por VIH. En estos países, donde el VIH está causando un aumento de la carga de tuberculosis, la capacidad de los instrumentos y estrategias actualmente disponibles para reducir esa carga se ha visto desbordada. En este artículo se resume el estado actual del

tratamiento de la tuberculosis y se describen los últimos cambios teóricos y estratégicos requeridos para controlar la enfermedad en los entornos de alta prevalencia de infección por VIH. Revisamos la información sobre medicamentos antituberculosos disponible en el dominio público y resaltamos la necesidad de hacer un esfuerzo continuo y concertado (en particular mediante inversiones financieras, humanas y en infraestructura) para desarrollar nuevas estrategias y nuevos agentes antituberculosos.

## ملخص

### معالجة السل: الوضع الحالي والآفاق المستقبلية

الحالي لتدبير السل وتصف الفكر الحالي والتحديات اللازمة في استراتيجيات مكافحة السل في المواقع ذات الانتشار العريض لفيروس الإيدز. ونستعرض أيضاً في هذه الورقة المعلومات المتاحة للجمهور والمتعلقة بالأدوية المضادة للسل، ونبرز الحاجة إلى جهود مستمرة ومتضافرة (تشمل في ما تشمل الاستثمار المالي والبشري والاستثمار في البنية الأساسية) لإعداد استراتيجيات جديدة وأدوية جديدة مضادة للسل.

شهدت السنوات الأخيرة ظهوراً متزامناً للسل وأمراض أخرى ناجمة عن فيروس العوز المناعي البشري (فيروس الإيدز)، في شكل جائحة تآزرية. ويتسم عدد الحالات الجديدة للسل بالثبات أو الانخفاض، إلا في البلدان ذات الانتشار المرتفع لعدوى فيروس الإيدز. ففي هذه البلدان التي تؤدي العدوى بفيروس الإيدز فيها إلى تفاقم عبء مرض السل، تم تعزيز قدرة الوسائل والاستراتيجيات الحالية على خفض عبء السل. وتلخص هذه الورقة الوضع

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