Chapter 5
Treatment

Abstract In this chapter the treatment of drug sensitive and drug resistant TB and timing of antiretroviral treatment for HIV infected patients will be reviewed. Emphasis is placed on results of recent trials of fluoroquinolones for treatment shortening of drug sensitive TB. The use of two relatively novel agents in MDR-TB treatment, bedaquiline and delamanid, will be discussed.

Keywords First-line antituberculous treatment · Rifampicin · Isoniazid · Pyrazinamide · Streptomycin · Ethambutol · HIV associated tuberculosis · Antiretroviral therapy (ARV, ART) · Treatment of drug-resistant tuberculosis · Fluoroquinolones · Bedaquiline · Delamanid

5.1 First-Line Antituberculous Treatment

The introduction of rifampicin to the first-line combination regimen in the late 1970s allowed the shortening of treatment for TB from 18–24 months to 6 months. This "short-course" regimen, consists of an 'intensive phase' of 4 first line drugs; ethambutol (EMB) [or streptomycin (SM)], isoniazid (INH), pyrazinamide (PZA) and rifampicin (RIF) for 2 months followed by a 'continuation phase' of 2 months of RIF and INH (Table 5.1). The continuation phase may be extended in more complex cases and some countries still use an 8-month standard regimen which is no longer recommended by WHO. Ethambutol should be used in place of the injectable streptomycin where possible for HIV-infected individuals. Since the development of the short-course regimen, standard TB-treatment has remained largely unchanged for the past 40 years. Daily, directly observed therapy (DOT) is preferable to intermittent regimens and fixed dose combination (FDC) drugs may be used to ensure multi-drug therapy (Nunn et al. 2014). Pyridoxine should be administered with isoniazid to prevent peripheral neuropathy. The historic events that have led to the current treatment schedule are comprehensively reviewed by Diacon and colleagues (Diacon et al. 2012).

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Table 5.1 Drugs used in the treatment of tuberculosis

	Drug	Adult dose mg/kg (range); [maximum dose]	Pediatric dose mg/kg (range); [maximum dose]	Common side effects[a]
Group 1: first-line oral drugs				
	Isoniazid[b]	5 (4–6) [300 mg]	10 (7–15) [300 mg]	Hepatitis; peripheral neuropathy
	Rifampicin (rifapentine/rifabutin alternative rifamycins)	10 (8–12) [600 mg]	15 (10–20) [600 mg]	Hepatitis; orange discoloration of secretions; drug-drug interactions
	Pyrazinamide	25 (20–30)	35 (30–40) [2000 mg]	Hepatitis; arthralgia
	Ethambutol	15 (15–20 mg/kg)	20 (15–25) [1200 mg]	Visual disturbance (acuity, colour vision)
Second-line drugs (group 2, injectables)				
	Streptomycin (S)	15 (12–18) [1000 mg]	Not recommended as first-line. 15 (12–18) [1000 mg]	Auditory nerve damage
	Kanamycin (Km)	15–20 mg/kg [1000 mg]	15–30 [1000]	Renal failure (usually reversible)
	Amikacin (Am)	15–20 mg/kg [1000 mg]	15–22.5 [1000]	Proteinuria, serum electrolyte disturbances including hypokalaemia and hypomagnesaemia
	Capreomycin (Cm)	15–20 mg/kg [1000 mg]	15–30 [1000]	Nephrotoxicity (20–25 %), tubular dysfunction, azotaemia, proteinuria, urticaria or maculopapular rash
Group 3: fluoroquinolones				
	Levofloxacin (Lfx)	750 mg [1000 mg]	7.5–10	Generally well tolerated
	Moxifloxacin (Mfx)	400 mg daily dose	7.5–10	
	Ofloxacin (Ofx)	800 mg [1000 mg]	15–20 [800]	

(continued)

Table 5.1 (continued)

	Drug	Adult dose mg/kg (range); [maximum dose]	Pediatric dose mg/kg (range); [maximum dose]	Common side effects[a]
Group 4: oral bacteriostatic second-line				
	Ethionamide (Eto)	15–20 mg/kg [1000 mg]	15–20 mg/kg [1000 mg]	Severe gastrointestinal intolerance (nausea, vomiting, diarrhoea, abdominal pain, excessive salivation, metallic taste, stomatitis, anorexia and weight loss. Unable to tolerate 1 g as a single dose
	Prothionamide (Pto)	15–20 mg/kg [1000 mg]	15–20 mg/kg [1000 mg]	
	Terizidone (Trd)	15–20 mg/kg [900 mg]	10–20 [1000]	Neurological and psychiatric disturbances, including suicidal and psychotic episodes
	Cycloserine (Cs)	15–20 mg/kg [1000 mg]	10–20 [1000]	Neurological and psychiatric disturbances, including headaches, irritability, sleep disturbances, aggression, and tremors, gum inflammation, pale skin, depression, confusion, dizziness, restlessness, anxiety, nightmares, severe headache, drowsiness
	Para-aminosalicylic acid (PAS)	150 mg/kg [8 g]	150 mg/kg [8 g]	Gastrointestinal intolerance (anorexia and diarrhoea); hypo-thyroidism (increased risk with concomitant use of ethionamide)

(continued)

Table 5.1 (continued)

	Drug	Adult dose mg/kg (range); [maximum dose]	Pediatric dose mg/kg (range); [maximum dose]	Common side effects[a]
Group 5: Agents with unclear role in treatment of drug resistant-TB[c]				
	Clofazimine (Cfz)	100 mg daily		Ichthyosis, and dry skin; pink to brownish-black discoloration of skin, cornea, retina and urine; anorexia and abdominal pain
	linezolid (Lzd)	600 mg daily		Gastrointestinal disturbance, vision disturbances, anaemia
	Amoxicillin/clavulanate (Amx/Clv)	875 twice daily		Gastrointestinal disturbance, psychiatric disturbance, sleep disturbance
	Thioacetazone (Thz)[d]	2.5 mg/kg [150]		Gastrointestinal disturbance, arthralgia, seizures, hepatitis
	High-dose isoniazid (high-dose H)	16–20 mg/kg/day		Hepatitis; peripheral neuropathy
	Clarithromycin (Clr)	500 mg daily		Gastrointestinal disturbance
Novel Agents	Bedaquiline	400 mg once daily		Nausea, arthralgia, headache, vomiting, gastrointestinal disturbance, QT prolongation
	Delaminid	200 mg twice daily		QT prolongation

[a]Hypersensitivity reactions and drug rashes may occur with any anti-tuberculous drug
[b]Pyridoxine should be given with isoniazid to prevent peripheral neuropathy. Guidelines variously recommend 10 or 25 mg/kg daily
[c]Optimal dose and long-term safety not well established for group 5 drugs
[d]Do not use thioazetone for HIV-infected individuals (significant risk of Stevens-Johnson syndrome)

WHO treatment guidelines can be found at http://www.who.int/tb/publications/tb_treatmentguidelines/en/index.html. Treatment recommendations for pediatric TB were revised in 2010, with an increased dose of all first-line drugs (http://whqlibdoc.who.int/publications/2010/9789241500449_eng.pdf) and a request not to use streptomycin as a first-line drug in children (World Health Organisation

2014). This followed systematic review of evidence showing that children achieve inadequate serum exposure when receiving the same dose/kg as adults and there was no evidence of adverse toxicity from the higher doses. Pharmacokinetic data from South Africa showed substantially improved serum levels with the novel regimen but it remains to be demonstrated if these doses are sufficient to achieve improved outcomes (Thee et al. 2011).

5.2 HIV Associated Tuberculosis

The advent of HIV has severely impacted the burden of TB. All HIV patients should be screened for TB and all TB patients should be offered HIV testing. Dual treatment of HIV and TB is complex, as patients are faced with a higher pill-burden, increased risk of toxicity, drug-interactions and IRIS (Lawn et al. 2013; Lai et al. 2013). Routine administration of co-trimoxazole (960 mg/day) is recommended in all patients with HIV-associated TB, since it has been shown to substantially reduce mortality in patients in Sub Saharan Africa. Rifampicin is an inducer of the cytochrome P450 2B6 enzyme, which is the main pathway for the non-nucleaside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) either of which are the basis of ARV treatment (Bonnet et al. 2013). The most commonly used NNRTI is efavirenz. Although the US FDA recommends that the dose of efavirenz should be increased when co-administered with rifampicin, this is not substantiated in the most recent clinical trials, which show excellent virological response in those patients receiving standard dose (600 mg) of efavirenz (Kwara et al. 2010). Nevarapine is an alternative NNRTI used for those patients who cannot tolerate efavirenz, but plasma levels are very low in patients receiving rifampicin during the lead-in phase of nevarapine. This may predispose to resistance formation and virological failure. Dose increase is not recommended because concerns of toxicity, however it is plausible to omit the 14 day lead-in phase of nevirapine dosing after the CARENIMO trial showed that nevirapine was well tolerated at full dose when introduced in patients with CD4 cell counts <250/mm^3 while receiving rifampicin (Bonnet et al. 2013). The co-administration of second-line ARV regimens containing PIs remains a challenge and there is an urgent need for clinical trials evaluating safety and efficacy. ‘Superboosting’ of ritonavir or doubling dose of lopinavir/ritanovir combination formulation are suggested, as is substituting rifabutin for rifampicin (Lawn et al. 2013).

Timing of initiation of ARV treatment in ARV-naïve TB/HIV patients has been evaluated in a recent series of clinical trials published in 2011 (SAPIT [NCT00398996], CAMELIA[NCT01300481] and the AIDS clinical trial group study A5221). Results showed that there is a reduction in mortality in patients with CD4 cell counts lower that 200/mm^3 (CAMELIA trial) or 50/mm^3 (other two trials) when ARV treatment was initiated within 2 weeks of TB treatment (GRADE A^3), (Abdool Karim et al. 2010, 2013; Blanc et al. 2011). However this carries an increased risk of IRIS and treatment toxicity. The management in patients with

higher CD4 cell counts is less clear and it may be acceptable to defer ARV treatment until the continuation phase of TB treatment. The majority of patients in these trials had pulmonary TB. For patients with TB meningitis, a recent large Vietnamese randomised controlled trial showed no benefit of early initiation of ARVs and deferred treatment at 2 months was associated with less toxicity and less occurrence of IRIS (Torok et al. 2011). Patients in this cohort had extremely low median CD4 count and the results may not be generalizable to other populations.

5.3 Treatment of Drug-Resistant Tuberculosis

The use of multi-drug therapy for TB treatment from the early days of discovery of antituberculous drugs has actually preserved the efficacy of the five first line agents for TB remarkably well for over 50 years. However, drug resistance in *M. tuberculosis* is increasing and has now reached alarming levels, particularly in the former Soviet states, India, South Africa and part of Asia. Approximately 8 % of *M. tuberculosis* cases globally are now resistant to isoniazid. Multi-drug resistant TB (MDR TB) is defined as TB resistant to at least isoniazid and rifampicin, the two key first line drugs in the treatment regimen. MDR TB is much harder to treat, requiring a minimum of 18 months treatment with expensive, toxic and weak second line drugs. Worldwide, 3.6 % of newly diagnosed and 20 % of patients previously treated for TB have MDR TB but there are dramatic regional variations with the highest proportion in Eastern Europe and Central Asia (WHO 2014).

In 2012 there were an estimated 450,000 new cases of MDR TB worldwide and 170,000 deaths but only 17 % were diagnosed and enrolled into high quality treatment programmes. This figure does however represent a 42 % increase on 2011, reflecting scale-up efforts for MDR detection and treatment. In 2006 WHO defined a new category of drug resistant TB as extensively drug resistant TB (XDR TB). XDR TB is MDR TB additionally resistant to a fluoroquinolone and a second line injectable drug (amikacin, capreomycin or kanmycin). This followed a documented outbreak in Kwa-Zulu Natal province of South Africa in which 53 cases of XDR TB were identified among HIV patients, all but one of whom died with a median survival time of 16 days from diagnosis. Following acceptance of the definition of XDR TB, 92 countries have reported cases by 2013 (Fig. 5.1). It is estimated 10 % of MDR cases are in fact XDR and it is now clear that XDR TB is present in almost every country although the extent of transmission within communities is not established due to the limited availability of second-line drug susceptibility testing for *M. tuberculosis*. The term totally drug resistant TB has been used in the literature to describe *M. tuberculosis* strains resistant to all first and second line drugs but the use of this term is not recognised by WHO due to the difficulty of standardising drug susceptibility testing for second line drugs and the introduction of treatment options (Cegielski et al. 2012).

Drug resistant TB should be treated with at least four drugs to which the organism is susceptible, prioritising any first-line agents and then including a

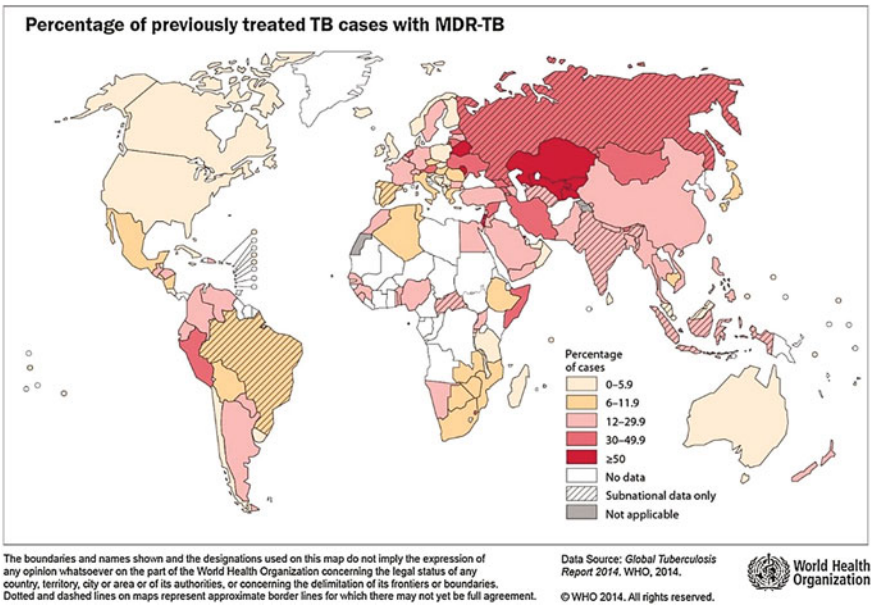

Fig. 5.1 Percentage of previously treated TB cases with multidrug-resistant TB. *Source* WHO, reprinted with permission

fluoroquinolone and an injectable agent. In order to protect against drug resistance amplification, a single drug should never be added to a failing regimen (Daley and Caminero 2013). Key principles of MDR treatment are summarised in Table 5.2 (Kaufmann et al. 2014; Ulrich et al. 2006).

Comprehensive CDC guidelines on both susceptible and drug resistant TB can be found on http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm.

The painstakingly sluggish decline in incidence of TB and the rise of MDR- and XDR-TB underlines the inadequacies of current treatment and prevention measures. Priority questions for research, in addition to the search for novel agents include shortened regimens, optimal regimens for all forms of drug resistant TB, optimal dose of drugs (especially rifampicin), and treatment of HIV-associated TB.

Several existing and newly developed compounds are under evaluation for drug-sensitive and drug-resistant TB (Fig. 5.2). In light of the growing epidemic of MDR-TB and lack of new drug development there has been renewed interest in obsolete compounds for TB (Chang et al. 2013). In 2010, the Damien Foundation published the results of an observational study, comparing six regimens for MDR-TB, derived by sequential modification. The addition of gatifloxacin and use of clofozimine throughout the regimen apparently allowed a reduced duration of treatment, to between 9–12 months, depending on time to smear conversion. All 427 patients received clofazimine in the intensive phase and 206 patients received a shortened regimen of 9–12 months, using clofazimine throughout treatment [4(+) KCGEHZP, 5 GCEZ]. Treatment success-rate was highest in the short regimen

Table 5.2 Guidelines for the management of tuberculosis caused by drug-resistant organisms

Do not add a single drug to a failing regimen
When starting or modifying therapy, add three previously unused drugs (one an injectable) to which there is likely to be susceptibility
Use any of the first-line oral agents (Group 1) that are likely to be effective
In multidrug-resistant tuberculosis (MDR TB), when there is resistance to additional first-line drugs, treat with 4–7 drugs (dependent on degree of confidence in susceptibility and strength of derived regimen)
Patients with MDR TB have the highest priority for directly observed therapy because treatment failure may be associated with extensively drug-resistant TB
Intermittent therapy should not be used (except for injectables after 2–3 months)
Do not use drugs to which the *M. tuberculosis* isolate is resistant. Low-level resistance to isoniazid may be an exception
There is cross-resistance among rifamycins but not between streptomycin and other aminoglycosides. Amikacin or kanamycin are preferred aminoglycosides for MDR as most MDR strains are resistant to streptomycin
Drug susceptibility testing for pyrazinamide is complex technically and not performed in most laboratories. Monoresistance to pyrazinamide suggests *M. bovis*
Drug susceptibility results for second line agents (except fluoroquinolones and aminoglycosides) may be unreliable and should be interpreted within context of treatment history
Levofloxacin, or moxifloxacin are preferred flouroquinolones. Ciprofloxacin should not be used to treat TB

treatment group with a relapse-free cure of 87.9 % (95 %CI 82.7–91.6), with relatively good tolerability (Van Deun et al. 2010). This shortened 'Bangladesh' regimen is now being subjected to a large multicentre (including sites in Ethiopia, India, South Africa, Vietnam) randomised controlled trial, known as the STREAM trial (ISRCTN78372190). The STREAM trial is being conducted by the British Medical Research Council and will compare the standard MDR regimen (according to local National TB program guidelines, duration ranging from 18–24 months) with a modified form of the Bangladesh regimen. Moxifloxacin, clofazimine, ethambutol and pyrazinamide will be given for nine months, supplemented by kanamycin, isoniazid and prothionamide in the four months of the intensive phase. All drugs are given daily except for kanamycin which is administered thrice weekly after 12 weeks. The target is to include at least 400 participants. The results of this major trial are expected in October 2016.

5.4 The Role of Fluoroquinolones

The fluoroquinolones levofloxacin, gatifloxacin and moxifloxacin have strong antimycobarterial activity with an early bactericidal activity (EBA) similar to that of isoniazid and are the strongest of the second-line agents. Fluoroquinolones are the keystone of MDR treatment regimens and should also be considered in cases of non-MDR drug resistant TB requiring additional agents or if a first-line agent in the standard regimen is not tolerated, particularly in case of hepatotoxicity. Fluoroquinolones are excreted via the kidneys and thus have a lower potential to disturb liver function. They inhibit bacterial replication via the DNA gyrase, a mechanism distinct from those of the first-line agents. They have broad-spectrum antibacterial activity, particularly against gram-negative bacteria, favourable pharmacokinetic profile, are relatively safe, have good tissue penetration and high in vitro activity against *M. tuberculosis*. Fluoroquinolones may therefore work synergistically to the other TB agents and penetrate well in the tuberculoma. A recent Cochrane review, evaluating RCTs on ofloxacin, levofloxacin, moxifloxacin and gatifloxacin, reported that there is insufficient evidence to be clear whether fluoroquinolones, either added to the first-line regimen or as a substitution for ethambutol or isoniazid, may prevent relapse or death, or increase sputum culture conversion at 8 weeks (Ziganshina et al. 2013). Three large multicountry trials have been established to determine if the use of fluoroquinolones can shorten treatment regimens to four months rather than six: OFLOTUB (NCT00216385), REMOX TB (NCT00864383) and RIFAQUIN (ISRCTN44153044) studies (Merle et al. 2014; Gillespie et al. 2014; Jindani et al. 2013). The RIFAQUIN trial reported in April 2013 and showed inferiority of the four month regimen; Two months of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by two months of twice weekly moxifloxacin (500 mg) and rifapentine (900 mg) compared to the standard 6-month WHO regimen (2HRZE/4HR).

The OFLOTUB trial which tested a 4 month regimen of 2 months gatifloxacin (400 mg/day), isoniazid, rifampicin and pyrazinamide followed by two months gatifloxacin, isoniazid and rifampicin reported in September 2013 and (2GHRZ/2GHR) failed to show non-inferiority of the Gatifloxacin regimen at the pre-specified 6 % margin (Merle et al. 2014). Although Gatifloxacin has been banned by the FDA due to toxicity concerns, there was no increased risk of disgylcemia or QTc prolongation with the gatifloxacin regimen. The REMOX trial which tested two moxifloxacin containing regimens lasting 17 weeks, reported in 2014. The moxifloxacin-containing regimens produced a more rapid initial decline in bacterial load, as compared with the control group. However, noninferiority for these regimens was not shown, which indicates that shortening treatment to 4 months was not effective in this setting (Gillespie et al. 2014). Several existing and newly developed compounds are under evaluation for drug- sensitive and drug-resistant TB (Fig. 5.2) (Ma et al. 2010; Chang et al. 2013; Gopal et al. 2013).

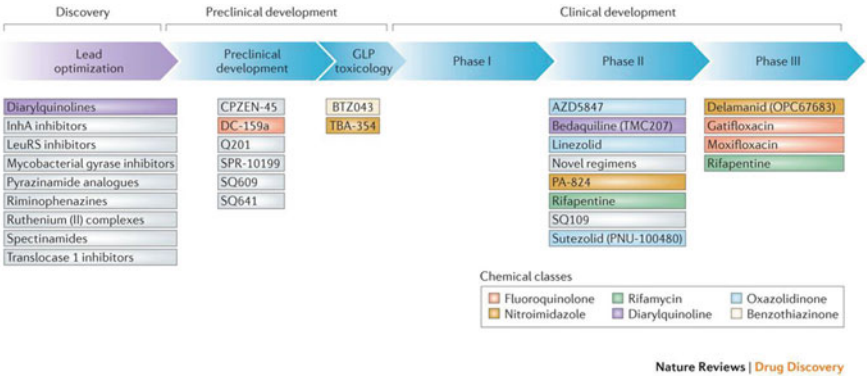

Fig. 5.2 TB drug discovery pipeline

5.5 Bedaquiline

Bedaquiline (trade name Sirtuto) is a diarylquinoline drug, formerly known under its code name TMC207, which was discovered in 2005 by Koen Andries and colleagues in Belgium. It has a novel mode of action, acting by inhibiting ATP synthase, and is active against replicating and non-replicating bacilli. The first phase II trial on 47 patients was published in 2009 in the New England Journal of Medicine and showed that addition of TMC207 to a standard second line regimen led to a higher proportion of patients with sputum conversion at 8 weeks of treatment (48 % vs. 9 %), (Diacon et al. 2012). The long-term 2 year follow up results for this pilot trial were published in 2012 and showed a significant reduction in time to sputum conversion in the TMC207 patients compared to placebo and less acquisition of resistance to companion drugs in the TMC207 group, however this did not reach statistical significance. With the exception of nausea, which was more frequently reported in the TMC207 patients, the occurrence of adverse events was not different between the two groups (Diacon et al. 2014). These results combined with two other phase II trials have led to accelerated approval of the drug by the FDA in 2012. This was the first new TB drug added to the arsenal of agents in decades. FDA approval was conditional upon prioritisation of phase three trials, but these have not yet started. The WHO and CDC have published provisional guidelines on the use of bedaquiline: http://www.who.int/tb/challenges/mdr/bedaquiline/en/index.html and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm?s_cid=rr6209a1_e (Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis 2013).

5.6 Delamanid

Delamanid, (OPC 67683) is a nitro-dihydro-imidazooxazole derivative which acts by blocking the synthesis of myolic acids, thus interfering with cell-wall integrity of the mycobacteria. It was first proposed to be a potential new candidate for treatment of TB in 2006 by Japanese scientists working for Otsuka Pharmaceutical. Subsequently it has shown promising results in phase IIa and b trials. In a seminal RCT including 481 patients recruited in 17 centers in 9 countries, the proportion of sputum positive MDR-TB patients that converted to sputum negative after 2 months of treatment with delamanid (100 mg BID) added to an optimised background regimen (n = 161) was 45.4 % opposed 29.6 % in those patients receiving a background regimen and placebo (n = 160) (p = 0.008). The patients receiving delamanid had significantly shorter time to sputum negativity and, additionally, a mortality benefit was observed for those in the active arms of this trial (Gler et al. 2012). Phase III trials are underway.

The European Medicines Agency (EMA) approved the drug for use in MDR-TB in November 2013, making Delamanid the second drug to be approved for use in (MDR-)TB in 50 years. It will be manufactured under the name of Deltyba.