Eur Respir J 2002; 20: Suppl. 36, 87s–94s
DOI: 10.1183/09031936.02.00309102

European Respiratory Journal
ISSN 0904-1850

Tuberculosis therapy: past, present and future

M.D. Iseman

Tuberculosis therapy: past, present and future. M.D. Iseman. ©ERS Journals Ltd 2002.

ABSTRACT: The major historical landmarks of tuberculosis (TB) therapy include: the discovery of effective medications (streptomycin and para-aminosalicylic acid) in 1944; the revelation of "triple therapy" (streptomycin, para-aminosalicylic acid and isoniazid) in 1952, which assured cure; recognition in the 1970s that isoniazid and rifampin could reduce the duration of treatment from 18 to 9 months; and the observation in the 1980s that adding pyrazinamide to these drugs allowed cures in only 6 months.

To combat noncompliance, intermittent regimens, twice or thrice weekly, have been proven to cure even far-advanced TB in as few as 62–78 encounters over 26 weeks.

However, these regimens are not sufficiently short or convenient to facilitate effective treatment in resource-poor countries. Therefore, drug-resistant strains have emerged to threaten TB control in various areas of the world, including India, China, Russia and the former Soviet Union. For these reasons, it is vital that new medications are developed to shorten the duration of therapy, increase the dosing interval of intermittent regimens and replace agents lost to resistance. Other special considerations include identifying optimal therapy for persons with acquired immune deficiency syndrome, particularly noting the problems of drug/drug interactions for those receiving antiretroviral treatment.

Finally, the Alchemist's Dream of tuberculosis should be pursued: modulating the immune response to shorten treatment and/or overcome drug resistance.

Eur Respir J 2002; 20: Suppl. 36, 87s–94s.

Clinical Mycobacteriology Service, Dept of Medicine, National Jewish Medical and Resource Centre, Denver, CO, USA.

Correspondence: M.D. Iseman, Clinical Mycobacteriology Service, Dept of Medicine, National Jewish Medical and Resource Centre, 1400 Jackson Street, Denver, CO 80206-9982, USA.
Fax: 1 3033981780
E-mail: isemanm@njc.org

Keywords: Acquired immune deficiency syndrome
directly observed therapy
drug resistance treatment
immunomodulation
tuberculosis

Received: January 25 2002
Accepted after revision: March 13 2002

It is difficult to discuss tuberculosis (TB) therapy, present and future, without reviewing the history of the treatment. Scientific "knowledge" is a continuously evolving process, and recognising how today's paradigms have been arrived at is critical to understanding how advances might be made in the future.

Past

Efforts to treat "phthisis" or "consumption" over the Millennia have been largely tales of tragedy and frustration. A variety of herbal concoctions, dietary interventions and climatic prescriptions were among the more benign remedies offered. By contrast, bleeding and purging probably amplified and accelerated mortality.

At the turn of the 20th century, George Bernard Shaw, *via* one of the characters in his play "A Doctor's Dilemma", described the medical treatment of TB in England as "a huge commercial system of quackery and poison". However, with the discovery of sulfonamides and penicillin in the 1930s, truly effective antimicrobial therapy became a reality. Inspired by observations that soil microbes seemed capable of preventing the growth of other species "in their turf", Selman Waksman's research in New Jersey lead to the identification of streptomycin (SM) in 1944. In the same year, Jorgen Lehman, working in Sweden, synthesised the para-amino salt of salicylic acid (PAS). Rapidly pressed into use, these two agents had clearly identifiable activity against clinical TB. Serendipitously, due to a shortage SM, the British Medical Research Council (BMRC) performed one of the first randomised clinical trials comparing PAS or SM alone with the combination of both agents [1]. The results, which were published in 1950, demonstrated that the combination was more effective at both achieving cures and preventing acquired drug resistance. These insights substantially shaped future treatment trials (table 1).

Gerhard Domagk's research, which led to the discovery of sulfonamides in the 1930s, eventuated in the discovery of the anti-TB activity isonicotinic

Table 1. – Landmarks in tuberculosis (TB) therapy

Date	Landmark
1944	SM and PAS
1948	Randomised trial, SM *versus* PAS *versus* SM/PAS
1952	Triple therapy, isoniazid/SM/PAS, 24 months
1960s	EMB replaces PAS, 18 months
1970s	RIF added to INH/EMB/SM, 9 months
1980s	PZA added to INH/RIF, 6 months

SM: streptomycin; PAS: para-amino salt of salicylic acid; RIF: rifampicin; EMB: ethambutol; INH: isonicotinic acid hydrazide; PZA: pyrazinamide.

acid hydrazide (INH) in 1952. Adding INH to PAS and SM ("triple therapy") resulted in predictable cures for 90–95% of patients, the Holy Grail. Unfortunately, it required up to 24 months of continuous treatment to achieve this objective [2]. This was related to the persistence of viable bacilli in tissues long after sputum cultures had become negative. Perhaps the most fundamentally important principle derived from triple therapy was that such treatment, reliably given, effectively precluded acquired drug resistance.

The replacement of PAS by ethambutol (EMB) in the 1960s had two benefits. EMB was much better tolerated than PAS and it allowed reduction in the duration of treatment to 18 months [3].

The next major advance in therapy was the introduction of rifampicin (RIF). Derived from *Streptomyces mediterranei*, RIF was studied in early trials by the BMRC in East Africa [4] and Hong Kong [5], demonstrating that practical combinations of INH, SM, EMB and RIF resulted in predictable cures in >95% of cases in just 8–9 months. The particular activity of RIF that facilitated this compression of treatment was its pronounced capacity of rifamycin to kill mycobacteria undergoing sporadic metabolism, the so-called "sterilising effect".

The next step forward was the recognition that the inclusion of pyrazinamide (PZA) allowed a reduction in the duration required to achieve predictable cures. PZA was found to accelerate the time required to achieve culture negativity and to yield >95% cure rates in 6 months when combined with INH and RIF [5–7]. It has been speculated that the singular role of PZA is activity against tubercle bacilli in the acidic debris in pulmonary cavity walls [8]. This is consistent with the observation that PZA exerts all of its beneficial effects in the first 2 months of therapy.

Present

Despite progressive reduction, from 24 to 6 months of the duration of therapy required for cure, noncompliance or abandonment of treatment remain the major impediments to effective therapy. To combat these factors, directly observed therapy (DOT) has been widely endorsed [9]. To facilitate such supervision, intermittent (less than daily) regimens have become very important. Multiple studies have shown that 6-month regimens given thrice weekly throughout [6, 10] or twice weekly following a 2-week daily induction phase [11] are as efficacious as daily regimens. These regimens involve as few as 62–78 encounters with the patients over 6 months to deliver curative treatment.

Such regimens have allowed the USA to increase the proportion of patients receiving DOT from 4% in 1990 to ~70% in 2000 [12]. With the widespread use of DOT, case rates in the USA have steadily declined from 1993 to the present (fig. 1). Indeed, decline of case rates from 1995–2000 averaged 7.8%·yr^{-1}. This was the most rapid rate of reduction over any 5-yr period since 1953, the beginning of the era of modern chemotherapy.

Globally, DOT has been endorsed by the World Health Organization (WHO) in a modified model called "DOTS", directly observed therapy short-course [13]. Acknowledging that directly observed treatment for the entire duration may not be feasible, WHO originally stipulated that DOTS should have the following five elements: 1) political commitment to effective treatment; 2) an assured supply of medications; 3) diagnosis by sputum microscopy; 4) analysis of the entire cohort of patients initiated on treatment; and 5) directly-observed treatment, especially during the first 2 months. Most programmes in the developing world do not use intermittent regimens since all doses are not supervised. Rather, they rely on daily self-administered treatment assuming that, by employing various support measures, an adequate number of doses will be taken.

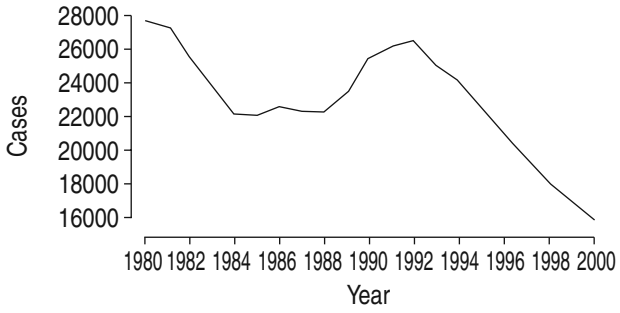

Fig. 1.–Reported tuberculosis (TB) cases in the USA between 1980 and 2000. TB cases rose between 1984–1992 due to the effects of human immunodeficiency virus (HIV)-infection, immigration and deterioration of the public health infrastructure, particularly in urban areas. Throughout the 1990s considerable investment was made into the development of directly-observed therapy short-course (DOTS) programmes. By 2000, >70% of the potentially communicable cases were on DOT. Despite the continued effects of HIV and immigration (which did not abate in the 1990s), case rates have dropped consistently.

The most controversial element of the DOTS model is reliance upon sputum microscopy, not culture, for diagnosis. The two major drawbacks of microscopy are its insensitivity and inability to identify drug-resistant strains of TB. Microscopy in developing nations is typically performed on unconcentrated sputum using Ziehl-Neelsen staining. Unfortunately, this system only detects patients with very extensive, typically cavitary, lung disease. Thus, while it has been argued that the most advanced cases that are most likely to transmit to others are found, roughly one-half of the patients with active pulmonary TB would not be detected by this approach, and these unrecognised patients would continue to spread TB until death or diagnosis intervene.

Inability to detect drug resistance is the other drawback of microscopy. In the DOTS model, drug resistance is inferred by failure to respond to treatment, typically after 6 months of therapy. Three obvious problems arise from this approach: 1) progressive damage to the lungs, even death, from uncontrolled disease; 2) ongoing transmission of microbes that are extremely difficult to treat; and 3) the possibility of "amplifying" drug resistance, *e.g.* the patient begins therapy with INH- and RIF-resistant disease and, during treatment, acquires resistance to

PZA and/or EMB. The current author believes that it is essential that drug-susceptibility testing be developed for use in less prosperous regions of the world.

The epidemiology of drug resistance has been analysed in two recent international surveys sponsored by the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD). These surveys documented wide-ranging rates and patterns of drug resistance around the globe [14, 15]. Resistance was seen most frequently to INH and SM, the two agents used most extensively over the years. Clinically, the most significant pattern involves resistance to both INH and RIF, so-called "multidrug-resistant TB" (MDR-TB).

Analysing the importance of various patterns of drug resistance, MITCHISON and NUNN [16] at the BMRC recognised early on the ominous implication of MDR-TB. Indeed, multiple studies from the BMRC have shown that resistance to INH alone has very little impact on the outcome of therapy [6, 10, 17]. Thus, it has become apparent that the rifamycin antibiotics are the keystone of modern, short-course therapy and that future strategies must focus upon conserving susceptibility to those agents.

Future

Looking toward the future of TB treatment, the next section will focus on the issues identified in table 2. These issues will be addressed below.

Shorter treatment?

Figure 2 represents a meta-analysis of treatment trials involving regimens of varying duration. The "shoulder" of the sigmoid curve is between 4.5 and 6 months of therapy. Assuming that an appropriate objective for performance of a regimen is 95%+ cure rates, steps that can be taken to "shift the curve to the left" should be considered. Conceptually, this might be accomplished by strengthening either the early bactericidal activity (EBA) or the late sterilising effects (killing bacilli in diminished states of metabolism so that relapses do not occur after treatment is terminated) of the regimen. Early mycobacterial death has been shown to primarily be the product of INH, RIF and PZA [8]. Although INH had the most prominent EBA as a single agent in a BMRC study [18], the dramatic killing effect seen in the first week seems not to be vital to curative therapy. Thus, attention shifts to the rifamycins and PZA, and consideration must be given to novel compounds that might enhance either the EBA or sterilising phase.

Table 2. – Future issues in tuberculosis (TB) therapy

Can the duration of curative chemotherapy be shortened?
Can the periodicity (days between doses) of therapy be increased?
Can new drugs be developed?
What is optimal therapy of TB in persons with AIDS?
Can chemotherapy be supplemented with immunomodulation to shorten treatment or overcome drug resistance?

AIDS: acquired immunodeficiency syndrome.

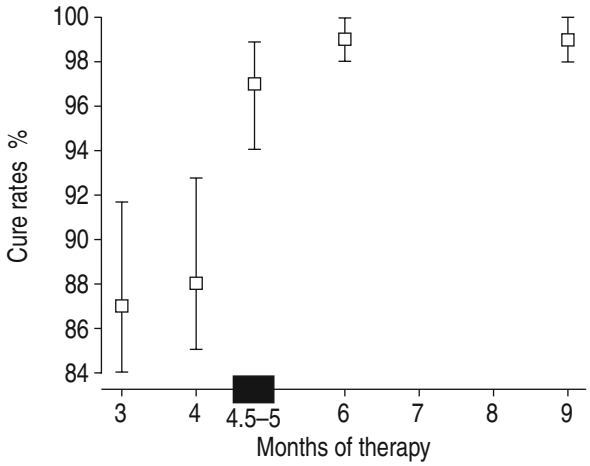

Fig. 2. – A meta-analytical representation of cure rates for tuberculosis regimens (reported in trials from around the world) of varying duration and constituents (American College of Chest Physicians, 1995). The 9-month regimens consisted of isonicotinic acid hydrazide (INH) and rifampicin (RIF), usually with streptomycin (SM) and/or ethambutol (EMB) but not pyrazinamide (PZA). All of the shorter regimens included INH, RIF, PZA, and SM or EMB. The trials were all done under "study conditions" including directly-observed therapy. Thus, they reflect the regimens' capabilities, not the predictably less successful outcomes under "programme conditions". Data are presented as mean±95% confidence limits.

RIF is the standard rifamycin. It is typically given to adults in daily or intermittent schedules at 600 mg dosage (or 450 mg for those weighing <50 kg). Increasing the dose in daily therapy is not likely to yield improved results: in a USA trial, 750 mg daily did not have a greater effect than 600 mg [19]. In intermittent regimens, increasing the dose above 600 mg resulted in increased toxicity [20]. Other rifamycins currently in use include rifabutin and rifapentine. Both of these agents have substantially longer half-lives than RIF, but they have significantly different pharmacokinetics and toxicity. Rifabutin's peak serum level following a standard dose of 300 mg is typically in the range of 0.4–0.5 mcg·mL^{-1} [21]. In clinical trials, rifabutin has shown no advantage over RIF [22, 23]. When the dose of rifabutin is increased to 450 mg, increased toxicity is seen, particularly neutropenia and thrombopenia [24].

The 13-h half-life of rifapentine is much longer than the half-life for RIF, 2.5–3 h. In addition, maximum serum concentrations for rifapentine are considerably higher than RIF, in the range of 20 mcg·mL^{-1} *versus* 8–12 mcg·mL^{-1} [25], and maximum inhibitory concentrations (MICs) for rifapentine are lower than for RIF, 0.015–0.6 *versus* 0.06–0.25 mcg·mL^{-1} [26]. All of these parameters suggest that rifapentine might have therapeutic advantages over RIF. However, rifamycin is only active in the unbound state and rifapentine is 95% protein bound *versus* 80% for RIF.

Thus far, clinical trials have focussed on rifapentine's

long half-life and the potential for once-weekly treatment (see below). However, the current author believes that studies should be performed to determine whether rifapentine in the initial phase might accelerate early killing beyond RIF, thus allowing shorter regimens.

In addition to agents such as the rifamycin which are primarily effective in killing organisms undergoing routine metabolism, attention is being focussed on compounds that are active against tubercle bacilli in a nonmultiplying, semidormant state. Agents that interfere with these "housekeeping" functions are discussed below in the New Drugs? section.

Increased periodicity?

To facilitate DOT, once-weekly treatment schedules have been studied employing rifapentine. Three major studies have been performed in Hong Kong [27], South Africa/USA [28] and USA/Canada [29], employing slightly different protocols. All trials concluded with 4 months of once-weekly rifapentine and INH, compared to twice- or thrice-weekly RIF and INH. In all three trials, the RIF arms modestly outperformed the rifapentine arms. However, for patients in the Centres for Disease Control and Prevention (CDC) whose sputum cultures became negative after 2 months of treatment, outcomes were comparable [30]. The current author′s interpretation of these trials suggests that the once-weekly rifapentine regimens could be strengthened by increasing the dose of rifapentine, adding additional agents, such as a potent fluoroquinolone (see below), or improving INH delivery.

An alternative approach would be to employ rifapentine throughout therapy, including the twice-weekly continuation phase treatment. The current author believes that the sustained high-level exposure to a rifamycin, which would be realised with twice-weekly rifapentine might reduce the duration required to assure 95%+ cure rates to the range of 4–4.5 months.

Rifalazil (KRM-1648) is a novel rifamycin that has an extremely long half-life, possibly related to its propensity for concentration within macrophages [31]. Its activity has been demonstrated in the mouse model [32–36] and may have potential in the treatment of active disease or of latent infection. However, it is far away from human trials.

New drugs?

The following questions should be asked about new medications. Can they replace medications lost to resistance? Can they improve the performance of conventional regimens *versus* drug-susceptible disease?

The fluoroquinolones (FQNs) are by far the most promising agents in both of these dimensions. Wild strains of *Mycobacterium tuberculosis* are predictably susceptible *in vitro* to FQN [37, 38], and various FQNs have been demonstrated to be active in murine models [39, 40]. The most potent of the currently available drugs in descending order of *in vitro* activity are moxifloxacin, gatifloxacin, levofloxacin, ofloxacin and ciprofloxacin [40–44]. Considerable experience in human disease documents the utility of ciprofloxacin, ofloxacin and levofloxacin against TB including MDR strains [45–49]. Indeed, data from Hong Kong [49] and Turkey [50] indicated that the outcome of treatment of MDR-TB was substantially better with *in vitro* susceptibility to the FQNs.

While recent studies suggest that moxifloxacin is particularly active, the long-term tolerability and safety of third-generation FQNs like moxifloxacin or gatifloxacin have not been established as they have for ofloxacin and levofloxacin [51, 52], and given the unanticipated toxicity of such agents as temafloxacin, trovafloxacin, sparfloxacin, and grepafloxacin, this should not be regarded lightly. Nonetheless, these drugs merit careful study both as agents to augment conventional therapy and as major drugs for MDR-TB.

The oxazolidinones are a novel group of antimicrobials [53]. One member of the family, linezolid, has been introduced into clinical medicine primarily for the treatment of drug-resistant Gram-positive coccal infections. Based on *in vitro* and murine activity *versus* TB [54], the current author and others have used it in the management of extensive drug-resistant TB (INH, RIF, and multiple other first-line and retreatment agents); it has shown some apparent efficacy (unreported data). However, its utility is compromised by toxicity (haematological disturbances and painful peripheral neuritis) and extreme expense. Another member of the family, designated as PNU 10048, apparently has more activity than linezolid *versus M. tuberculosis* with MICs ranging from 0.03–0.5 $mg \cdot mL^{-1}$ [55]. However, plans for its clinical development are not apparent.

Compounds that have potential activity *versus* nonmultiplying bacilli include congeners of metronidazole and isocitrate lyase inhibitors. Nitroimidazopyrans have been shown to be active compared to static *M. tuberculosis* populations, and replicate bacilli [56]. Metronidazole itself has limited activity against nonreplicating bacilli, but analogues may be more active [57]. Recent studies of tubercle bacilli living in a semidormant state in lung tissue have identified the importance of the glyoxylate shunt, particularly involving the enzymatic pathway isocitrate lyase [58]. Research is underway to find agents capable of disruption of this system under the premise that this might dramatically improve "sterilisation".

Other novel drugs with potential utility against TB were recently reviewed by AGRAWAL *et al.* [59]. Promising agents included thiolactomycins that have activities somewhat analogous, albeit less potent, to INH [60]. Additionally, analogues to pyrazinamide or morphazinamide that may be both more active than these agents and not cross-resistant with PZA have been described by a research consortium including CYNAMON *et al.* [61–63] and L. Heifets (National Jewish Medical and Research Centre, Denver, CO, USA, personal communication).

Optimal therapy for tuberculosis in persons with acquired immune deficiency syndrome

The human immunodeficiency virus (HIV) has greatly augmented the TB epidemics in sub-Saharan Africa as well as focal populations of South-East Asia, Latin America, the Indian subcontinent, Russia, and urban, industrialised communities.

Most authorities suggest that regimens that are effective among non-HIV-infected TB patients are comparably efficacious in those with acquired immune deficiency syndrome (AIDS) [64]. However, there are problems in this arena. Several reports suggest that relapse rates are higher in the presence of AIDS, albeit modestly so [65–67], and as persons with AIDS live longer due to antiretroviral therapy and opportunistic infection prophylaxis, it is plausible that they will survive long enough to allow more relapses. Furthermore, RIF, the mainstay of modern therapy, has such profound pharmacological effects (*via* induction of the hepatic Cytochrome P-450 pathways) that it is not compatible with contemporary antiretroviral regimens [68, 69]. Rifabutin, which does not have analogous effects on the cytochrome system, has been used as an alternative [69]. However, it is not free from complicating drug/drug interactions [69]. Rifapentine is intermediate between RIF and rifabutin in terms of its effect on the cytochrome system [70]. However, its use in persons with AIDS has been discouraged due to the evolution of rifamycin monoresistance in a small number of patients in a USA Centres for Disease Control trial [71].

Other problems that loom in this field include possible malabsorption of TB medications [68] and dealing with "the immune reconstitution system" or paradoxical late-worsening of TB when antiretroviral therapy restores immunologically mediated inflammation [72–76].

Immunomodulation

In Shaw's "Doctor's Dilemma", the same character who lambasted drug therapy advised that people must "stimulate the phagocytes. Drugs are a delusion". Presumably, inspired by his friend, the Nobel-prize winning immunologist Sir Thomas Almroth-Wright, Shaw anticipated the 20th Century preoccupation with a vaccine to prevent or cure TB.

The bacillus of Calmette and Guérin (BCG), a living vaccine derived from an attenuated strain of *M. bovis* (a very close relative of *M. tuberculosis*), has been given to nearly 5 billion persons since its widespread use in the 1930s. Although it does appear to lessen disease, particularly extrapulmonary TB, in young people following primary infection, it has had very meager effects upon adult pulmonary disease [77–80]. Thus, transmission and deaths rage on largely uncontrolled despite immense programmes of BCG vaccination in developing nations.

BCG presumably exerts its benefits by lessening dissemination through accelerated immune defenses following primary pulmonary infection. Considerable work is being directed at finding a vaccine that is more efficient or durable at this task than BCG [81, 82].

There is also consistent interest in developing an immunomodulating agent, "vaccine" or otherwise, that might help control active disease. This concept is based broadly on the notion that part of the "pathogenic strategy" of TB is the corruption of the human immune response. As tuberculous disease is initiated and advances in the body, there appears to be a shift from a T-helper cell type 1 (Th1) protective response to a T-helper cell type 2 (Th2) pathway which is less effective and more injurious to tissue. Vaccines derived from *M. vaccae*, a saprophytic rapid-growing mycobacterium, have been studied in this regard with highly variable results [83, 84].

Other agents that have been studied or are under consideration include interferon-γ [85, 86], interferon-α [87], imiquimod [88], interleukin-12 [89], granulocyte-macrophage colony-stimulating factor [90–92], levamisole [93, 94] or transfer factor [95–99].

Summary

Although the usual case of drug-susceptible TB can be predictably cured in 6 months with a reasonably nontoxic, economical regimen involving as few as 62–78 encounters, novel methodologies must be established if TB is going to be controlled in the decades ahead.

Given the drugs/drug-groups available now and in the near future, it is highly unlikely that the duration of therapy will be able to be reduced to <4 months. To shorten therapy below this level will take either novel agents that are active *versus* the semidormant, sporadically multiplying microbes left behind after the initial dramatic killing effects, or an immunological modulator that substantially enhances the host's cellular immunity.

Unfortunately, despite the massive burden that tuberculosis constitutes, there are not good economic incentives for the pharmaceutical industry to invest in these endeavors. In response, the "Working Alliance for Tuberculosis Drug Development" was formally launched in Cape Town, South Africa in February 2000 [100]. It pledged to accelerate the development of new tuberculosis drugs by a system of partnerships, formulation of plans, reassessment of pharmacoeconomics, and advocacy. Sponsored by an array of nongovernmental organisations, private philanthropy and governmental agencies, this "Global Alliance" has embarked upon a vital but formidable task.

References

1. Medical Research Council. Treatment of pulmonary tuberculosis with streptomycin and para-aminosalicylic acid. *BMJ* 1950; 2: 1073–1085.
2. Medical Research Council. Various combinations of isoniazid with streptomycin or with PAS in the treatment of pulmonary tuberculosis. *BMJ* 1955; 1: 435–445.
3. Doster B, Murray FJ, Newman R, Woolpert SF.

Ethambutol in the initial treatment of pulmonary tuberculosis. U.S. Public Health Service Tuberculosis Therapy Trials. *Am Rev Respir Dis* 1973; 107: 177–190.
4. East African/British Medical Research Council. Second East African/British Medical Research Council Study. Controlled clinical trial of four 6-month regimens of chemotherapy for pulmonary tuberculosis. Second Report. *Am Rev Respir Dis* 1976; 114: 471–475.
5. Hong Kong Chest Service, BMR Council. Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis: The results up to 24 months. *Tubercle* 1979; 60: 201–210.
6. Hong Kong Chest Service, BMR Council. Controlled trial of 4 three-times weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Second report: The results up to 24 months. *Tubercle* 1982; 63: 89–98.
7. Singapore Tuberculosis Service, BMR Council. Long-term follow-up of a clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. *Am Rev Respir Dis* 1986; 133: 779–783.
8. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946–1986, with relevant subsequent publications. *Int J Tuberc Lung Dis* 1999; 3: S231–S279.
9. Bayer R, Wilkinson D. Directly observed therapy for tuberculosis: history of an idea. *Lancet* 1995; 345: 1545–1548.
10. Hong Kong Chest Service/BMR Council. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide: Results at 30 months. *Am Rev Respir Dis* 1991; 143: 700–706.
11. Cohn DL, Catlin BJ, Peterson KL, Judson FN, Sbarbaro JA. A 62-dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis. A twice-weekly, directly observed, and cost-effective regimen. *Ann Int Med* 1990; 112: 407–415.
12. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States. 1999. Atlanta, Georgia, Centers for Disease Control and Prevention, 2000.
13. World Health Organization. WHO Tuberculosis Programme: Framework for effective tuberculosis control. *WHO/TB* 1994; 94: 179.
14. Pablos-Méndez A, Raviglione MC, Laszlo A, *et al.* Global surveillance for antituberculosis-drug resistance, 1994–1997. *N Engl J Med* 1998; 338: 1641–1649.
15. Espinal MA, Laszlo A, Simonsen L, *et al.* Global trends in resistance to antituberculosis drugs. *N Engl J Med* 2001; 344: 1294–1303.
16. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis* 1986; 133: 423–430.
17. Tam CM, Chan SL, Kam KM, *et al.* Rifapentine and isoniazid in the continuation phase of a 6-month regimen. Interim report: no activity of isoniazid in the continuation phase. *Int J Tuberc Lung Dis* 2000; 4: 262–267.
18. Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *Am Rev Respir Dis* 1980; 121: 939–949.
19. Long MW, Snider DE, Farer LS. U.S. Public Health Service cooperative trial of three rifampin-isoniazid regimens in treatment of pulmonary tuberculosis. *Am Rev Respir Dis* 1979; 119: 879–894.
20. Singapore Tuberculosis Service/British Medical Research Council. Controlled trial of intermittent regimens of rifampicin plus isoniazid for pulmonary tuberculosis in Singagore. The results up to 30 months. *Am Rev Respir Dis* 1977; 116: 807–820.
21. Blaschke TF, Skinner MH. The clinical pharmacokinetics of rifabutin. *Clin Infect Dis* 1996; 22: Suppl. 1, S15–S22.
22. Gonzalez-Montaner LJ, Natal S, Yongchaiyud P, Olliaro P. Rifabutin for the treatment of newly-diagnosed pulmonary tuberculosis: a multinational, randomized, comparative study *versus* Rifampicin. *Tubercle Lung Dis* 1994; 75: 341–347.
23. McGregor MM, Olliaro P, Wolmarans L, *et al.* Efficacy and safety of Rifabutin in the treatment of patients with newly diagnosed pulmonary tuberculosis. *Am J Respir Crit Care Med* 1996; 154: 1462–1467.
24. Griffith DE, Brown BA, Wallace RJ Jr. Varying dosages of rifabutin affect white blood cell and platelet counts in human immunodeficiency virus-negative patients who are receiving multidrug regimens for pulmonary *Mycobacterium avium* complex disease. *Clin Infec Dis* 1996; 23: 1321–1322.
25. Tam CM, Chan SL, Lam CW, Dickinson JM, Mitchison DA. Bioavailability of Chinese rifapentine during a clinical trial in Hong Kong. *Int J Tuberc Lung Dis* 1997; 1: 411–416.
26. Heifets LB, Lindholm-Levy PJ, Flory MA. Bactericidal activity *in vitro* of various rifamycins against *Mycobacterium avium* and *Mycobacterium tuberculosis*. *Am Rev Respir Dis* 1990; 141: 626–630.
27. Tam CM, Chan SL, Lam CW, *et al.* Rifapentine and isoniazid in the continuation phase of treating pulmonary tuberculosis. Initial report. *Am J Respir Crit Care Med* 1998; 157: 1726–1733.
28. Hoechst-Marion-Roussel. Presentation to the US Food and Drug Admistration, Rockville, MD, USA, 1998.
29. Vernon A. TBTC Study 22 (Rifapentine Trial): preliminary results in HIV negative patients. *Am J Respir Crit Care Med* 2000; 16: Suppl., A252.
30. Catanzaro A, Horsburgh R, for the TB Trials Consortium. TBTC Study 22: risk factors for relapse with once-weekly isoniazid/rifapentine (HP) in HIV-negative TB patients (abstract). *Am J Respir Crit Care Med* 2000; 161: Suppl., A252.
31. Mor N, Simon B, Heifets L. Bacteriostatic and bactericidal activities of Benzoxazinorifamycin KRM-1648 against *Mycobacterium tuberculosis* and *Mycobacterium avium* in human macrophages. *Antimicrob Agents Chemother* 1996; 40: 1482–1485.
32. Saito H, Tomioka H, Sato K, Kawahara S, Hidaka T, Dekio S. Therapeutic effect of KRM-1648 with various antimicrobials against *Mycobacterium avium* complex infection in mice. *Tubercle Lung Dis* 1995; 76: 51–58.
33. Klemens SP, Cynamon MH. Activity of KRM-1648 in combination with isoniazid against *Mycobacterium tuberculosis* in a murine model. *Antimicrob Agents Chemother* 1996; 40: 298–301.
34. Lenaerts AM, Chase SE, Chmielewski AJ, Cynamon MH.

Evaluation of rifapentine in long-term treatment regimens for tuberculosis in mice. *Antimicrob Agents Chemother* 1999; 43: 2356–2360.
35. Shoen CM, Chase SE, DeStefano M, Harpster TS, Chmielewski AJ, Cynamon MH. Evaluation of rifalazil in long-term treatment regimens for tuberculosis in mice. *Antimicrob Agents Chemother* 2000; 44: 1458–1462.
36. Lenaerts AM, Chase SE, Cynamon MH. Evaluation of rifalazil in a combination treatment regimen as an alternative to isoniazid-rifampin therapy in a mouse tuberculosis model. *Antimicrob Agents Chemother* 2000; 44: 3167–3168.
37. Tsukamura M. *In vitro* antituberculosis activity of a new antibacterial substance ofloxacin (DL8280). *Am Rev Respir Dis* 1985; 131: 348–351.
38. Heifets LB, Lindholm-Levy PJ. Bacteriostatic and bactericidal activity of ciprofloxacin and ofloxacin against *Mycobacterium tuberculosis* and *Mycobacterium avium* complex. *Tubercle* 1987; 68: 267–276.
39. Tsukamura M. Antituberculosis activity of ofloxacin (DL8280) on experimental tuberculosis in mice. *Am Rev Respir Dis* 1985; 132: 915.
40. Baohong JI, Nacer L, Maslo C, Truffot-Pernot C, Bonnafous P, Grosset JH. *In vitro* and *in vivo* activities of moxifloxacin and clinafloxacin against *Mycobacterium tuberculosis. Antimicriol Agents Chemother* 1998; 42: 2066–2069.
41. Ji B, Lounis N, Maslo C, Truffot-Pernot C, Bonnafous P, Grosset J. *In vitro* and *in vivo* activities of moxifloxacin and clinafloxacin against *Mycobacterium tuberculosis. Antimicrob Agents Chemother* 1998; 42: 2066–2069.
42. Miyazaki E, Miyazaki M, Chen JM, Chaisson RE, Bishai WR. Moxifloxacin (BAY12-8039), a new 8-methoxyquinolone, is active in a mouse model of tuberculosis. *Antimicrob Agents Chemother* 1999; 43: 85–59.
43. Zhao BY, Pine R, Domagala J, *et al.* Fluoroquinolone action against clinical isolates of *Mycobacterium tuberculosis*: effects of a C-8 methoxyl group on survival in liquid media and in human macrophage. *Antimicrob Agents Chemother* 1999; 43: 661–667.
44. Saito H. Comparative antimicrobial activities of the newly synthesized quinolone BAY 12-8039 and gatifloxacin. *Drugs* 1999; 58: Suppl. 2, 400–401.
45. Tsukamura M. Therapeutic effect of a new antibacterial substance ofloxacin (DL8280) on pulmonary tuberculosis. *Am Rev Respir Dis* 1985; 131: 352–356.
46. Kennedy N, Berger L, Curram R, *et al.* Randomized controlled trial of a drug regimen that includes ciprofloxacin for the treatment of pulmonary tuberculosis. *Clin Infect Dis* 1996; 22: 827–833.
47. Kohno S, Koga H, Kaku M, Maesaki S, Hara K. Prospective comparative study of ofloxacin or ethambutol for the treatment of pulmonary tuberculosis. *Chest* 1992; 102: 1815–1818.
48. Hong Kong Chest Service/BMR Council. A controlled study of rifabutin and an uncontrolled study of ofloxacin in the retreatment of patients with pulmonary tuberculosis resistant to isoniazid, streptomycin and rifampicin. *Tuberc Lung Dis* 1992; 73: 59–67.
49. Yew WW, Chan CK, Chau CH, *et al.* Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. *Chest* 2000; 117: 744–751.
50. Tahaoglu K, Törün T, Sevim T, *et al.* The treatment of multidrug-resistant tuberculosis in Turkey. *N Engl J Med* 2001; 345: 170–174.
51. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. *Clin Infect Dis* 1999; 28: 352–364.
52. Berning SE, Madsen L, Iseman MD, Peloquin C. Long-term safety of ofloxacin and ciprofloxacin in the treatment of mycobacterial infections. *Am J Respir Crit Care Med* 1995; 151: 2006–2009.
53. Diekema DJ, Jones RN. Oxazolidinones: a review. *Drugs* 2000; 59: 7–16.
54. Cynamon MH, Klemens SP, Sharpe CA, Chase S. Activities of several novel oxazolidinones against *Mycobacterium tuberculosis* in a murine model. *Antimicrob Agents Chemother* 1999; 43: 1189–1191.
55. Barbachyn MR, Hutchinson DK, Brickner SJ, *et al.* Identification of a novel oxazolidinone (U-100480) with potent antimycobacterial activity. *J Med Chem* 1996; 39: 680–685.
56. Stover CK, Warrener P, van Devanter DR, *et al.* A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. *Nature* 2000; 405: 962–966.
57. Ashtekar DR, Costa-Perira R, Nagrajan K, Vishvanathan N, Bhatt AD, Rittel W. *In vitro* and *in vivo* activities of nitroimidazole CGI 173421 against *Mycobacterium tuberculosis. Antimicrob Agents Chemother* 1993; 37: 183–186.
58. McKinney JD, Honer zu Bentrup KH, Munoz-Elias EJ, *et al.* Persistence of *Mycobacterium tuberculosis* in macrophages and mice requires the glyoxylate shunt enzyme isocitrate lyase. *Nature* 2000; 406: 735–738.
59. Agrawal S, Thomas NS, Dhanikula AB, Kaul CL, Panchagnula R. Antituberculosis drugs and new drug development. *Curr Opin Pulm Med* 2001; 7: 142–147.
60. Slayden RA, Lee RE, Armour JW, *et al.* Antimycobacterial action or thiolactomycin: an inhibitor of fatty acid and mycolic acid synthesis. *Antimicrob Agents Chemother* 1996; 40: 2813–2819.
61. Kremer L, Douglas JD, Baulard AR, *et al.* Thiolactomycin and related analogues as novel antimycobcterial agents targeting KasA and KasB condensing enzymes in *Mycobacterium tuberculosis. J Biol Chem* 2000; 275: 16857–16864.
62. Cynamon MH, Speirs RJ, Welch JT. *In vitro* antimycobacterial activity of 5-chloropyrazinamide. *Antimicrob Agents Chemother* 1998; 42: L462–L463.
63. Cheng DL, Thibert L, Sanchez T, Heifets L, Zhang Y. pncA mutation as a major mechanism of pyrazinamide resistance in *M. tuberculosis. Antimicrob Agents Chemother* 2000; 44: 528–532.
64. Small PM, Schecter GF, Goodman PC, Sande MA, Chaisson RE, Hopewell PC. Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1991; 324: 289–294.
65. Hawken M, Nunn P, Gathua S, *et al.* Increased recurrence of tuberculosis in HIV-1-infected patients in Kenya. *Lancet* 1993; 342: 332–337.
66. Elliott AM, Halwiindi B, Hayes RJ, *et al.* The impact of human immunodeficiency virus on mortality in patients treated for tuberculosis: Two-year follow-up of cohort in Lusaka, Zambia. *Tran Royal Soc Trop Med Hygiene* 1995; 89: 75–82.
67. Chaisson RE, Clermont HC, Holt EA, *et al.* Six-month supervised intermittent tuberculosis therapy

in Haitian patients with and without HIV infection. *Am J Respir Crit Care Med* 1996; 154: 1034–1038.
68. Burman WJ, Gallicano K, Peloquin CA. Therapeutic implications of drug interactions in the treatment of human immunodeficiency virus-related tuberculosis. *Clin Infect Dis* 1999; 28: 419–430.
69. Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. *Am J Respir Crit Care Med* 2001; 164: 7–12.
70. Keung A, Reith K, Eller MG, McKenzie A, Cheng L, Weir S. Enzyme induction observed in healthy volunteers after repeated administration of rifapentine and its lack of effect on steady-state rifapentine pharmacokinetics: Part I. *Int J Tuberc Lung Dis* 1999; 3: 426–436.
71. Vernon A, Burman WJ, Benator D, Khan A, Bozeman L. Acquired rifamycin mono-resistance among patients with HIV-related tuberculosis treated with supervised once weekly rifapentine and isoniazid. *Lancet* 1999; 353: 1843–1847.
72. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med* 1998; 158: 157–161.
73. Phillips P, Kwiatkowski MB, Copland M, Craib K, Montaner J. Mycobacterial lymphadenitis associated with the initiation of combination antiretroviral therapy. *J Acquir Immune Defic Syndr* 1999; 20: 122–128.
74. Race EM, Adelson-Mitty J, Kriegel GR, *et al.* Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet* 1998; 351: 252–255.
75. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1-infected persons after initiation of highly active antiretroviral therapy. *Ann Intern Med* 2000; 133: 447–454.
76. Wendel KA, Alwood KS, Gachuhi RMS, Chaisson RE, Bishai WR, Sterling TR. Paradoxical worsening of tuberculosis in HIV-infected persons. *Chest* 2001; 120: 193–197.
77. Frimodt-Møller J, Acharyulu GS, Kesava Pillai K. Observations on the protective effect of BCG vaccination in a South Indian rural population: fourth report. *Bull Int Un Tuberc* 1973; 48: 40–50.
78. Fine PEM. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet* 1995; 346: 1339–1345.
79. Pönninghaus JM, Fine PEM, Sterne JAC, *et al.* Efficacy of BCG vaccine against leprosy and tuberculosis in northern Malawi. *Lancet* 1992; 339: 636–639.
80. Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG, and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. *Lancet* 1996; 348: 17–24.
81. Young DB. Current tuberculosis vaccine development. *Clin Infect Dis* 2000; 30: Suppl. 3, S254–S256.
82. Fine PEM. Bacille Calmette-Guérin vaccines: A rough guide. *Clin Infect Dis* 1995; 20: 11–14.
83. von Reyn CF, Marsh BJ, Waddell R, *et al.* Cellular immune responses to mycobacteria in healthy and human immunodeficiency virus-positive subjects in the United States after a five-dose schedule of *Mycobacterium vaccae* vaccine. *Clin Infect Dis* 1998; 27: 1517–1520.
84. Durban Immunotherapy Trial Group. Immunotherapy with *Mycobacterium vaccae* in patients with newly diagnosed pulmonary tuberculosis: a randomised controlled trial. *Lancet* 1999; 354: 116–119.
85. Raad I, Hachem R, Leeds N, Sawaya R, Salem Z, Atweh S. Use of adjunctive treatment with interferon-g in an immunocompromised patient who had refractory multidrug-resistant tuberculosis of the brain. *Clin Infect Dis* 1996; 22: 572–574.
86. Condos R, Rom WM, Schluger NW. Treatment of multidrug-resistant pulmonary tuberculosis with interferon-γ *via* aerosol. *Lancet* 1997; 349: 1513–1515.
87. Giosué S, Casarini M, Alemanno L, *et al.* Effects of aerosolized interferon-α in patients with pulmonary tuberculosis. *Am J Respir Crit Care Med* 1998; 158: 1156–1162.
88. Arevalo I, Ward B, Miller RM, *et al.* Successful treatment of drug-resistant cutaneous leishmaniasis in humans by use of Imiquimod, an Immunomodulator. *Clin Infect Dis* 2001; 33: 1847–1851.
89. Bermudez LE, Petrofsky M, Wu M, Young LS. Clarithromycin significantly improves interleukin-12-mediated anti-*Mycobacterium avium* activity and abolishes toxicity in mice. *J Infect Dis* 1998; 178: 896–899.
90. Steward WP. Granulocyte and granulocyte-macrophage colony-stimulating factors. *Lancet* 1993; 342: 153.
91. Bermudez LE, Kemper CA, Deresinski SC. Dysfunctional monocytes from a patient with disseminated *Mycobacterium kansasii* infection are activated *in vitro* and *in vivo* by GM-CSF. *Biotherapy* 1995; 8: 135–142.
92. Kemper CA, Bermudez LE, Deresinski SC. Immunomodulatory treatment of *Mycobacterium avium* complex bacteremia in patients with AIDS by use of recombinant granulocyte-macrophage colony-stimulating factor. *J Infect Dis* 1998; 177: 914–920.
93. Singh MM, Kumar P, Malaviya AN, Kumar R. Levamisole as an adjunct in the treatment of pulmonary tuberculosis. *Am Rev Respir Dis* 1981; 123: 277–279.
94. A Kenyan/Zambia/BMR Council Collaborative Study. Controlled clinical trial of levamisole in short-course chemotherapy for pulmonary tuberculosis. *Am Rev Respir Dis* 1989; 140: 990–995.
95. Whitcomb ME, Rocklin RE. Transfer factor therapy in a patient with progressive primary tuberculosis. *Ann Intern Med* 1973; 79: 161–166.
96. Dwyer JM, Gerstenhaber BJ, Dobuler KJ. Clinical and immunologic response to antigen-specific transfer factor drug-resistant infection with *Mycobacterium xenopi. Am J Med* 1983; 74: 161–168.
97. Fudenberg HH, Wilson GB, Smith CL. Immunotherapy with dialyzable leukocyte extracts and studies of their antigen-specific (transfer factor) activity. *Proc Virchow-Pirquet Med Soc* 1980; 34: 3–87.
98. Rubinstein A, Melamed J, Rodescu D. Transfer factor treatment in a patient with progressive tuberculosis. *Clin Immunol Immunopathol* 1977; 8: 39–50.
99. Thestrup-Pedersen K, Thulin H, Zachariae H. Transfer factor applied to intensify the cell-mediated immunological reactions against *Mycobacterium avium. Acta Allergol* 1974; 29: 101–116.
100. Working Alliance for TB Drug Development. Working Alliance for TB Drug Development, Cape Town, South Africa, February 8th, 2000. *Int J Tuberc Lung Dis* 2000; 4: 489–490.