Current Thinking on the
Management of Tuberculosis

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Abstract

High-income countries are moving toward tuberculosis (TB) elimination. Sophisticated diagnostic tests and effective treatment regimens are readily available. The range of available resources even make effective treatment of multidrug-resistant tuberculosis (MDRTB) possible. The introduction of highly active antiretroviral therapy (HAART) and specific TB control measures have reduced the incidence of HIV-associated TB disease. Unfortunately, the situation in low-income countries, who carry 95% of the global TB burden, is less positive. TB diagnosis still relies upon sputum smear microscopy. The management of MDRTB remains problematic though guidelines for DOTS-plus programs have been developed and cheaper second-line drugs are becoming available. The HIV epidemic continues to confound TB control efforts, particularly in sub-Saharan Africa. The appropriate package of interventions for controlling HIV/TB disease remains undefined and unimplemented. The international community must provide the funding and technical support to address the alarming dichotomy in TB control that exists between rich and poor countries.
Tuberculosis (TB) has been called the perfect expression of an imperfect civilisation [1]. A review of the medical literature on TB management published during the last 12 months confirms this quotation. Low-income countries, who bear 95% of the global TB burden and have only minimal resources, are confronting major problems with TB control, HIV/TB co-infection and multidrug-resistant tuberculosis (MDRTB)[2]. Meanwhile, the high-income countries, who carry 5% of the global TB burden, have used their considerable capabilities to address these same problems and are now planning for TB elimination. This review will highlight this dichotomy while summarising recent publications on the management (ie. investigation and treatment) of TB in individual patients, in specific patient sub-groups (eg. MDRTB patients) and at the population level.

**Innovations in TB diagnostics**

The dichotomy between high- and low-income countries is most obvious when considering the field of TB diagnostics. High-income countries have a plethora of expensive intricate diagnostic tests to detect an increasingly small number of TB patients. The BACTEC radiometric culture system is being replaced by non-radiometric culture methods of equal speed and performance for the detection and susceptibility of *Mycobacterium tuberculosis* [3]. These culture methods are being supplemented by numerous molecular methods that further speed diagnoses. For example, El-Hajj et al described a single-tube PCR assay, employing five probes targeting the *rpoB* gene and labelled with different
fluorophores, that can identify rifampicin-resistant *M. tuberculosis* directly from sputum within three hours [4].

In contrast, accurate case detection remains the weak link in the WHO DOTS strategy in low-income countries [5]. Sputum microscopy, which is the only diagnostic test widely available in these settings, is insensitive, is labour-intensive, tends to detect advanced rather than early disease, and is inadequate for detecting many HIV/TB cases as well as paediatric and extrapulmonary disease. The new culture and molecular methods are too expensive and complex for routine use in low-income countries. Despite improvements in the range and quality of antigens, serological tests continue to be confounded by limited sensitivity and/or specificity. For example, the sensitivity and specificity of a rapid card-based immunochromatographic test for detecting antibodies to *M. tuberculosis* ranged between 65-83% and 46-100%, respectively [6]. The most exciting advance in TB diagnostics for low-resource settings has been the development of the *FastPlaque*TB™ rapid phage-based test for TB detection and susceptibility testing [7]. This system uses a mycobacteriophage as an indicator of the presence of viable *M. tuberculosis*. The test is completed within two days and requires no specialised equipment. Albert et al reported that the assay had an overall sensitivity and specificity of 75.2% and 98.7%, respectively, compared to routine culture on Löwenstein-Jensen media [7].
Innovations in TB treatment

The principles that guide the design of appropriate anti-tuberculous regimens to effect high cure rates (95-98%) and limit the risks of acquired drug resistance and disease relapse remain unchanged. Namely the use of 2-3 agents to which the organism is fully susceptible, a treatment period of sufficient duration, and never adding a single drug to a failing regimen. Given treatment is reliant on the same few effective agents, careful application of these basic rules remains crucial and implementation of treatment (daily or intermittent) must be backed by careful patient supervision.

Newer agents that are at least as effective as the “antiquated” mainstays of treatment, isoniazid and rifampicin, and that allow for less frequent dosing and/or a shorter treatment period are desperately needed. Although research in TB drug development has intensified since the early 1990s, the target date for a substantial advance in TB chemotherapy is still 2010 [8].

Fixed dose combinations

The advent of TB drugs in fixed dose combination (FDC) offers the advantage of making treatment delivery less complex and also may prevent acquired drug resistance [9]. Ensuring bioavailability of each component in the FDC, particularly that of rifampicin, remains the major concern. Evidence suggests that such combination agents are comparable to separate formulations at the same dose
WHO supports the use of FDC on a daily basis only and providing quality control requirements are confirmed by an accredited laboratory.

Shorter or less frequent treatment

Reducing the standard 6-month regimen to 4 months (ie. isoniazid and rifampicin throughout with pyrazinamide for the first 2 months only) has only been shown to be effective in smear- and culture-negative patients who are not immune-suppressed, have limited pulmonary disease and have little likelihood of drug resistance [11]. Hence, in many high-risk settings, this abridged treatment would not be satisfactory. Furthermore, studies of culture-negative disease have inherent problems: risk of over-diagnosis and inclusion of inactive TB disease or non-tuberculous disorders. All of these biases tend to over-state the benefit of the 4-month regimen.

An agent that allows for less frequent dosing would be of benefit both to the patient and the treatment service. Rifapentine, a semi-synthetic derivative of rifampicin with a significantly longer serum half-life, has been the subject of clinical trials. Recent reports on studies of HIV-negative subjects utilising once weekly rifapentine and isoniazid compared with twice weekly rifampicin and isoniazid only in the continuation phase of treatment offer the prospect of some simplification of treatment [12,13]. Overall the Hong Kong and CDC studies showed that the once weekly rifapentine 600mg/isoniazid 900mg regimen resulted in relapse rates significantly higher than the standard twice-weekly
rifampicin based regimen [12,13]. However, the results of the CDC study suggested that the difference in outcome is less significant if the rifapentine regimen is restricted to those with non-cavitary and less-extensive pulmonary disease and sputum cultures at the end of the 2-month intensive phase are negative [13].

A sub-optimal dose of rifapentine due to the drug's higher protein binding is one explanation for these inferior results. Hence, an increased dose may be more effective. Another CDC study to consider safety as a prelude to phase III efficacy studies demonstrated that higher doses (900mg and 1200mg) were tolerated [14].

The above studies disagreed as to the impact of the lower weekly dose of isoniazid in the rifapentine study groups. The detection of acquired resistance to rifampicin in advanced HIV-positive cases following the use of an intermittent regimen in the continuation phase suggests the once-weekly isoniazid dose may be too low [12,15]. Once-weekly rifapentine is ill-advised in this high-risk subset of patients.

New Agents

The use of fluoroquinolones has been limited to the treatment of MDRTB. The use of murine models to assess the newer agents, moxifloxacin and gatifloxacin, have shown promise for wider fluoroquinolone use. A recent study involving mice
found that the addition of moxifloxacin, both in the initial daily phase (2 weeks, combined with isoniazid, rifampicin and pyrazinamide) and also the once-weekly continuation phase (5.5 months, with rifapentine and isoniazid) was almost as effective as the standard short-course regimen [16]. The results inferred a pronounced sterilising effect from the addition of moxifloxacin in the continuation phase and hence presents a potential alternative to isoniazid, which has limited sterilising activity.

In a separate murine-model study [17], the activity after 12 weeks of gatifloxacin in combination with ethionamide, ethambutol and pyrazinamide compared favourably with that of isoniazid and rifampicin with or without gatifloxacin. From their overall results, the investigators suggested that the combination of gatifloxacin, ethionamide, pyrazinamide with or without ethambutol would likely be of benefit in the treatment of MDRTB. The benefit of gatifloxacin used in a higher dose needs further evaluation.

**Potential New Agents**

A nitroimidazopyran compound, PA824, has been the subject of recent interest because of demonstrated bactericidal activity comparable to isoniazid in a mouse model [8]. The other interesting feature of this new agent was activity against non-replicating bacilli suggesting possible potential for shortening TB treatment as well for treatment of latent infection.
Management of patients with multidrug-resistant tuberculosis

High-income countries have all of the resources required for effective management of MDRTB: modern laboratory facilities that can provide prompt accurate drug susceptibility test (DST) results, expert medical teams experienced in MDRTB management, and the funds to pay for the expensive second-line drugs [18]. They also have the thoracic surgical services to perform pulmonary resections, an intervention that continues to be found effective (perhaps essential) in selected MDRTB patients. For example, Park et al described 49 MDRTB patients treated over five years in a Korean tuberculosis hospital by a combination of chemotherapy and pulmonary resection achieving a cure rate of 90.4% [19]. However, the treatment of latent MDRTB infection remains problematic even in resource-rich settings. Current guidelines recommend the use of pyrazinamide and a fluoroquinolone. Papastavros et al reported that all 17 patients with suspected latent MDRTB infection failed to complete a course of pyrazinamide and levofloxacin due to musculoskeletal, neurological, dermatological and other adverse reactions [20]. Guidelines on monitoring these treatments and alternative regimens are obviously required.

Meanwhile, TB control programs in low-income countries and their international advisers are still contemplating the advantages and disadvantages of instituting MDRTB treatment (ie. so-called DOTS-plus initiatives). However, there has been some important new information in the last 12 months that will guide this decision-making process. Schaaf et al followed 119 South African children
exposed to MDRTB and found that the incidence of infection and disease was comparable to that occurring in contacts of drug-susceptible index cases [21]. Dye et al have also modelled the spread of MDRTB following the introduction of combination chemotherapy and estimated that the relative reproductive fitness of MDRTB strains is comparable to but “at the lower end of the range” of drug-susceptible strains (ie. $f \approx 0.3$)[22]. Localised areas with high prevalences of MDRTB are therefore most likely due to poor treatment programs rather than local transmission of an MDRTB superbug. These modelling studies confirm that TB control programs should continue to concentrate on effective management of drug-susceptible disease using the DOTS strategy.

However, models also suggest that MDRTB incidence in the “hot spots” will be reduced more rapidly by effective treatment of drug-resistant cases in well-run DOTS-plus programs [22]. WHO and other authorities have proposed various circumstances (based on indicators such as the prevalence of primary MDRTB and a TB control program’s existing treatment success rate) in which DOTS-plus treatment would be justified [23,24]. Guidelines for establishing MDRTB treatment centres have been developed, cheaper second-line drugs are becoming available, and supervision by the Green Light Committee (GLC) make DOTS-plus programs increasingly possible in resource-poor settings. The success of a pilot project providing a standardised MDRTB treatment regimen in Peru confirms that such DOTS-plus programs are feasible at least in middle-income countries [25]. Rational recommendations on the indications for MDRTB
treatment programs will be developed over the next few years based on the clinical, epidemiological and economic analyses of other DOTS-plus pilot projects established through the GLC and other initiatives.

**HIV and tuberculosis**

The dichotomy between affluent and poor countries is also evident when considering the co-epidemics of HIV and TB. About a third of the 43 million people living with HIV worldwide are co-infected with *M. tuberculosis* [26]. Only a small minority (estimated to be 60,000) live in North America [27]. In the US and other affluent countries, the advent of highly active antiretroviral therapy (HAART) has seen a decline in the number of TB cases among HIV-positive individuals [27]. Treatment of latent TB infection (LTBI) in HIV-positive individuals, early recognition of HIV/TB disease, and effective infection control measures have further limited the number of HIV/TB cases.

The optimal management options for HIV/TB cases in high-resource countries have also been determined [27]. The standard 6-month antituberculosis regimen is considered adequate therapy for HIV-positive patients, who are relatively immunocompetent and respond promptly to antituberculosis therapy. Treatment combinations comprising rifabutin and selected antiretrovirals have been developed to minimise adverse drug interactions. The phenomena of paradoxical reactions, characterised by worsening clinical and/or laboratory findings despite effective antituberculosis therapy, have been well-recognised particularly in
HIV/TB patients receiving HAART [27,28]. Symptomatic treatment with anti-inflammatory agents or corticosteroids is recommended [27,28]. To avoid drug interactions, treatment disruptions and paradoxical reactions, HAART should be deferred until the continuation phase of TB therapy (ie. 2 months or later) in stable HIV-positive patients (ie. CD4 > 100 x 10^6 cells /L)[29]. HIV/TB patients with advanced disease (ie. CD4 < 100 x 10^6 cells /L) will benefit from HAART, which may be started after 1-2 months of antituberculosis therapy [27,29].

The appropriate response to HIV/TB co-infection is far less clear and more problematic in the resource poor countries of Africa and SE Asia where the vast majority of such cases occur [30]. Effective tuberculosis treatment has been shown to be one of the most cost-effective interventions in addressing the HIV/AIDS epidemic in Africa [31]. Modelling also suggests that high TB treatment rates can blunt the amplifying effect of HIV on TB epidemics [32]. To achieve these high treatment rates, the standard DOTS strategy may need to be supplemented by active case finding where TB transmission rates are high (eg. in prisons and hospitals) and among HIV-positive individuals [33]. Such specific interventions targeting HIV-related disease require that individuals know their HIV serostatus. The “promote HIV voluntary counselling and testing initiative” (ProTEST) promotes voluntary HIV testing as one step in developing a coherent response to TB in HIV-endemic areas [30].
Other interventions that can then be considered as part of a HIV/TB control package include co-trimoxazole prophylaxis and isoniazid preventative therapy (primary and secondary)[33]. By preventing death from some other HIV-related infections, co-trimoxazole prophylaxis reduced the mortality rate among HIV-positive TB patients in Côte d’Ivoire. However, this intervention may not be generalisable to other countries with different disease patterns and antibiotic resistance profiles, and may risk the development of further antibiotic resistance [33,34]. High rates of recurrent disease due to TB reinfection in HIV-positive patients suggest that TB prophylaxis should be considered in this patient group [35]. Isoniazid prophylaxis has proven effective in preventing TB in HIV-positive individuals but the protective benefit of the standard 6-month regimen is short-lived (ie. < 12 months) where TB transmission rates are high [36].

Of course, introduction of HAART could have the greatest impact on the HIV/TB epidemics in sub-Saharan Africa. Badri et al have reported that HAART reduced the incidence of HIV-associated TB by more than 80% in a cohort of 264 South African patients [37]. However, HAART remains prohibitively expensive for all but a minority of HIV patients in low-income countries [30]. Pharmaceutical companies and the international community must continue striving for equitable access to HAART. Health delivery systems within the low-income countries must also be developed to deliver HAART safely and securely [33]. TB and AIDS control programs will need to work cooperatively to achieve this goal.
DOTS strategy

The WHO strategy, well known as DOTS (directly observed therapy-short course), has become the programmatic benchmark and remains the backbone of efforts to control TB, particularly in resource poor settings [38]. Although DOTS appears to have improved TB control in many areas, the strategy’s relatively slow uptake and tardy progression towards the global targets of 70% case detection and 85% cure rate have led to the Global Stop TB partnership, the Global Drug Facility and Global DOTS Expansion Plan [39]. These initiatives reflect an attempt to expand TB control efforts and harness additional resources (financial and human) through promoting partnerships between government and non-government organisations and public and private sectors.

The DOT (ie. directly observed therapy) element of DOTS has been strongly advocated as best practice for treatment of the individual. The consensus appears to be that DOT improves overall treatment outcomes but this has yet to be established at the evidence-based level [40,41]. Varying methodologies to assess outcomes and difficult program conditions are cited as key reasons for the failure to confirm the effectiveness of DOT. Barriers to the successful application of DOT include inadequate resourcing and poor implementation, difficulty and cost of accessing treatment, and social and cultural factors [40,42,43]. Hence, a treatment program should incorporate a mixture of strategies tailored to the socio-cultural context to enhance patient adherence.
This program must also be flexible and sensitive to individual needs, and gain the commitment of local community and staff [42,44,45].

**Tuberculosis management issues in low-incidence high-income countries**

The WHO-recommended DOTS strategy is not entirely appropriate for high-income countries with a low TB incidence [46]. The DOTS strategy does not account for the technical and financial resources available in these countries, and the increasing importance of LTBI in these settings. A consensus document has therefore been published recommending the following initiatives for TB control and elimination in low-incidence countries: government commitment to TB elimination, establishment of a multi-skilled national TB control committee, adequate education of health personnel about TB, improved case detection in symptomatic patients, active case-finding in special groups, outbreak investigation, standardised treatment for TB disease and infection, accessibility to TB services, and maintenance of TB surveillance systems [46].

The problems in implementing some of these initiatives are highlighted in other publications. For example, Reichler et al reviewed the contact investigations conducted in five US states in 1996 [47]. Thirteen percent of TB patients had no contacts identified (only half of these patients were known to have been interviewed); less than two-thirds of TB contacts actually completed screening; and incomplete documentation of risk factors for TB transmission was noted in contact investigation records. A mathematical model has been developed in an
attempt to improve the cost-effectiveness of such contact investigations [48].

Certain case, contact and environment characteristics (eg. smear-positive case with cavitary disease, exposure time per month) were identified that predicted contacts with a positive tuberculin skin test (TST) result. Public health officials should consider using such models to better target TB contact tracing.

Another problem confronting TB control in low-incidence countries is that the current generation of medical staff is unfamiliar with TB and is confronted with fewer cases. This unfamiliarity with pulmonary TB disease leads to diagnostic delay, greater patient morbidity and mortality, and nosocomial transmission of TB [49]. Interestingly, the increased use of fluoroquinolones for the treatment of community-acquired pneumonia (CAP) may be another factor delaying TB diagnosis in high-income low-incidence countries. Dooley et al reported that almost one-half of their cohort of new pulmonary TB patients had received a fluoroquinolone for presumed CAP, had improved symptomatically because of the drug's anti-tuberculosis activity, and subsequently had a significantly delayed institution of appropriate antituberculosis treatment [50].

Non-specific presentations of extrapulmonary TB disease make prompt diagnosis and treatment even more problematic in low incidence countries. For example, TB peritonitis can be easily confused with spontaneous bacterial peritonitis in certain patients and the diagnosis will not be made unless the appropriate investigation (ie. mycobacterial culture of a peritoneal biopsy) is ordered [51].
Doctors in high-income countries are also being required to prevent, diagnose and treat TB in special patient groups (eg. immunosuppressed transplant recipients and patients with chronic renal failure) where a high index of suspicion is required to make the diagnosis and treatment may be confounded by adverse drug reactions [52-54].

_Treatment of latent tuberculosis infection_

Cost-effective treatment of LTBI is of particular importance for TB control programs in high-income low-incidence countries. Treatment choice has until recently centred on the use of isoniazid unless isoniazid resistance is strongly suspected. Although daily monotherapy for a minimum of six months has been generally accepted, 9 months is preferred and certainly advised in children and the HIV-infected. Intermittent use on a supervised basis is probably equally effective [55].

The recent ATS/CDC recommendations have also been expanded to support use of the 2-month rifampicin/pyrazinamide regimen in HIV-positive persons based on demonstrated efficacy and safety [55]. Concerns over the use of this regimen in the HIV-negative person were raised following reports of associated serious hepatotoxicity and death [56]. Revisions have therefore been made accepting its use but providing no other hepatotoxic agent is regularly used and there is no underlying liver damage. Cautious (but contentious) regular two-weekly monitoring has been firmly advocated.
References and recommended reading


This study provides very sound scientific support for the use of a rifapentine based regimen in the continuation phase of therapy if confined to patients with limited disease and an appropriate early treatment response (culture conversion within 2 months).


Excellent review of the epidemiology, clinical aspects, management, and treatment monitoring of MDRTB.


A useful review of the epidemiological and modelling studies of MDRTB that makes several important conclusions. HIV has been linked to MDRTB in small-scale (nosocomial) outbreaks however there is no evidence linking MDRTB and HIV in international comparisons. The reproductive fitness of MDRTB is "at the lower end" of the range for susceptible strains. The DOTS strategy with standard short-course chemotherapy will limit the emergence of MDRTB but DOTS-plus programs with effective MDRTB treatment programs will be required to reduce the incidence of MDRTB more rapidly.


The first published report of an MDRTB treatment program using a standardised regimen in a low- or middle-income country. Of 466 Peruvian patients enrolled to receive an 18-month regimen, 255 (48%) were cured at completion of treatment. The program cost US$0.6 million per year or 8% of the national TB budget. The study concludes that MDRTB treatment is feasible in a middle-income country with an effective pre-existing DOTS program.


Thoughtful review of interventions required to control HIV/TB in sub-Saharan Africa. Reference list cites all of the important publications on each of the potential strategies.


A cohort of 326 South African mineworkers were followed after successful treatment for pulmonary TB. Recurrent disease was investigated clinically and by IS6110 RFLP genotyping. HIV infection was associated with recurrence due to reinfection (hazard ration 18.7, 95% CI 2.4-143), but not relapse (0.58; 0.24-1.4). Interventions to prevent reinfection, such as chemoprophylaxis, should be considered.


An observational study in South Africa of 264 patients receiving HAART and 770 non-HAART patients found that HAART reduced the incidence of HIV-associated TB by 81% (95% CI 62-91)
in an area endemic for HIV and TB. The number of TB cases averted was greatest in patients with WHO clinical stage 3 or 4 disease and in those with CD4 counts less than 200 cells/μl.


This paper presents an excellent review of published studies on DOT outcomes. Using treatment failure and post treatment relapse as the key outcome measures (rather than simply treatment completion) the study examines the varied methodologies of outcome assessment and the shortcomings of treatment outcome despite DOT.


A set of recommendations that recognise that low-incidence high-income countries can and must do more than the basic WHO DOTS strategy to control and eliminate TB. These additional interventions include active case detection in high-risk groups, outbreak investigation, treatment of LTBI, establishment of multidisciplinary national TB control committees, and human resource development. These recommendations provide useful guidance for TB control personnel in all such countries.


A sobering review of health department records for all contacts of 349 adult patients with culture-confirmed pulmonary TB from 5 study areas in the United States. Forty-five (13%) patients had no contacts identified and another 38 (11%) had no close contacts identified. Only 6 of 12 patients residing in a homeless shelter had no contacts identified. Only 55% of contacts
completed screening. Improvements in the process of contact investigation are obviously required.


