Tuberculosis into the 2010s: Is the Glass Half Full?

Anna P. Ralph, Nicholas M. Anstey, and Paul M. Kelly

During the 16 years since the World Health Organization declared tuberculosis (TB) a global emergency, major new challenges have emerged—in particular the spread of extensively drug-resistant (XDR)-TB and its overlap with human immunodeficiency virus infection. However, during this period, we have also witnessed the creation of—and major commitments from—agencies dedicated to TB control, research, and funding, and tangible positive achievements have occurred; these include improvements in both new and existing TB diagnostics, a developmental pipeline of new candidate TB drugs, better treatment outcomes for multidrug-resistant TB and XDR-TB, heightened recognition of the importance of nosocomial transmission, and improved strategies to reduce mortality associated with concurrent human immunodeficiency virus infection and TB. We suggest updates to the 2006 International Standards of Tuberculosis Care to embrace these developments. The incorporation of these recent advances into optimized directly observed treatment, short course (DOTS), programs, in conjunction with more widespread deployment and enhanced political will, all provide grounds for improved control.

Mycobacterium tuberculosis is the consummate human pathogen. Millennia of evolution alongside human hosts have led to elaborate immune evasion and transmission strategies [1, 2]; as such, M. tuberculosis is thought to infect one-third of humans, and in 2007, it accounted for an estimated 9.27 million new cases of tuberculosis (TB) and ~1.7 million deaths [3]. Compounding this already crippling burden are the expanding threats of TB drug resistance and of concurrent human immunodeficiency virus (HIV) infection and TB. Primary transmission is the most common mode of acquisition seen in some settings for both extensively drug-resistant (XDR) and multidrug-resistant (MDR) TB [4–6]. The overlapping of HIV and TB epidemics in sub-Saharan Africa in particular creates a health care crisis and renders it unlikely that the Millennium Development Goal 6.C of reduction in TB prevalence and mortality by 50% by 2015 will be achievable in this region [7, 8].

Amid these grim realities, however, exciting recent developments with the potential to bring about important reductions in TB-related burden of disease have been achieved, including in achievements in under-resourced settings. However, their implementation poses new challenges due to resource constraints, policy-change inertia, and the need to prioritize basic TB care, as articulated by the World Health Organization’s (WHO’s) directly observed therapy, short-course (DOTS), and Stop TB partnership strategies [9, 10]. As has been clearly articulated, it is incumbent upon those with expertise and resources to take a serious role in bringing these developments into action in under-resourced TB-burdened settings [11]. Indeed, investing in TB control in resource-poor settings might be more cost-effective for developed nations in improving their own TB control than alternative approaches [12].

The TB literature is characterized by bleak statistics that provide substance for, in health-promotion terms, “fear-based” appeals; there is merit in directing attention in this manner to the dire global state of TB. However, there is an equal place for the alternative approach.
of positive appeals as effective strategies to promote a shift in mindset and uptake of new practices [13]. Here, we review important recent gains made in TB management and knowledge, discuss how these might be incorporated into existing DOTS programs, suggest a revision of several standards contained within the comprehensive 17-point 2006 International Standards of TB Care (ISTC), and recommend an 18th Standard [14]. Contrasting with negative appeals, we show that there is scope for optimism.

**TB DIAGNOSTICS**

Rapid recent developments have occurred in the field of TB diagnostics, as evidenced by the need to establish a subgroup within the Stop TB Partnership’s New Diagnostics Working Group to provide ongoing systematic reviews of diagnostic methods (Table 1) [15].

Of greatest priority are affordable ways to improve case detection through smear microscopy at field laboratories. Simple procedures recently shown to be of benefit include more clear instruction of people on how to produce an adequate sputum specimen [16], a reduction in the required number of specimens from 3 to 2 [17], more rapid specimen collection [18], and the processing of sputum specimens prior to examination (Table 1) [15, 19]. Fluorescence microscopy is more sensitive and rapid than conventional microscopy [19], and a light-emitting diode light source has recently been shown to be a reliable alternative to the expensive, short-lived mercury vapor lamps [20]. Such approaches provide solutions to the valid assertion that substandard TB diagnostics are unacceptable in resource-poor countries [11].

Transportation of specimens to a reference laboratory can be achieved despite challenging barriers: fresh sputum samples can be stored at 4°C for up to 6 weeks before unrefrigerated transportation, achieving excellent *M. tuberculosis* recovery without excessive contamination [21]. At laboratories with adequate capacity, early resistance detection—a critical tool in prevention of resistance amplification that is associated with better treatment outcomes for management of MDR-TB [22]—is now achievable with rapid molecular and culture-based methods. Line-probe assays (eg, Genotype MTBDRplus assay [Hain Lifescience]), which detect *M. tuberculosis* gene mutations that confer resistance to rifampicin (*rpoB*) and isoniazid (*katG* and *inhA*), provide sensitive and specific results in 6 h to 2 days [23–25]. Culture-based rapid methods for resistance detection are outlined in Table 1.

These improvements over traditional direct Ziehl-Neelsen staining and use of solid-culture media require rapid dissemination and uptake. Promotion of new technologies, via WHO endorsement [25], inclusion in guidelines [26], or internationally accepted standards [14], is the first step in their deployment, but innovative means are required to traverse the formidable barriers to dissemination of these messages to national TB control programs and the practitioners who implement these programs.

**NEW DRUG REGIMENS**

New anti-TB drugs are required to permit shorter treatment durations for drug-susceptible TB [27], which mathematical modeling indicates could effect major reductions in TB incidence and mortality [28], and to provide less toxic, more effective, and shorter regimens for MDR-TB. The TB literature has long lamented the absence of new drug developments since rifampicin in the 1960s. Barriers to TB drug development include the need to evaluate drugs in combination over long follow-up periods in resource-limited settings; a lack of good animal models for preclinical drug evaluation [29]; metabolic adaptability of *M. tuberculosis*, whereby genetic targets that appear promising have not proven to be so [30]; and the perception by pharmaceutical companies that antibiotic development is unrewarding [31]. Modeling performed in 2006 that incorporated the high attrition in drug development, found only a 5% chance of a new TB drug being ready for clinical use in humans by 2010 [32]. Despite these impediments, there are now ~30 new drugs for TB under development (Table 2) [29, 33–35]. PA-824 (a nitroimidazole) was shown to be successful against *M. tuberculosis* in vitro and in mouse models [36] and is now in phase II human trial stage (http://www.clinicaltrials.gov/show/NCT00567840). The diarylquinoline TMC207 (also called R207910) has appeared to be particularly promising in animal studies [37, 38], and a phase IIa randomized trial involving people with smear-positive pulmonary TB has been recently completed (http://www.clinicaltrials.gov/show/NCT00523926). Benzothiazinones (eg, BTZ043) are a propitious new antimycobacterial class which kill *M. tuberculosis* in vitro and in mice by targeting *M. tuberculosis* cell wall synthesis [39], and have important potential in drug-susceptible and drug-resistant TB.

The requirement for prolonged treatment has been hypothesized to arise from the development of a nonrepli cating, nephnotypically drug-resistant phase of *M. tuberculosis* driven by hypoxia and low-level nitric oxide; these factors, which characterize the internal environment of granulomata, up-regulate dormancy genes to yield the metabolically inert state [30, 40–42]. To shorten treatment regimens, new drugs inhibiting mechanisms underlying this nonreplicating state may have promise [30].

A second strategy that may permit shorter TB treatment regimens is the use of drugs that are bactericidal against rapidly metabolizing *M. tuberculosis*. Replacement of ethambutol with moxifloxacin has been shown to significantly increase the 2-month sputum culture conversion rate, from 63% to 80% [43]. Both moxifloxacin and gatifloxacin improved the sterilizing
<table>
<thead>
<tr>
<th>Method, test</th>
<th>Comments</th>
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<tr>
<td><strong>Sputum collection</strong></td>
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<tr>
<td>Improved sputum-submission guidance</td>
<td>If smear positive pulmonary TB case detection is impaired by poor-quality specimen submission, case detection can be improved by provision of adequate instructions</td>
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<td>Reduce number of collections from 3 to 2</td>
<td>Because incremental yields from subsequent sputum specimens are small, WHO recommends examining 2 smears; this can alleviate laboratory workloads, decrease time for diagnosis, and decrease the number of patients who “drop out” of the diagnostic pathway</td>
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<td><strong>Sputum smear microscopy</strong></td>
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<tr>
<td>Processing of sputum sample prior to smear examination (eg, use of bleach then centrifugation or use of bleach or sodium hydroxide then overnight sedimentation)</td>
<td>This is 18%–23% more sensitive than direct microscopy</td>
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<tr>
<td>Fluorescence microscopy</td>
<td>This is 10% more sensitive than conventional microscopy; use to determine viability of Mycobacterium tuberculosis in follow-up sputum specimens to detect treatment failure</td>
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<tr>
<td>Fluorescence microscopy using light-emitting diode light source</td>
<td>These light sources are cheaper, last longer, and have less potential for environmental contamination than do traditional lamps used in this method</td>
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<td><strong>Culture-based methods</strong></td>
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<tr>
<td>Liquid culture (eg, automated mycobacteria growth indicator tube)</td>
<td>Faster and more sensitive than solid media; recommended standard practice</td>
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<tr>
<td>Microscopic observation drug susceptibility assay</td>
<td>Yields faster culture and DST results than do liquid or solid media and is inexpensive, but requires inverted microscope and skilled technician to interpret culture appearance of M. tuberculosis</td>
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<tr>
<td>Thin-layer agar methodology</td>
<td>Yields faster culture and DST results than do liquid or solid media and is inexpensive, but requires skilled technician to recognize M. tuberculosis colony formation</td>
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<td>Colorimetric DST methods using redox indicators, tetrazolium salts, or a nitrate reductase assay</td>
<td>These are low-cost, low-tech, and able to yield DST results within 2 weeks; potential for biosafety hazard</td>
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<td><strong>Molecular methods</strong></td>
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<td>Line probe assays (eg, Genotype MTBDRplus assay [Hain] and INNO-LiPA Rif.TB assay [Immunogenetics])</td>
<td>High sensitivity and specificity for detection of rifampicin (with or without isoniazid) resistance, with a 1–2 day turnaround time directly for smear-positive sputum; requires DNA extraction and amplification facilities</td>
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<td>Nucleic acid amplification tests</td>
<td>High specificity; important role in confirming mycobacterial identity; poor negative predictive value for pulmonary and extrapulmonary TB; updated US CDC guidelines recommend sputum M. tuberculosis nucleic acid amplification tests for cases of suspected, unconfirmed TB if results would alter management [111]</td>
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<tr>
<td>Cytokine assays: T cell interferon-γ release assays</td>
<td>Useful in targeted strategies for LTBI detection in low TB-incidence settings; more specific than tuberculin skin test; cannot distinguish active from treated TB or LTBI</td>
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**NOTE.** From [15–17, 19, 20, 112, 113]. CDC, Centers for Disease Control and Prevention; DST, drug susceptibility testing; LTBI, latent tuberculosis infection; TB, tuberculosis; WHO, World Health Organization.

activity of regimens for drug-susceptible TB [27] (gatifloxacin has since been withdrawn from some markets on the basis of adverse glycemic effects). Although, in a multicenter study, moxifloxacin failed to accelerate sputum culture negativity at 2 months, 1-month culture conversions were more frequently achieved [44]. The later-generation fluoroquinolones have a well-established place in the treatment of MDR-TB; the possibility that they might also permit shorter treatment durations for drug-susceptible TB is lent credibility by these recent findings.

**VACCINES AND ADJUNCTIVE IMMUNOTHERAPIES**

The need for an improvement on bacille Calmette-Guérin has been long recognized as a major priority [45]. The status of
promising candidate recombinant TB vaccines, including the commencement of phase II trials of MVA85A, has been reviewed in detail elsewhere [45–47].

Investigation of adjunctive immunotherapies is identified as one of several priority research areas [48–51]. They offer an attractively novel strategy to shorten TB treatment and to conserve antimicrobial efficacy in the face of growing resistance. Despite negative results from many studies using inactivated Mycobacterium vaccae as an adjunct to TB chemotherapy [52, 53], hope persists that this immunotherapy given in multiple doses might yet have potential as an adjunctive treatment in MDR-TB or previously treated TB [54] or as a preventative vaccine in previously bacille Calmette-Guérin–vaccinated HIV-infected persons [55, 56].

The concept of micronutrients as potential adjunctive immunotherapy candidates has gained currency since specific antimycobacterial mechanisms of action of vitamin D3 in macrophages (chiefly, up-regulation of LL-37/cathelicin) were demonstrated [57, 58]. The amino acid L-arginine has been found to influence antimycobacterial T cell responses via expression of the zeta chain of the CD3/T-cell receptor complex [59], and the metabolic product of L-arginine, nitric oxide, mediates important macrophage antimycobacterial responses [58]. Some multiple-micronutrient interventions in TB have been associated with benefits in patient subgroups or in non-bacteriological end points [60–62]. Whole-food nutritional support poses logistical challenges and has yet to be shown to be cost-effective or to improve bacteriological outcomes, but it can improve weight and possibly other parameters [63, 64]. The WHO recommends nutritional support in the management of MDR TB [26], and many programs already incorporate this.

An alternative adjunctive therapeutic strategy, immunosuppression, has long been employed in TB-related meningitis and has proven to be beneficial, with corticosteroids shown to decrease risk of death and drug-induced hepatitis [65, 66]. On the basis of the hypothesis that amelioration of cytokine-mediated pathology might be advantageous in some forms of TB, other combined immunosuppressive-therapeutic strategies have also been advocated [67, 68].

**IMPROVED MANAGEMENT AND PREVENTION OF MDR-TB AND XDR-TB**

Assigning a name to XDR-TB in 2005 brought it to public attention, accompanied by fears of a return to the preantibiotic era and the specter of untreatable TB [69]. Rapid fatality in people with XDR-TB in Tugela Ferry, South Africa, illustrated the tragic consequences of this infection in the setting of high rates of concurrent HIV infection and nosocomial spread [5].
Although, in sub-Saharan Africa, this burden remains fearsome [6, 7, 70], and although a failure to detect MDR-TB obscures the true scale of this crisis [3], a new picture emerged during 2008 in which XDR-TB cure is a realistic aim and decreases in MDR-TB rates can be achieved, including in resource-limited settings [71–73]. Retrospective cohort studies from diverse locations reported their experiences with MDR-TB and XDR-TB treatment in late 2008 [22, 71, 72, 74], offering an optimistic “potentially favorable perspective for patients” with XDR-TB [22] (eg, cure rates of 66.3% and 60.4% for MDR-TB and XDR-TB, respectively [72]). Level 1 (randomized, controlled trial–derived) evidence is required, as articulated by the Cambridge Declaration on clinical trials for drug-resistant TB [75], but meta-analysis of retrospective observational cohort studies was recently performed. This has identified the WHO recommendations of a treatment duration of ≥18 months after culture conversion and administration of DOT throughout as the factors associated with the greatest chance (almost 70%) of treatment success [76]. Drug susceptibility testing–tailored regimens were associated with nonstatistically significantly better outcomes than were standardized regimens, and inconsistent reporting of HIV status rendered examination of this variable difficult [76]. MDR-TB and XDR-TB treatment programs providing additional measures, such as nutritional and economic assistance for patients, have reported high rates of cure and treatment completion [71, 72], but the relative efficacy of such supports is unknown. High rates of successful treatment outcome may not be widely generalizable; major differences in outcomes are seen in South Africa, even accounting for HIV infection, possibly attributable to low use of quinolones; patient factors (higher use of alcohol, tobacco, and other drugs; malnutrition; and host immunity) and/or M. tuberculosis strain factors (differing virulence) [70], although meta-analysis did not find these factors to have a significant impact on MDR-TB outcome [76].

Even the best outcomes for MDR-TB treatment remain substantially worse than the WHO’s cure target of 85% for drug-susceptible TB, and the pool of undiagnosed MDR-TB and XDR-TB seriously threatens control efforts. Nevertheless, good cure rates provide a notably more positive outlook than the dire reports from only 2–3 years ago. Despite the expenses of MDR-TB treatment, modeling including drug, laboratory, and personnel costs indicates that MDR-TB treatment can be highly cost-effective [77]. There is a clear imperative for managing drug-resistant TB in accordance with current guidelines (eg, in DOTSPlus projects, accessing second-line anti-TB drugs through the Green Light Committee) [26] while not diverting funds away from the core business of basic TB service provision.

An additional cause for optimism is the recent decrease in MDR-TB rates documented in Estonia, Latvia, Hong Kong, and the United States [73]; the next important step is to identify the factors responsible for these successes. Infection control is emerging as a critical focus for MDR-TB and XDR-TB prevention, because they are frequently nosocomially transmitted [4–6, 78], requires renewed enthusiasm for more stringent respiratory infection control. This need not be complicated: modeling of XDR-TB transmission in Tugela Ferry indicated that appropriate use of existing resources (a combination of use of face masks, reduced duration of hospitalization, and a shift to outpatient therapy) could prevent nearly one-third of XDR-TB
cases [79]. Elsewhere, natural ventilation achieved by opening windows and doors was estimated to achieve lower TB transmission than costly, maintenance-requiring mechanical ventilation systems [80]. Recent reevaluation of 1950s experimental designs, using exhaust air from a TB ward passed into guinea pig enclosures, demonstrated that low-cost ultraviolet lights prevented 70% of TB infections, and negative air ionization prevented 60% of TB infections [81]. Nosocomial XDR-TB transmission can occur even with good ventilation, limited patients per room, and ultraviolet lamps [4]. Nevertheless, evidence indicates that the ISTC [14] should require an additional 18th standard: that respiratory infection control measures should be implemented in facilities treating patients with newly diagnosed smear-positive TB, especially in areas with a high prevalence of MDR-TB or XDR-TB.

**IMPROVED HIV-TB MANAGEMENT**

HIV infection increases the risk of latent TB reactivation 20-fold [82, 83], and in southern Africa, TB is the leading cause of death among people with HIV infection [84]. Identifying HIV infection presents an important TB control opportunity through the use of antiretroviral therapy and isoniazid preventive therapy, both of which reduce the risk of developing active TB and require continued up-scaling [85–88]. Advances in the understanding of management of concurrent HIV infection and TB include improved guidelines on HIV testing in persons with HIV infection is based on evidence that ART reduces the risk of developing active TB [85, 86] and improves survival when it is started during TB treatment, compared with if it is deferred [93–96], with the benefits of early ART initiation in people with TB outweighing the disadvantage of potential increased occurrence of immune reconstitution disease [7, 106]. Furthermore, ART achieves as-good virological and immunological responses as in people without TB [106].

First-line antiretroviral therapy recommended for persons with concurrent HIV infection and TB by Centers for Disease Control and Prevention and WHO comprises standard-dose efavirenz plus 2 nucleoside reverse-transcriptase inhibitors [91, 92], on the basis of the understanding that the 20% lower serum efavirenz concentration caused by rifampicin remains effective in suppressing HIV replication [98, 99]. Efavirenz may be safer in pregnancy than hitherto realized [92, 100, 101], although it remains a Category D listing. Nevirapine concentrations are more likely to be subtherapeutic in combination with rifampicin [102], and virological failure risk may be higher [103]. Despite this, nevirapine-based antiretroviral therapy is considered a suitable choice for second- or third-line treatment if efavirenz is contraindicated or unavailable and if rifampicins with less potency in inducing cytochrome P450 enzymes (rifapentine or rifabutin) are unavailable (as is generally the case where TB is endemic) [91, 92].

Determining optimal timing for antiretroviral therapy commencement after initiation of TB treatment is challenging because of drug toxicities, interactions, the heavy pill burden and attendant adherence risk, and immune reconstitution inflammatory syndrome [104, 105]. Although immune reconstitution inflammatory syndrome may increase with wider and earlier antiretroviral therapy use [94], it has not been associated with increased mortality, and to date, the risks appear to be outweighed by the benefits of early antiretroviral therapy [7, 106]. Recent cohort studies and preliminary data from one trial indicate that the optimal strategy is to begin antiretroviral therapy during TB treatment and that integration of HIV and TB care offers valuable benefits [93–96]. WHO guidelines recommend commencement of antiretroviral therapy 2–8 weeks after initiation of TB treatment if the CD4 cell count is <350 cells/mm³ or unknown [7, 89, 91]. Additional data, including data from

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Table 3. Summary of Recommendations for Antiretroviral Therapy (ART) in Patients with Concurrent Human Immunodeficiency Virus (HIV) Infection and Tuberculosis (TB)

<table>
<thead>
<tr>
<th>CD4 T cell count</th>
<th>ART recommendation</th>
<th>Timing of ART initiationa</th>
<th>Drug-susceptible TB</th>
<th>Multidrug-resistant TB</th>
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<tr>
<td>≤200 cells/mm³</td>
<td>Yes</td>
<td>2–8 weeks after starting TB treatment</td>
<td>2 weeks or when anti-TB regimen is tolerated</td>
<td></td>
</tr>
<tr>
<td>200–350 cells/mm³</td>
<td>Yes</td>
<td>After 8 weeks</td>
<td>After 8 weeks</td>
<td></td>
</tr>
<tr>
<td>&gt;350 cells/mm³</td>
<td>No</td>
<td>Reevaluate at 8 weeks and every 6 months thereafter</td>
<td>Reevaluate at 8 weeks and every 6 months thereafter</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>Yes</td>
<td>2–8 weeks after starting TB treatment</td>
<td>2–8 weeks or when anti-TB regimen is tolerated</td>
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</table>

**NOTE.** The recommended first-line ART regimen is efavirenz (600 mg daily) plus 2 nucleoside reverse-transcriptase inhibitors, with a rifampicin-based TB regimen given 5–7 times weekly [91, 92]. The rationale for using ART to prevent TB and to improve TB treatment outcome in persons with HIV infection is based on evidence that ART reduces the risk of developing active TB [85, 86] and improves survival when it is started during TB treatment, compared with if it is deferred [93–96], with the benefits of early ART initiation in people with TB outweighing the disadvantage of potential increased occurrence of immune reconstitution disease [7, 106]. Furthermore, ART achieves as-good virological and immunological responses as in people without TB [106].

a From [7, 89, 91].
the SAPIT (Starting Antiretrovirals at Three Points in Tuberculosis Therapy) trial [96], should provide further clarity. On the basis of the evidence summarized above, ISTC Standard 13, which recommends antiretroviral therapy in selected patients with concurrent HIV infection and TB, can be updated to incorporate advice regarding antiretroviral therapy regimen selection and timing of commencement (Figure 1 and Table 3).

**TOWARD THE STABILIZATION OF THE “GLOBAL EMERGENCY”**

The reported number of TB cases per capita has been decreasing globally since 2003, and funding for TB control has improved, peaking in 2008 at US $3.3 billion [8]. Although the challenges posed by HIV infection and MDR-TB remain formidable worldwide, 3 of the 6 WHO regions (the Americas, the Eastern Mediterranean, and South-East Asia) will meet 2015 targets for reductions in TB case numbers and fatalities [3]. Progress in industrialized countries includes downward trends in TB rates in Indigenous populations. Over the past 20 years, the TB incidence has decreased among Australian Aborigines [107], Canadian First Nations populations [108, 109], and Native Americans [110], attributed to factors that include improvements in case finding and treatment in the early 1990s [108, 109]. These figures do not permit relaxation in TB control but illustrate that, where adequate resources can be directed toward at-risk populations, major benefits can result, and downward trends ought to be maintainable.

New challenges continually arise in TB, but these become opportunities for the recognition and development of innovative TB control strategies. For these advances to translate into mainstream practice in a timely manner, national TB programs need to embrace new evidence, and clinicians in areas where TB is endemic require workable mechanisms to achieve continuing education alongside their heavy workloads. Such mechanisms include the more vigorous promotion of international standards at a national level and timely implementation by practitioners. The 2006 ISTC [14] has proven to have been useful in convincing national professional societies and academic institutions to support implementation of internationally recognized standards of TB care [8]. Such has been the rapidity of progress in the past 3 years that we suggest that the ISTC be updated to incorporate the elements summarized in Figure 1. In many parts of the world, such strategies may appear unrealistic. However, even in circumstances of poverty or instability, there can be scope for optimization of resource allocation and mobilization of political will to allow modern TB management to be adopted where it is needed most. Enthusiasm for adopting such changes can be generated by disseminating cost-effective TB success stories. Despite major new challenges, wider incorporation of recent advances, and further optimization of DOTs programs provide grounds for improved TB control.

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