INT J TUBERC LUNG DIS 7(5):410–414

CONSENSUS STATEMENT

A prioritised research agenda for DOTS-Plus for multidrug-resistant tuberculosis (MDR-TB)

Stop TB Working Group on DOTS-Plus for MDR-TB*

MULTIDRUG-RESISTANT tuberculosis (MDR-TB) is defined as a form of tuberculosis (TB) due to *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampicin, the two most powerful anti-TB drugs. This form of TB was documented in nearly every country surveyed by the World Health Organization (WHO)/International Union Against Tuberculosis and Lung Disease (IUATLD) Global Drug Resistance Surveillance Project during the period 1994–2000. Some settings, such as those in the former Soviet Union, show a high proportion of MDR-TB cases among new TB cases.[1,2] Other settings show a lower proportion, but have a considerable MDR-TB burden in terms of total number of patients due to the size of the population and the magnitude of TB as a whole.[3] The diversity in the epidemiology of MDR-TB poses a challenge for its management in various settings.

Drug resistance in bacteria is a natural phenomenon, but selective pressure induced by man-made mechanisms is the primary cause of MDR-TB. Drug resistance in TB (to isoniazid, para-aminosalicylic acid [PAS], streptomycin, and capreomycin) was documented shortly after the advent of these chemotherapeutic agents, and principles to manage such patients were proposed accordingly.[4–6] With the implementation of the internationally accepted DOTS† strategy for TB control and its essential component of standardised short-course chemotherapy (SCC), a comprehensive control strategy is available that, when followed properly, prevents the emergence of drug resistance. All currently recommended regimens are based upon the first-line drugs isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin.[7] Unfortunately, some of the same principles promoting resistance in patients in the 1950s remain intact and prevalent today, in combination with other new factors: lack of adherence to treatment, use of low quality drugs, improper diagnosis of TB patients, and lack of use of standard SCC.[8] Given that MDR-TB patients are resistant to at least the two anchor drugs of SCC, a supplement to the DOTS strategy is now needed for the management of these patients. This is further supported by evidence showing that SCC offers cure rates of on average 52% and 29% in new MDR-TB patients and re-treatment MDR-TB cases, respectively.[9]

To address MDR-TB in low- and middle-income settings, the WHO and its partners created 'DOTS-Plus for MDR-TB', a management strategy built upon the foundation and principles of DOTS. DOTS-Plus is under testing and development through pilot projects and operational research conducted by members of the international Stop-TB Working Group (WG) on DOTS-Plus for MDR-TB.[10] Although standard principles exist to manage MDR-TB,[11] and several pilot projects (via the access to treatment initiative known as the Green Light Committee) are underway,[12,13] much remains to be answered in the field of MDR-TB. To date, there is only little evidence from which policy can be established for low- and middle-income settings. Compounding this obstacle is the fact that management of MDR-TB appears to be setting-specific; thus, potentially, approaches are required that are tailored for each particular setting. Nonetheless, constructing a minimal package that could be adapted to specific countries wishing to implement DOTS-Plus is possible. Accordingly, the WG established a priority research agenda for DOTS-Plus in order to help derive final policy recommendations for the management of MDR-TB in low- and middle-income settings.

CONSENSUS PROCESS

Over 50 academic institutions, national governments, civil society agencies and United Nations institutions were involved in the consensus process. The initial discussions of research priorities emerged during the

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† DOTS consists of five elements: political commitment, case detection using sputum microscopy, standard short-course chemotherapy with first-line drugs under proper management conditions including directly observed treatment (DOT), regular drug supply, and a standardised recording and reporting system.

KEY WORDS: drug resistance; tuberculosis; research; DOTS-Plus

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meeting of the WG in Lima, Peru, 25–27 January 2001. More than 100 individuals, including National Tuberculosis Programme (NTP) managers, epidemiologists, microbiologists and clinicians, gathered to discuss several issues. One of the objectives of the meeting was to develop a research agenda for DOTS-Plus MDR-TB. Four priority areas were outlined by four experts in a plenary session: operational research, epidemiological/clinical research, diagnostics, and advocacy issues. The plenary session was followed by separate meetings of four sub-groups to outline five priority questions for each area. Participants were asked to choose the sub-group most suited to their area of work. Sub-groups were composed of 20–25 participants representing a variety of fields of expertise. Following the sub-group meetings, another plenary session took place to present and discuss each sub-group's findings.[14]

In addition to the four sub-groups, a special fifth sub-group also discussed separately the prospects for a double-blind randomised clinical trial on the management of MDR-TB. This sub-group first concluded that the feasibility of such a trial is extremely difficult, due to the ethical and methodological problems involved: 1) it is not ethical to assess the efficacy of a MDR-TB regimen in comparison with a control group that is not receiving treatment or is receiving a clearly suboptimal regimen; 2) comparing two regimens is a problem, as the results of drug susceptibility testing forbid the randomisation of subjects to regimens that could include drugs to which they are resistant; 3) the sample size required to generate sufficient power in the studies (to account for the overall low incidence of MDR-TB, and the variation in resistance patterns and disease progression among patients) would require a large multi-centre study to guarantee that the adequate sample size is achieved; and 4) although less of an issue, that economics of such a trial is also seen as an obstacle, as costs are estimated at at least US$7 million.

Alternative options are possible, however, such as case-control studies or conducting a programmatic trial using an individualised approach in one community versus a standardised approach based on surveillance information in another. Another possibility is to undertake a feasibility study to assess the practicability of organising the administration of a second-line drug regimen to chronic TB patients or confirmed MDR-TB patients. A third option is to randomise patients into two regimens with second-line drugs (replacing one or two drugs in one of the arms) in settings where drug susceptibility testing is limited to confirmation of MDR-TB and testing for second-line drugs is not available. These options would contribute significantly to the evidence-based need for developing policy.

Throughout 2001 and 2002, the WG refined and prioritised the research agenda through an interactive process that included e-mails, phone calls and smaller meetings (coordinated by the WHO-based secretariat of the WG). In 2002, at the WG's annual meeting in Tallinn, Estonia (10–12 April), a proposed priority research agenda was presented and discussed among more than 150 participants. At this point it was deemed important to further refine and prioritise the agenda by selecting and ranking the topics in most urgent need of an answer.[10] The finalisation process consisted of distributing a questionnaire to all WG members (including those unable to attend either the Lima or Tallinn meetings), requesting members to select and rank the research topics to create a prioritised research agenda for DOTS-Plus for MDR-TB.

PRIORITY RESEARCH AGENDA FOR DOTS-PLUS FOR MDR-TB

The priority research agenda for DOTS-Plus for MDR-TB is divided into four topics (ranked from highest to lowest priority by WG members). Primary topics are those critical research activities that will serve as a foundation for international policy and that *must be answered*. Secondary topics are key issues that will strengthen the evidence base from which policy is generated (Table).

Primary topics

Topic 1: Identify optimal standardised protocols to treat MDR-TB

This topic includes issues related to different chemotherapeutic approaches, management strategies for adverse events, and interventions promoting adherence to treatment. Regarding the multiple clinical treatment regimen options for MDR-TB patients, two research questions are of priority: the effectiveness in adults and children of standardised and individualised approaches to treatment, and the clinical efficacy of different standard and individual MDR-TB regimens across multiple settings and against various drug resistance patterns. For specific treatment regimens, the frequency of dosing in the intensive and continuation phases, including the efficacy of intermittent therapy, needs to be assessed. With respect to adverse events, it is important to determine the prevalence of adverse events in patients treated with second-line anti-tuberculosis drugs and the most cost-effective protocols for their management. In reference to adherence, a significant issue concerns factors promoting adherence in MDR-TB patients.

Table Priority research agenda for DOTS-Plus for MDR-TB

Primary topics
Identify optimal standardised protocols to treat MDR-TB
Identify optimal protocols for diagnostic testing
Identify the minimum requirements for constructing and implementing DOTS-Plus
Secondary topics
Identify threshold indicators for implementing DOTS-Plus
Other operational issues

Topic 2: Identify optimal protocols for diagnostic testing

The topic includes an assessment of the most effective use of current diagnostic tools and the utility of new diagnostic tools. Important issues to resolve include the ideal time points for identification of MDR-TB patients; the minimal and ideal times for smear-microscopy, culture, and drug susceptibility testing of MDR-TB patients; and an assessment of the programmatic utility of new rapid diagnostics tests for resistance to isoniazid and rifampicin, or rifampicin alone. Regarding drug susceptibility testing, the need to establish standards and parameters (such as criteria for critical proportions and critical concentrations) for testing second-line anti-tuberculosis drugs requires urgent attention. Although much emphasis is placed on utilising susceptibility testing results in the clinical management of MDR-TB patients, there is still debate about the in vivo application of in vitro results, especially in relation to low-dose isoniazid resistance and cross resistance among families of second-line drugs (i.e., fluoroquinolones and aminoglycosides).

Topic 3: Identify the minimum requirements for constructing and implementing DOTS-Plus

Setting-specific DOTS-Plus approaches, as dictated by the epidemiology of the disease and the social, political, and economic context of the setting, may be required. It is thus essential to determine the minimum requirements for DOTS-Plus in any given setting. Specifically, data from projects need to be evaluated to determine: 1) the minimal programmatic infrastructure for a standardised, individualised approach (at the local, district and national levels); 2) level of resources (human and financial); 3) infection control system; 4) laboratory capabilities (susceptibility testing for rifampicin alone, rifampicin plus isoniazid, all first-line drugs, all first- and second-line drugs; centralised or decentralised system); and 5) clinical expertise/training. This information will determine the minimum requirements for a MDR-TB management programme.

Secondary topics

Topic 4: Identify threshold indicators for implementing DOTS-Plus

Multiple priorities often exist for health care programmes, and economic constraints prevent countries from addressing all priorities. While mobilising additional resources for MDR-TB can be an effective solution, countries require information about when and how much to invest in DOTS-Plus to prevent the deterioration of basic TB services, to ensure the investment yields positive results (in terms of reduction of the burden of drug-resistant cases), and to prevent greater expenditure in health care costs in the future. Global indicators will probably not be sufficient to make such setting-specific decisions; mathematical models therefore need to be constructed for the range of settings/scenarios and incorporate parameters such as the dynamics and epidemiology of MDR-TB transmission (including fitness of drug-resistant strains), programme effectiveness, cost-benefit/cost-effectiveness, and amplification of drug-resistant strains, in order to accurately assess the impact of various strategies in a given setting.

Topic 5: Other operational issues

To ensure the success of DOTS-Plus, several important operational activities need to be undertaken and evaluated. Standard cohort definitions and a core data set, as proposed by members of the WG, need to be operationalised and tested in the field to determine their utility.[14] Standard materials for staff training should be developed. Determining how to increase the participation of the private sector in helping to reduce the number of MDR-TB cases is of concern. Risk factors in subgroups—household contacts of known MDR-TB patients or TB patients who die while on treatment, persistently smear-positive patients, specific occupations (miners, health care workers, etc.), patients with co-morbid conditions such as HIV, and patients with relevant social risk factors (such as the homeless and prisoners)—should be quantified in each setting.

Other research issues

The field of paediatric MDR-TB is relatively unexplored, and the clinical management of MDR-TB in children needs to be further assessed in terms of safety and efficacy (especially in relation to the use of second-line drugs such as fluoroquinolones). Basic science issues are beyond the scope of this document, but some of them are worthy of note. Genetic markers for drug resistance should be identified, and may hold important implications for the development of rapid diagnostic tests to detect drug resistance. The issue of fitness of MDR strains needs further study.

CONCLUSIONS

This prioritised research agenda is based on a wide variety of experiences and expertise, ranging from policy-setting institutions to institutions providing direct care to patients. The research agenda also combines the varied interests of many groups involved in MDR-TB issues, and represents a consensus opinion taking these interests into account. The next steps for the Working Group are to catalogue all research activities occurring in the field of MDR-TB, and to match these activities with the issues outlined in the research agenda for DOTS-Plus. Those items that are not currently being addressed in the global TB community will need to be focused upon by the WG, and research activities will need to be established accordingly. Ensuring that the research agenda is achieved is the responsibility of all parties involved in the

management of MDR-TB. If achieved, it will generate a solid evidence-base from which final global policy can be derived.

Acknowledgements

We would like to thank Cinzia Delaunay for assistance in preparing the Appendix, and Cora Dolores for helping with the organization of the meetings of the Working Group.

The financial support of the Bill and Melinda Gates Foundation and the United States Agency for International Development is gratefully acknowledged.

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APPENDIX

Participants in the meetings of the Working Group in Peru and Estonia, where the Research Agenda was discussed and developed (in alphabetical order by institution).

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