

## Scaling-up treatment for HIV/AIDS: lessons learned from multidrug-resistant tuberculosis

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**The UN has launched an initiative to place 3 million people in developing countries on antiretroviral AIDS treatment by end 2005 (the 3 by 5 target). Lessons for HIV/AIDS treatment scale-up emerge from recent experience with multidrug-resistant tuberculosis. Expansion of treatment for multidrug-resistant tuberculosis through the multipartner mechanism known as the Green Light Committee (GLC) has enabled gains in areas relevant to 3 by 5, including policy development, drug procurement, rational use of drugs, and the strengthening of health systems. The successes of the GLC and the obstacles it has encountered provide insights for building sustainable HIV/AIDS treatment programmes.**

Political momentum is building to scale up treatment programmes for HIV/AIDS in resource-limited settings. WHO has declared poor access to antiretroviral medicines for HIV/AIDS a global health emergency,<sup>1</sup> and has joined with partners to pursue the 3 by 5 target: provision of treatment to 3 million people in developing countries by the end of 2005.<sup>2</sup> To reach this target, supplies of safe, effective, affordable antiretrovirals need to be delivered to programmes in some of the poorest regions of the world, and the drugs must be used correctly by health-care workers and patients.

As solutions are sought to hasten the scale-up of HIV/AIDS treatment, valuable insights could be gained from experience with another complex infectious disease, multidrug-resistant tuberculosis. This disease, which has an 18–24 month treatment period, has many similarities with HIV/AIDS: multidrug treatment that can have serious adverse events; prevention and treatment are components of a comprehensive management strategy; and the threat of drug resistance at individual and population levels. Furthermore, the diseases share many management requirements that are especially difficult to meet in regions where resources are scarce: long-term follow-up and assessment of patients; adequate supply, availability, and affordability of drugs and diagnostic tools; intensive patient support to ensure adherence to treatment; the need for laboratory monitoring; and the absence of evaluated, evidence-based policy for management in resource-limited settings coupled with the humanitarian imperative to provide access to treatment.

In general, patients with multidrug-resistant tuberculosis in industrialised countries receive treatment with second-line drugs.<sup>3–8</sup> However, until recently such treatment was not widely implemented in developing countries for reasons including: high costs (up to US\$20 000 perperson for some treatment regimens); long duration of treatment; the possibility of serious adverse events; the potential for further development of drug resistance; the focus on prevention rather than treatment

of the disease; and the intensive laboratory monitoring purportedly required for successful treatment.<sup>9–11</sup>

### Meeting multiple challenges: the Green Light Committee

To increase access to effective treatment for multidrug-resistant tuberculosis the simultaneous challenges of supplying drugs and ensuring their rational use—ie, adherence to best practices—had to be resolved. Solutions to the supply issues through a multi-stakeholder initiative have been described elsewhere.<sup>12</sup> The need to treat patients immediately had to be balanced with ensuring supplies in the long-term by increasing the pool of quality-assured generic suppliers. To meet these two ends, interlinked strategies were applied—negotiations were consolidated under one demand source, negotiations were made directly with monopoly-producers to bring about price concessions, and advance capital and forecasts of demand were arranged to provide leverage for production increases. Furthermore, strategies were developed to increase the number of drug suppliers, and a system of tendering was devised to allow orders to be divided across several companies. These strategies ensured that existing suppliers remained in the market, while encouraging new manufacturers to participate. The outcome was a price drop for treatment regimens of second-line tuberculosis drugs of up to 95% and an increase in the number of suppliers of the drugs. Prices of individual second-line drugs fell by up to 99%, no drugs remained under monopoly production, and current manufacturers of the products were a mix of generic and research-based industries.<sup>12</sup> However, reduced prices were only available to the WHO designated procurement agent, who was not permitted to sell the concessionally-priced drugs outside of WHO endorsed projects.

Programme planners had to address the need for rational use of medicines. Because of the lack of scientific consensus on management of multidrug-resistant tuberculosis in resource-poor settings, several clinical, programme, and laboratory experts were asked to develop basic guidelines for the implementation of pilot projects.<sup>13</sup> Next, a structure was needed to decide which projects would have access to concessionally-priced drugs.<sup>14</sup> Unsuccessful applicants were offered technical assistance to bring them to the appropriate standards. However, a once-off review process could not guarantee that accepted projects would maintain high standards and continuous quality assurance of sponsored projects was needed.

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Finally, if projects were to help guide policy on multidrug-resistant tuberculosis, then the review, selection, and monitoring processes needed to be integrated into continuing policy development mechanisms. Essentially, the process would have to be comprehensive and provide a package of services ranging from drugs to technical assistance.

The international community formulated a partnership known as the Green Light Committee (GLC), designed to foster access to treatment for multidrug-resistant tuberculosis via an integration of the negotiated concessional prices and a system for ensuring proper use of second-line drugs. Details of this partnership have been described elsewhere.<sup>15</sup> The main appeal of the GLC is the link it makes between the supply of drugs and mechanisms to support their rational use. The GLC does not control global distribution and use of second-line drugs. Rather, those with the financial capacity to do so can approach companies directly and pay open-market prices.

### Difficulties

Thus far, the management programme for multidrug-resistant tuberculosis has yielded positive results such as improved treatment outcomes (thereby keeping resistance to a minimum),<sup>16–18</sup> an increased number of patients who have access to treatment,<sup>15,18</sup> gains in cost-effectiveness,<sup>18,19</sup> increased rational use of resources,<sup>20</sup> overall improvement in tuberculosis services,<sup>21,22</sup> increased savings to national tuberculosis programmes,<sup>12</sup> better prices and availability for second-line drugs.<sup>12</sup> However, some difficulties have arisen.

Initially, the GLC evaluation criteria were, perhaps, too stringent. Projects were engaged in a long review process that addressed issues that were not always essential to the start of the project. Initial disagreement between international partners about the value of the GLC created a further challenge.

In the area of drug procurement, GLC target prices were based on estimates for the cost of production, some of which may have been too low. Use of such low sums for the setting of generic prices might, in turn, have created price expectations that were difficult for generic manufacturers to meet. Publicity surrounding the drop in drug prices resulted in several programmes attempting to place orders directly with producers or the designated procurement agent, hence bypassing the GLC mechanism. However, the procurement agent declined such orders and redirected agents from these programmes to the GLC.

Although these issues have been resolved, meeting operational costs is a continuing challenge, since the GLC member institutions finance much of the work. Additional resources will be needed as demand increases, which will almost certainly arise through the arrangement with the Global Fund to Fight AIDS, Tuberculosis, and Malaria that obliges all projects seeking funding for management of multidrug-resistant tuberculosis to go through the GLC mechanism. The present information exchange process between projects and the GLC is time-consuming and hampered by a shortage of human and financial resources. Although agents from the GLC can gather data from projects to inform policy development, there is no mechanism whereby information can be rapidly and regularly shared with other projects. Scarce human resources also affect the scope and speed of technical assistance to countries. Although many potential collaborators are qualified to address some aspects of multidrug-resistant tuberculosis, few have a comprehen-

sive knowledge of multidrug-resistant tuberculosis at a programme level. Attempts are being made to increase the number of technical assistance providers by recruiting regional and local collaborators for missions, but limited financial resources have constrained this process.

Furthermore, although the topics needed to develop policy are outlined in an operational research agenda for multidrug-resistant tuberculosis,<sup>23</sup> this agenda was created after the GLC was established. Therefore, plans for prospective studies were not integrated in the first set of pilot projects, forcing reliance on retrospective analyses. The agenda itself, focusing on matters specific to multidrug-resistant tuberculosis, should be expanded to address health system and financing issues.

### HIV/AIDS: a new way forward?

With growing support for the 3 by 5 initiative and creation of schemes like the AIDS Medicines and Diagnostics Services (AMDS),<sup>2</sup> the issue is no longer whether antiretroviral treatment should be expanded in low-income countries in sub-Saharan Africa and elsewhere, but how this can be done most rapidly and effectively. There are many lessons to be learnt from programmes to manage multidrug-resistant tuberculosis, especially with respect to policy development, drug procurement, rational use, and health systems development.

### Policy development

Clearly, the international health community must swiftly define—and then continuously improve—standards for programmes to implement antiretroviral treatment in resource-limited settings. Such standards should draw heavily upon the expertise of those who are currently managing treatment programmes in low-income areas. The technical and operational guidelines so far developed and revised by WHO and partners in pursuing 3 by 5 mark a major advance.<sup>24,25</sup> However, these interim recommendations must be tested and refined.

For HIV/AIDS today, as previously for multidrug-resistant tuberculosis, the vicious cycle must be broken in which the lack of guidelines and standards prevents the launch of programmes, and the absence of evidence from programmes makes it impossible to establish guidelines and standards. This cycle is at last beginning to be broken by actually treating patients,<sup>26–29</sup> yet the critical components of operational research and information sharing are still missing. Thus, a priority research agenda for HIV/AIDS should be established to ensure accurate policy development for the future while still providing the best possible treatment options for current patients.

Some work has been done in this area<sup>25,30</sup> and may serve as a starting point for such an agenda, but international consensus must be reached. Additionally, because rapid scale-up of antiretroviral treatment allows an unprecedented opportunity to look at broader issues, topics such as the effect of resultant changes on the health system should be assessed. In conjunction, prospective operational research projects should be planned to assess the effectiveness of interventions, and how to improve treatment. A system to promote data collection, evaluation of data, and rapid and consistent dissemination of results would support the building of operational research systems within each project and link each project to the global policy development process. The information gathering process should be coordinated such that it captures information in several areas of management (including clinical, laboratory, operational, drug procurement and distribution, and health systems) in a single effort. As major issues are resolved, policy will

be revised accordingly. In the context of the HIV/AIDS global emergency, the traditional, and often lengthy, policy development process must be efficiently redesigned and accelerated through innovative approaches.

#### **Drug procurement**

HIV treatment programmes should be supported by reliable drug supply mechanisms that ensure high quality drugs can be obtained at low prices. Unlike the GLC model, pooled procurement for antiretrovirals need not be consolidated under a single entity because of the enormous differences in demand between multidrug-resistant tuberculosis and HIV. Procurement of drugs is more likely to be appropriate at a multicountry or single-country level, dependent on the respective demands.

Pooled procurement for antiretrovirals should incorporate a tiered tender process to encourage the participation of several suppliers. Local producers of generic drugs need to be involved as a long-term solution, whether via outsourcing, voluntary or compulsory licensing, technology transfer (as was done with multidrug-resistant tuberculosis),<sup>31</sup> or other options.<sup>32</sup> Such inclusion is especially important, since the market for antiretrovirals is much larger than that for second-line antituberculosis drugs, and multiple generic suppliers might emerge. A further lesson learned from the GLC suggests that adequate forecasts of product demand, paying producers in advance, and planning of procurement orders could lead to shorter delivery times, provide an incentive for new manufacturers to enter the market, and encourage the development of new products. However, advance financing should be used as an initial approach to stimulate the market, rather than as a permanent practice. Such advance capital could be raised through a revolving fund like that used by the Pan American Health Organization<sup>33</sup> or through the Global Fund to Fight AIDS, Tuberculosis, and Malaria.

The problem of quality assurance will pose major challenges, as demand for antiretrovirals rises and the number of potential suppliers increases. The current prequalification scheme established by WHO and its international partners for antiretrovirals, antituberculosis drugs, and antimalarials has been important in identifying some quality-assured producers.<sup>34</sup> However, our experience suggests that quality assurance should be a continuous process to guarantee reliable products in the long term, especially with the emergence of new suppliers in a quite new market. Technical assistance and incentives for local producers to rise to global standards must be provided, and the capacity of within-country regulatory agencies to ensure product quality should be strengthened. Care is also needed to ensure that regulatory standards themselves are not biased in favour of a particular group of producers. If the current global prequalification system is used, substantial resources must be invested to address these concerns.

#### **Rational use**

Ideally, the various drug procurement mechanisms for antiretrovirals should do more than guarantee low prices, high product quality, and a wide supplier base. Such mechanisms should also be linked to groups that give technical assistance to strengthen programme performance, improve treatment outcomes, and prevent the onset and spread of drug resistance. The GLC's key operating principle is that WHO and its technical partners form a cohesive group to systematically link the supply of drugs to rational use components. This highly integrated approach enables the GLC to offer a package of services

that appeals to workers within programmes and to policymakers.

A similar packaging of services would seem highly desirable in the case of HIV/AIDS treatment. Experience with the GLC for multidrug-resistant tuberculosis suggests inclusion, at a minimum, of two key services:

*Intensive technical assistance*—almost every project area receives direct visits by GLC members. The GLC works directly with the local authorities implementing the programme and offers onsite technical assistance. Once a project is approved, yearly monitoring missions provide an opportunity to plan additional technical assistance. Such visits are not punitive, but rather enable dialogue on management practices and programme needs (including capacity strengthening). A similar strategy, also focused on the “mutually reinforcing components” of prevention and treatment,<sup>35</sup> could help in the rapid implementation and expansion of HIV treatment programmes, but would have to be scaled-up greatly to respond efficiently and effectively.

*Data collection and information exchange*—as part of its monitoring process, the GLC collects data and uses this information to assist in the process of policy development for multidrug-resistant tuberculosis. Data collection and information exchange should be continuous, so that policy is regularly revised to pursue best practice.

#### **Strengthening health systems**

In many countries, the effect of HIV/AIDS is distorting health systems. The global 3 by 5 effort has the potential to reduce these pressures and to strengthen health systems in countries severely affected by the disease. To positively affect health systems, HIV/AIDS treatment scale-up must incorporate a strategy for the management of chronic disease. 3 by 5 must catalyse improvements in the wider health systems to sustain the life-long treatment needed by people on antiretrovirals.

The lessons from multidrug-resistant tuberculosis programmes for this key aspect of HIV/AIDS treatment expansion are only beginning to emerge, as the GLC's effect on overall health systems has yet to be thoroughly assessed. One potentially important finding thus far, however, is that GLC technical assistance not only improves multidrug-resistant tuberculosis programmes, but also strengthens other aspects of tuberculosis control. The GLC mechanism has helped to improve laboratory services and the general diagnosis of patients with tuberculosis in some settings. It has also prompted expansion of basic tuberculosis services, and helped prevent the threatened dismantling of national tuberculosis programmes in at least two countries.<sup>21,22</sup>

As with the GLC, the roster of personnel trained to provide technical assistance for HIV programmes needs to be rapidly expanded (drawing on as many local and regional collaborators as possible) through, for example, onsite joint missions with experts as part of a “learning by doing” approach. The number of trained staff providing health care services will be a difficult issue to address for HIV—more so than for tuberculosis, since workers in multidrug-resistant tuberculosis often are already part of national tuberculosis programmes. However community members or other auxiliaries can be trained to deliver some basic health services.<sup>36</sup>

Learning from the GLC model, WHO and international 3 by 5 partners must respond swiftly to countries' requests for technical cooperation. Furthermore, a broad definition of cooperation is needed to allow

support beyond the HIV/AIDS programmes to include assistance in addressing resultant challenges to health systems. Technical assistance through 3 by 5 could enable countries to achieve progress in areas that might have long-term implications for health systems. Such areas include drug procurement; the building of laboratory capacity; the expansion of the health workforce through accelerated recruitment and emergency training; and a range of functions associated with the management of chronic illnesses.

International donors' current willingness to support the scaling up of HIV/AIDS treatment programmes will mean substantial resources will be made available to some of the world's poorest health systems. The financing of multidrug-resistant tuberculosis treatment varies between countries, with some programmes heavily funded by the international community and others completely funded through the domestic system (although all programmes require full collaboration with, and commitment from, national governments to ensure sustainability). For multidrug-resistant tuberculosis, increased financial resources at the international level in the short term will help to reduce the multidrug-resistant tuberculosis burden in many countries. In fact, treatment will render patients uninfected, ultimately reducing incidence and prevalence of the disease. Better prevention methods (ie, improved management of drug-susceptible tuberculosis cases) will further reduce the incidence of multidrug-resistant tuberculosis. The end result of short-term investment from international sources would be a reduced financial burden for countries, such that programmes in the future could rely mainly on domestic finance.

By contrast, HIV/AIDS treatment will need longer-term international financial commitments. Early findings from the GLC offer a model for international health partners as they work to establish technical cooperation mechanisms to help countries achieve the maximum benefit from new investment in the health sector.

## Conclusions

The success of the GLC in expanding access to treatment for multidrug-resistant tuberculosis provides lessons for scaling-up HIV/AIDS treatment programmes. Several traditional indicators (such as treatment outcomes and cost-effectiveness) are being used to measure the GLC's success at global and local levels, and are helping to validate its usefulness in management programmes for other diseases. However, one major marker of progress cannot be captured in the data assessment process—the fundamental shift in the multidrug-resistant tuberculosis policy debate from “treatment *vs* no treatment” to “how to best increase access to effective treatment for all.”

In view of the differences between HIV/AIDS and multidrug-resistant tuberculosis, modifications of the GLC approach will be needed. Most fundamentally, the GLC operates as sole coordinating entity for the global multidrug-resistant tuberculosis issue, while HIV/AIDS will require a less centralised approach to account for the many actors involved in financing, technical assistance, and drug procurement. As the international community moves rapidly to bridge the HIV/AIDS treatment gap by strengthening health systems,<sup>37</sup> strategies developed for multidrug-resistant tuberculosis could help ensure that affordable, high quality antiretrovirals reach programmes and are used appropriately. In turn, these measures will help patients obtain the full lifesaving benefits of the drugs while preventing the spread of drug resistance.

## Contributors

R Gupta wrote the initial draft of the text. J Y Kim provided conceptual guidance for the initial draft of the text. All authors contributed on subsequent drafts.

## Conflict of interest statement

None declared.

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## Uses of error

### Clinical, teaching, and research misunderstandings

John P A Ioannidis

An HIV-infected patient was brought to the emergency room because for the past 2 h he had been catatonic and every 5 s repeated “I want to go to the bathroom. I want to go to the bathroom” like a stuck compact disc player. I spent 3 min with him, asked for a CT scan, and ran to the next case. The nurse who was watching over the patient soon called: he was agitated and needed sedation. I rebuffed her and asked her to get the scan. 10 min later I was called urgently from the radiology department. I rushed there to find two technicians, the nurse, and the patient engaged in martial arts. I joined the fight, got kicked, and in desperation placed all my weight on the patient by sitting on his legs. We administered a sedative cocktail only a minute before the patient pulled out his intravenous line with blood spilling all over. The bathroom request continued all along. Several minutes later, as I was still sitting on his legs, the patient paused for a while, and then changed his tune to “there is something on my legs. There is something on my legs”. As a clinician, I have since learned to listen to people who have spent more time with a patient than I have.

After having taught a 6 h evidence-based medicine course, I was confident that my medical students understood everything about advanced-level clinical epidemiology. Then, one of the best students knocked at my door: “Sorry, what exactly do you mean by the phrase

randomised controlled trial that you so often mention in class?” I was struck by lightning and realised that people are not born with understanding of fancy terms such as randomised controlled trials (RCT), numbers needed to treat, and random effects implanted in their brains. In a world of triumphant expert professorial opinion, one must go slowly, give many examples, and verify that the message gets through. Have I since been successful? Students on one of my most recent courses were asked to write the title of an RCT they had heard of. Answers I got included several blanks, “That famous study by our Professor”, “Smoking causes rheumatoid arthritis”, and “Indian neurology”. As a teacher, I have learned not to overestimate my ability to convey even the most basic messages.

Two colleagues and myself had just completed a research project. Just before submission, the lead author proposed two honorary authors. I was furious. He insisted. So I removed my name. Much later, I saw the publication. Of nine authors with prestigious affiliations, the previous lead author was fifth, and the other real author was sixth. Interestingly the previously proposed honorary authors were missing. I wondered whether the manuscript had changed occupants like an apartment for rent. I was happy my name was not on the article, but regretted having unwittingly helped as a ghost author. As a researcher, I learned to clarify upfront who the authors are in a study.

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