

Drug-resistant TB and HIV in resource-limited settings: what TB/HIV programmes can learn from each other

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Summary

Although management of drug resistance in tuberculosis (TB) and HIV in poor settings is in its infancy, lessons learned from TB may be relevant to HIV and vice versa. The experience with HIV has shown that rapid scale-up and lower drug pricing are achievable goals. The current prerequisites for obtaining drugs to treat multidrug-resistant TB (MDR-TB) may be too stringent given the immediacy of the MDR-TB problem. We call for a more rapid roll-out of treatment for MDR-TB with fewer administrative encumbrances and a greater sense of urgency in national TB control programmes. On the other hand, antiretroviral roll-out programmes should learn from the genesis of the MDR-TB problem; laboratory monitoring should be enhanced and compliance optimized to avoid the acquisition of additional drug resistance in HIV.

keywords multidrug-resistant tuberculosis, extensive-resistant tuberculosis, multidrug-resistant HIV infection, resource-limited settings

Multidrug-resistant tuberculosis (MDR-TB) (WHO 2008a) and MDR HIV infection (Monno *et al.* 2007) are growing threats to the global control of TB and HIV. In industrialized countries, treatment options exist for both, but in countries with limited resources, this is not the case. In fact, the clinical and public health benefits proffered by the introduction and increasing availability of antiretroviral therapy (ART) in poor settings could easily be offset by the emergence of drug resistance (Baggaley *et al.* 2006). Although management of drug resistance in poor settings is in its infancy, lessons learnt from TB may be relevant to HIV and vice versa.

Drug-resistant TB

By definition, MDR-TB is caused by a *Mycobacterium tuberculosis* isolate resistant to two first-line drugs, isoniazid (INH) and rifampicin (RIF). According to WHO (2008a,b), each year about 490 000 cases of MDR-TB emerge and more than 110 000 people die of it, mostly as a result of poor TB management. MDR-TB is spread by the respiratory route and poses tremendous risk to contacts in the household, the clinic and community settings. MDR-TB also has a profoundly negative impact on the survival of HIV-TB coinfecting patients (Sungkanuparph *et al.* 2007);

early detection and appropriate treatment of both drug-resistant TB and HIV infection significantly improve the outcome. It is disturbing, therefore, that both the number of MDR-TB cases treated and the projected numbers for MDR-TB cases to be treated in 2008, as reported by national TB programmes, are far below targets set out by the global extensively DR (XDR-TB) response plan (WHO 2008a).

There are several reasons for this. Developing countries lack the laboratory facilities for the diagnosis of MDR-TB and the clinical expertise and chemotherapeutic agents for its management. Although effective second-line drugs are available, they are expensive and treatment takes 18–24 months (Nathanson *et al.* 2006). Although the potency of second-line TB drugs is suboptimal and the therapeutic index (ratio of medium lethal dose to the medium effective dose) low, when these obstacles are overcome, drugs for MDR-TB are effective. For example, in a study of 1047 MDR-TB patients from Estonia, Latvia, Peru, the Philippines and the Russian Federation, treatment was successful in 70% of cases (Nathanson *et al.* 2006). Based on reports from national programmes, the treatment success rate for patients in projects supported by the Green Light Committee (GLC) for Access to Second-line Anti-TB Drugs of the World Health Organization was on average 57%

compared with 50% outside of GLC projects (WHO 2007a).

Developing countries should now have opportunities to treat MDR-TB through the resources of The Global Fund to Fight AIDS, TB and Malaria (Kazatchkine 2007), and President Bush's President's Emergency Plan for AIDS Relief (Kamwi *et al.* 2006). Further, the GLC provides access to second-line drugs at a fraction of their cost in industrialized countries (Gupta *et al.* 2002).

However, the roll-out of drugs for MDR-TB has been very slow. There are many reasons for this: the requirement that there be appropriate laboratory services for the diagnosis of MDR-TB; the historical dictum that approval by the GLC requires a national prevalence survey and properly functioning programme for directly observed therapy; and the fact that not enough countries apply for GLC funding. Currently Burkina Faso, the Democratic Republic of the Congo, Guinea, Kenya, Rwanda, Lesotho, Malawi and Uganda have approved GLC projects (WHO 2008a,b). Mozambique has submitted an application which is under review. Benin, Ethiopia, Mali, Namibia, Tanzania and Zambia have Global Fund-approved grants for the management of MDR-TB and plan to apply to the GLC in 2008 (WHO 2008b,c). From September 2007, national TB control programmes worldwide were enabled to provide high-quality drugs and cost-effective treatment to almost 30 000 patients (WHO 2008b,c). Access to second-line drugs is not restricted or controlled by any institution, but access to quality-assured, affordable, second-line anti-TB drugs through the Global Drug Facility is provided only to programmes approved by the GLC (WHO 2008a,b).

In 2006, XDR-TB (defined as resistance to RIF and INH, any fluoroquinolone and one or more of the injectable drugs kanamycin, amikacin, capreomycin) was reported in all regions of the world and was rapidly classified by WHO as a serious emerging threat to global public health, especially in countries with a high prevalence of infection with HIV (Mukherjee *et al.* 2004; Goldman *et al.* 2007; Matteelli *et al.* 2007). XDR-TB appears to develop step-wise from a series of failures to ensure compliance with treatment regimens and completion of TB treatment. XDR-TB may be incurable with currently available drugs (Padayatchi & Friedland 2007). Prevention of the development of XDR-TB, therefore, has become an important consideration in bolstering programmes for management of MDR-TB.

There has been a recent shift in the international attitude towards dealing with the MDR-TB burden. The goal now is to provide universal access to diagnosis and treatment of MDR-TB by the year 2015 (similar to the goal of universal access to ART) (WHO 2008a). The revised

Stop TB plan targets treatment of 1.6 million MDR-TB and XDR-TB patients by 2015, instead of 800 000 MDR-TB patients as stated in the original Global Plan. Whether the financial resources will be available to implement such a plan is less certain.

Drug-resistant HIV

Unlike the situation for MDR-TB, there is no international definition of MDR-HIV, although its existence is obvious. Industrialized countries dispose of a large variety of very effective antiretroviral drugs that can be substituted once a virus becomes resistant to one or more drugs of a regimen. The number of people infected with a resistant HIV infection is not known. In 2006, WHO estimated that about 1.3 million people with HIV infection in sub-Saharan Africa (coverage 24–34%) were on antiretroviral treatment (WHO 2007b). In a survey performed by WHO in 2006 in 23 developing countries, it was found that 4% of adults on antiretroviral treatment (or approximately 52 000) and 1% of the children were on a second-line regimen (Renaud-Théry *et al.* 2007). The percentage of patients living with a resistant virus is certainly higher than suggested by these estimates. Indeed, because of the lack of laboratory capacity to diagnose virological treatment failure, patients are switched to a second-line regimen only when immunological and/or clinical treatment failure is obvious (Vekemans *et al.* 2007).

In contrast to the situation with TB, there has been rapid scale-up of ART, including treatment with second-line ART in the same countries (Gilks *et al.* 2006; WHO/UNAIDS 2006). Access also has been expanded by the low cost of drugs available directly from the manufacturers as negotiated by international organizations such as the Clinton Foundation (2008). There is no requirement for approval by the equivalent of a GLC to gain access to these less-expensive ART regimens. The management of HIV treatment failure and presumed HIV drug resistance remains particularly challenging in resource-limited settings due to the general unavailability of viral load and resistance testing and the limited supply of second-line antiretroviral drugs. The decision to switch to second-line drugs is almost invariably made on clinical grounds rather than laboratory testing (Gilks *et al.* 2006). Moreover, in resource-limited settings, what the optimal empiric second-line ART regimens for first-line treatment failures should be remain unclear (Toni *et al.* 2007). Nonetheless, in a cohort study in Uganda, 30 of 40 patients (75%) on a second-line protease-containing regimen achieved viral suppression (<400 copies/ml) (B. Castelnova, personal communication). ART programmes pay relatively little attention to

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the issue of adherence to drug therapy although it is an active area for clinical investigation.

What can TB programmes learn from HIV?

Initial or acquired resistance is considered as a key indicator for programme performance. Resistance is a human-made problem, resulting from inadequate treatment regimens or poor compliance (WHO 2008b). Case-holding, or retention as it is commonly called in ARV programmes, is therefore of utmost importance to prevent the emergence of MDR-TB.

Rapid scale-up of MDR-TB treatment programmes and lower drug pricing are achievable goals. MDR-TB is spread by respiratory contact and poses a major public health risk. In view of this, it takes too long for effective drugs to become available to the patients who need them. While access to quality line drugs at preferential prices is available from the GLC to programmes that adhere to international recommendations, this requirement for GLC approval adds complexity and delay and the current prerequisites may be too stringent given the immediacy of the problem. Investment is needed to ensure well-functioning drug susceptibility testing laboratories, appropriate infection control measures and direct observed treatment short course for patients receiving treatment with second-line drugs. These measures are necessary to ensure that treatment of MDR-TB does not lead to the development of XDR disease, and they must become an urgent priority in national TB control programmes.

Expedited efforts to develop new drugs are required to combat the problem of XDR-TB. Testing new TB drugs in patients with drug-resistant TB makes it easier to determine their efficacy. Such a strategy was successfully used to bring new ARTs to market (Mitnick *et al.* 2007).

Certainly, rolling out MDR-TB treatment without the required infrastructure would be injudicious at this point. The experience of the South Africa XDR-TB epidemic has shown that underperforming MDR-TB programmes may create a catastrophic situation with enormous public health consequences, given the airborne transmission mechanism of TB. Therefore, TB support structures must urgently be strengthened in parallel with expanding access to MDR treatment.

What can HIV programmes learn from TB?

Empirical use of second-line drugs without laboratory confirmation of drug resistance and their general availability without safeguards to ensure compliance may create future problems with XDR strains. One would guess that stepwise acquisition of drug resistance will be more of a

problem in HIV than TB given the higher mutational frequency and rates of replication of HIV compared with *M. tuberculosis*. In view of the disappointing results of AIDS vaccine trials, we appear to be in 'for the long haul' in HIV treatment. It would be tragic if drug resistance got ahead of drug research and HIV strains became as untreatable as they were at the start of the epidemic. Not applying the above measures to prevent emergence of XDR-TB in HIV treatment is counterintuitive.

We call for more rapid roll-out of treatment for MDR-TB with fewer administrative encumbrances and a greater sense of urgency by national TB control programmes; and we call for greater attention to laboratory monitoring, enhancing compliance and acquisition of additional drug resistance in HIV infection.

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