Deaths from tuberculosis in African countries with a high prevalence of HIV-1

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Leaders of the world's most powerful countries recently agreed at the G8 Summit (July 22-23, 2000) to tackle the "three priority diseases of poverty"—namely HIV infection, tuberculosis, and malaria. They committed themselves to working in strengthened partnership with governments, the WHO, and other international organisations, industry, academic institutions, non-governmental organisations (NGOs), and relevant groups to deliver three critical United Nation targets: by 2010, to reduce the number of young people infected with HIV and AIDS by 25%, to reduce death from tuberculosis and prevalence of disease by 50%, and to reduce the burden of disease associated with malaria by 50%. We would like to focus on the target to reduce tuberculosis deaths by 50%. More than 95% of tuberculosis cases and deaths occur in resource-poor countries of the less-developed world,[1] so is this target realistic? Even if there is much concerted action and hard work on the ground, it may not be possible to achieve this target unless the two major issues of stopping the AIDS epidemic and reducing poverty are addressed. Nevertheless, targets enable organisations and institutions to concentrate on a problem and work towards a common goal. Having a target for reducing deaths could help tuberculosis control programmes and health services to focus on the needs of patients by improving the quality of care offered.

Tuberculosis deaths

Through the efforts of WHO and partners, more than 60% of the African population now has access to a directly observed therapy (DOTS) tuberculosis programme.[2] Tuberculosis programmes aim to prevent infection with *Mycobacterium tuberculosis* and reduce the burden of disease in the community by providing high quality care to individual patients who are the major source of transmission of the infectious agent. To achieve this aim, they should take responsibility for the outcome of such patients from the time of registration until treatment has been completed. If death occurs for any reason during the course of treatment, this would be regarded as a tuberculosis death. In countries with a high HIV-burden, many tuberculosis deaths will be a result of HIV infection, but recording these deaths as actual tuberculosis serves two purposes. It recognises the enormous difficulties experienced by resource-poor countries in establishing precise causes of death, and it may persuade responsible tuberculosis programmes to broaden their remit and to consider the implications of HIV infection.

In Malawi, more than 70% of patients with tuberculosis are HIV-positive.[3] The National Tuberculosis Control Programme (NTP) has recorded rising death rates in TB patients during the last 15 years. This rise is leading to loss of credibility among health-care staff, patients, and the wider community. Reducing deaths from tuberculosis will require a strengthening of tuberculosis control efforts and research focused on improving the care of HIV-positive tuberculosis patients.

Why do HIV-positive patients with TB die in Malawi?

HIV-positive patients have much higher death rates during the time they are being treated for tuberculosis than patients without HIV.[3] In sub-Saharan Africa, about 30% of HIV-positive patients die within 12 months of treatment. HIV-positive patients with smear-negative pulmonary tuberculosis (possibly because of more severe immunosuppression and diagnostic difficulties) fare even worse.[4] What are the reasons for these high death rates? There are the wide social, cultural, and economic issues of poverty, sex, illiteracy, and stigma that affect factors such as access to care, diagnosis and delivery of care, all of which have an important bearing on illness and death.

In many countries such as Malawi, the time between onset of symptoms and diagnosis of smear-positive pulmonary tuberculosis is about 3-4 months.[5-7] Even longer delays may be found in patients diagnosed with smear-negative pulmonary tuberculosis,[8] probably because of the need for access to radiographic facilities. Delay in the diagnosis and treatment of tuberculosis compromises the chances of a cure in HIV-positive patients by allowing the tuberculosis to advance unchecked and by accelerating the decline in immunocompetence.[9,10] The diagnosis of smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis in resource-poor countries is fraught with difficulty because of a shortage of trained health personnel, poor diagnostic facilities, and lack of appropriate and specific diagnostic guidelines. It is not uncommon to find patients, registered and being treated for tuberculosis, who have another disease other than tuberculosis.

The numbers of patients acquiring tuberculosis has increased by 300%-400% in high HIV-prevalent countries in the past decade.[3] Large numbers of patients with tuberculosis without a commensurate increase in resources reduce the quality of patient care. In some African tuberculosis programmes, patients are still admitted to hospital for 1-3 months to receive the initial phase oftreatment either because there are difficulties in administering directly observed treatment in the community or because patients are too ill for treatment at home. Overcrowded wards make good nursing and medical care difficult, and there is a substantial risk of other nosocomial infections being transmitted. Health-care staff are affected by the same HIV epidemic as the general adult population. The resulting high absentee rates due to illness or attending funerals, and high death rates due to AIDS, threaten the provision and quality of health-service delivery.

HIV-positive patients treated with standard regimens consisting of streptomycin, isoniazid, and thiacetazone have higher death rates compared with those given rifampicin-containing regimens.[11-13] Rifampicin-containing regimens might offer survival advantages because of the broad-spectrum antibacterial activity of rifampicin in preventing other bacterial infections. WHO recommends that patients with smear-negative pulmonary tuberculosis should receive a rifampicin-based initial phase followed by either rifampicin-isoniazid combinations or isoniazid-ethambutol combinations for the continuation phase.[14] The NTP in Malawi uses the isoniazid-ethambutol option. The effectiveness of this regimen in HIV-infected patients with tuberculosis is unknown.

HIV-positive patients with tuberculosis may run a stormy course while on anti-tuberculosis treatment, with fevers, chest infections, and recurrent diarrhoea, which may be associated with bacteraemia, cryptococcosis, and Kaposi's sarcoma. Each

of these complications could cause death if left undiagnosed and untreated. Adverse reactions to anti-tuberculosis drugs are more frequent, leading to interruptions of treatment and occasional deaths.[3] This is particularly true for thiacetazone, and, for this reason, thiacetazone is not advised for individuals who are HIV-positive.

The response to the threat posed by HIV

Some countries have mounted information, education, and communication campaigns for the general public and front-line health workers about the need for early submission of sputum samples for patients with a chronic cough. However, there is little evidence that this has had any effect in reducing diagnostic delays.[7] Algorithms are in place for the diagnosis of smear-positive pulmonary tuberculosis that incorporate chest symptoms, lack of response to antibiotics, negative sputum smears, and chest radiography.[15] Moves are afoot to decentralise the initial phase of treatment to peripheral health centres and the community with the use of family-based members, community-care groups, or shopkeepers to administer directly observed therapy.[16] Many patients have difficulties attending health centres for directly observed therapy (DOTS) on a daily basis. Therefore some programmes using rifampicin-containing regimens have moved from daily treatment in the initial phase to intermittent treatment, either three times or twice a week. DOT programmes record and report on treatment outcome of smear-positive pulmonary tuberculosis patients. Several programmes have now recognised the growing burden of smear-negative tuberculosis, and routinely monitor and report their treatment outcomes.

Little so far has been done to combat the high death rates associated with HIV. Highly-active antiretroviral treatment (HAART) has dramatically reduced death rates in HIV-infected patients in the more-developed world. Such therapy is not available to most HIV-infected patients in Malawi because of the enormous expense, the complicated drug regimens, and the difficulties of monitoring treatment. Other interventions have been assessed. A co-trimoxazole placebo controlled trial in Côte d'Ivoire in HIV-positive smear-positive pulmonary tuberculosis patients[17] showed a 48% reduction in deaths in the co-trimoxazole group.

Research needed to combat the high death rates

Further work is needed to enable a coordinated, multidisciplinary approach to reduce mortality. We suggest that the following objectives should be the focus of a research effort aimed at quickly enabling tuberculosis control programmes to reduce death rates in HIV-positive patients with tuberculosis in sub-Saharan Africa (panel).

Research objectives

To reduce delay in diagnosis of tuberculosis

To improve diagnosis of smear-negative pulmonary tuberculosis and extra-pulmonary tuberculosis

To provide adequate amounts of rifampicin in anti-tuberculosis treatment regimens

To improve the treatment of smear-negative pulmonary tuberculosis

To assess the role of adjunctive treatments such as corticosteroids, empirical antibiotic treatment, and antiretroviral therapy to reduce early death

To assess the role of adjunctive treatments such as antibiotic prophylaxis, multivitamins and micronutrients, and antiretroviral therapy to reduce overall deaths

To improve quality of care

To protect health-care workers from nosocomial tuberculosis

Diagnosis

Delays are often multifactorial. Delays may occur because of patient perceptions of the disease, fear of stigma, and difficult access to health facilities. They may also occur as a result of poor health-service performance in managing patients suspected of having tuberculosis. The first step needed in this line of research is to determine the association between delay and HIV infection, and the possible role played by diagnostic delay in leading to death. Second, a careful examination of the determinants of delay in diagnosis is needed at many areas of the health service and in many different locations. Research is needed to see whether delays to seeking care are longer between different social groups and are determined by factors such as poverty poverty and sex. New approaches are needed to reduce these delays through promotion of behavioural change and through innovative partnerships with community-based care providers. Priority should be given to groups with the longest delays and greatest difficulties in accessing care. Research is the key to reducing the system-related barriers to care access through an analysis of the operation of tuberculosis diagnosis and the promotion of a responsive quality assurance system. In areas where delay seems to be especially important, targets could be set by tuberculosis control programmes - for example, 75% of patients with tuberculosis should be diagnosed and offered treatment within 2 months of their symptoms starting and achievements could be monitored through the routine registration system and linked to a quality assurance system.

Although algorithms are in place for diagnoses, these may not be adhered to in routine practice.[18] Routine radiographic services may not function because of staff shortages, equipment malfunction, and poor supply of materials. Simpler and more practical ways to make the diagnosis of smear-negative tuberculosis need to be explored in the short-term. However, the cumbersome process of sputum-smear microscopy coupled with the difficulties of interpreting atypical chest radiographs in HIV-positive patients lends an urgent need to develop new diagnostic products. These products, to be useful in resource-poor countries, need to be reliable, easy to use, quick, cheap and safe.[19]

Tuberculosis treatment

There is some evidence that HIV-positive patients may malabsorb anti-tuberculosis drugs, particularly rifampicin.[20] Rifampicin is given at a dose of 10 mg/kg irrespective of whether it is administered daily, three times a week, or twice a week.[21] If rifampicin is malabsorbed, drug concentrations in tissues and blood may be considerably reduced if given to HIV-positive patients on an intermittent basis. Furthermore, in Malawi, the drug is not given strictly on an mg/kg weight basis but rather according to weight bands.[21] Careful clinical studies need to be done in HIV-positive patients to find out whether anti-tuberculosis treatment regimens, given on an intermittent basis, are as effective as regimens given on a daily basis. This should be coupled with research on rifampicin pharmacokinetics to determine in HIV-positive patients whether rifampicin concentrations are adequate with intermittent treatment and whether rifampicin concentrations are adequate within the spectrum of different weight bands. One of the reasons for the higher death rate in HIV-positive patients with smear-negative pulmonary tuberculosis may be the weaker regimen (often standard treatment) given to such patients.[11-13]

We need to establish whether the optimum treatment regimen for smear-negative patients is a 6-month regimen with rifampicin throughout, or an 8-month regimen with rifampicin only in the initial phase.

Adjunctive treatment

Adjunctive treatments may be needed to reduce early deaths. In Malawi, there is evidence that up to 40% of deaths from tuberculosis occur in the first month of treatment. There are several reasons for these early deaths: for example, late presentation of patients with severe and extensive tuberculosis; lifethreatening HIV-related complications such as severe anaemia and bacteraemia; and the occurrence of a Herxheimer-type reaction due to the rapid killing of tubercle bacilli by antituberculosis drugs.[22] The identification of bacteraemia is difficult, and ill patients might require an empirical course of antibiotics to treat commonly occurring infections due to *Streptococcus pneumoniae* and non-typhoidal Salmonella. In the case of a Herxheimer-type reaction, corticosteroids are one way to reduce these early deaths by reducing this toxic reaction.[22] Prospective controlled trials in the pre-HIV era showed a treatment benefit of corticosteroids in tuberculous meningitis, pericardial and pleural disease.[23] The only published controlled trial in HIV-positive patients confirmed the benefit of corticosteroids in decreasing mortality in tuberculosis pericardial effusion.[24]

There is also a high overall death rate during the whole course of treatment in HIV-positive patients. Although co-trimoxazole was shown in Côte d'Ivoire to significantly reduce the death rate,[17] it is not known whether this effect will be replicated in Malawi because of different prevalence of opportunistic infections and different patterns of resistance to co-trimoxazole by commonly occurring pathogens. Despite provisional recommendations by UNAIDS [25] that co-trimoxazole should be given to all people in Africa living with AIDS (by definition this includes HIV-positive patients with tuberculosis), it would be prudent to gather more evidence about the effectiveness, feasibility, optimum timing, and cost-effectiveness of this intervention. Even if co-trimoxazole is effective and feasible to use, its widespread use by AIDS patients might have serious adverse consequences, if accompanied by increased drug resistance developing in common bacteria and malaria. Other antibiotics, such as oral quinolones, which have good antibacterial effects against non-typhoidal *Salmonella* spp, should also be assessed. Non-antibiotic interventions such as multivitamins and trace elements may improve cell-mediated immunity in HIV-positive patients,[26,27] and efficacy should be determined in placebo-controlled trials.

Antiretroviral therapy is the adjunctive treatment most likely to have a major effect in reducing deaths from tuberculosis in HIV-positive individuals. After the 13th World AIDS Conference in July, 2000, there has been a concerted push by industrialised countries to improve access to antiretroviral drugs for less-developed countries. Despite this push, it will be logistically very difficult to introduce antiretroviral drugs in resource-poor settings with weak health infrastructures. However, well functioning control programmes have an established infrastructure with the ability to monitor treatment and check on compliance, and they could provide a good entry point for the provision on a wider basis of antiretroviral drugs in this setting. The use of HAART in HIV-positive patients with tuberculosis is problematic because of major interactions between rifampicin and protease inhibitors.[28] However, dual or triple nucleoside analogues or dual nucleoside analogues with a non-nucleoside inhibitor are therapeutic possibilities[28] that will need to be tested first in controlled clinical trials (to determine tolerability and safety) and then in district operational studies (to establish feasibility, equity issues, and drug security). There is also the need for modelling and cost-exercises to look at long-term cost benefit.

Regular clinical care and treatment for HIV-related complications in patients on antituberculosis treatment may be far from adequate in resource-constrained health facilities in sub-Saharan Africa. The adequacy of clinical care needs to be formally documented. If such deficiencies are identified, research into health systems and quality-of-care issues will need to be undertaken, with a particular focus on staff morale and motivation.

Protection of health-workers

Health-care workers in sub-Saharan Africa are at risk of nosocomial infections, particularly tuberculosis.[29] The degree of risk from tuberculosis needs to be better quantified, appropriate measures should be put in place to protect staff, and monitoring systems need to be set up and assessed.

Conclusion

We appreciate that the size of the problem that we are addressing is enormous, and there is a temptation to conclude that nothing can be done. We also recognise that our research focus is narrow and based on what we, as practitioners involved in tuberculosis control programmes, perceive to be some of the factors responsible for the deaths of so many of our patients. The research we suggest is relevant to the needs and resources of tuberculosis control programmes and health ministries, and, to a great extent, the results can be put into practice by our colleagues. By concentrating our efforts in these areas it is likely that we can begin to have an immediate effect on tuberculosis death rates. In the long-term we need to critically re-assess how far the current DOTS strategy, even with improvements made through our research agenda, can take us in reducing deaths from tuberculosis. HIV is the driving force behind the tuberculosis epidemic in sub-Saharan Africa, and stopping the AIDS epidemic is one of the keys to reducing tuberculosis in this region. The knowledge is there, but the rhetoric and the strategic plans need to be converted into action on the ground. The other crucial need is to reduce the number of people living in poverty.

International development agencies and donors are committed to eliminating world poverty as a challenge for the 21st century, and if part of this goal can be better education, better health, and better opportunities for poor people, then there is hope that tuberculosis and HIV control efforts can be improved in those countries most in need.

The WHO is promoting the ProTEST Initiative, which calls for HIV voluntary counselling and testing as an entry point for access to a range of tuberculosis and HIV care and prevention interventions with the goal of reducing the burden of these diseases in communities most affected. All these research efforts require a close collaboration between AIDS-control programmes and tuberculosis-control programmes, which is essential if there is going to be any progress in controlling this dual epidemic. In this respect, governments need to provide strong leadership, they need to acknowledge the link between tuberculosis and HIV, and they need to show a firm commitment to improving care for people with tuberculosis.

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References

1 Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC, for the WHO global surveillance and monitoring project. Global Burden of Tuberculosis: estimated incidence, prevalence, and mortality by country. JAMA 1999; 282: 677-86.

2 World Health Organization. Global Tuberculosis Control: WHO Report 2000. Geneva: WHO, 2000 (WHO/CDS/TB/2000.275).

3 Raviglione MC, Harries AD, Msiska R, Wilkinson D, Nunn P. Tuberculosis and HIV: current status in Africa. AIDS 1997; 11 (suppl B): S115-23.

4 Harries AD, Nyangulu DS, Kang'ombe C, et al. Treatment outcome of an unselected cohort of tuberculosis patients in relation to human immunodeficiency virus serostatus in Zomba hospital, Malawi. Trans R Soc Trop Med Hyg 1998; 92: 343-47.

5 Steen TW, Mazonde GN. Pulmonary tuberculosis in Kweneng District, Botswana: delays in diagnosis in 212 smear-positive patients. Int J Tuberc Lung Dis 1998; 2: 627-34.

6 Lawn SD, Afful B, Acheampong JW. Pulmonary tuberculosis: diagnostic delay in Ghanaian adults. Int J Tuberc Lung Dis 1998; 2: 635-40.

7 Salaniponi FML, Harries AD, Banda HT, et al. Care seeking behaviour and diagnostic processes in patients with smear-positive pulmonary tuberculosis in Malawi. Int J Tuberc Lung Dis 2000; 4: 327-32.

8 Salaniponi FML, Gausi F, Kwanjana JH, Harries AD. Time between sputum examination and treatment in patients with smear-negative pulmonary tuberculosis. Int J Tuberc Lung Dis 2000; 4: 581-83.

9 Lawn SD, Shattock RJ, Griffin GE. Delays in the diagnosisof tuberculosis: a great new cost. Int J Tuberc Lung Dis 1997; 1: 485-86.

10 Whalen CC, Nsubuga P, Okwera A, et al. Impact of pulmonary tuberculosis on survival of HIV-infected adults: a prospective epidemiologic study in Uganda. AIDS 2000; 14: 1219-28.

11 Nunn P, Brindle R, Carpenter L, et al. Cohort study of human immunodeficiency virus infection in patients with tuberculosis in Nairobi, Kenya. Am Rev Respir Dis 1992; 146: 849-54.

12 Okwera A, Whalen C, Byekwaso F, et al. Randomised trial of thiacetazone and rifampicin-containing regimens for pulmonary tuberculosis in HIV-infected Ugandans. Lancet 1994; 344: 1323-28.

13 Elliott AM, Halwindii B, Hayes RJ, et al. The impact of human immunodeficiency virus on mortality of patients treated for tuberculosis in a cohort study in Zambia. Trans R Soc Trop Med Hyg 1995; 89: 78-82.

14 WHO. Treatment of tuberculosis: guidelines for national programmes, 2nd edn. Geneva: WHO, 1997 (WHO/TB/97.220).

15 Ministry of Health. Manual of the National Tuberculosis Control Programme in Malawi, 4th edn. Malawi: Ministry of Health & Population, 1991.

16 Maher D, van Gorkom JLC, Gondrie PCFM, Raviglione M. Community contribution to tuberculosis care in countries with high tuberculosis prevalence: past, present and future. Int J Tuberc Lung Dis 1999; 3: 762-68.

17 Wiktor SZ, Sassan-Morroko M, Grant AD, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1 infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. Lancet 1999; 353: 1469-75.

18 Harries AD, Kamenya A, Subramanyam VR, et al. Screening pulmonary tuberculosis suspects in Malawi: testing different strategies. Trans R Soc Trop Med Hyg 1997; 91: 416-19. Foulds J, O'Brien R. New tools for the diagnosis of tuberculosis: the perspective of developing countries. Int J Tuberc Lung Dis 1998; 2: 778-83.

20 Peloquin CA, MacPhee AA, Berning SE. Malabsorption of antimycobacterial medications. N Engl J Med 1993; 329: 1122.

21 Enarson DA, Rieder HL, Arnadottir T, Trebucq A. Tuberculosis guide for low income countries, 4th edn. Paris: International Union against Tuberculosis and Lung Disease, 1996.

22 Ellis ME, Webb AK. Cause of death in patients admitted to hospital for pulmonary tuberculosis. Lancet 1983; 1: 665-67.

23 Alzeer AH, FitzGerald JM. Corticosteroids and tuberculosis: risks and use as adjunct therapy. Tuber Lung Dis 1993; 74: 6-11.

24 Hakim JG, Ternouth I, Mushangi E, et al. Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculosis pericarditis. Heart 2000; 80: 183-88.

25 UNAIDS. Provisional WHO/UNAIDS secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa. Geneva: UNAIDS, 2000.

26 Baum MK, Shor-Posner G, Lu Y, et al. Micronutrients and HIV-1 disease progression. AIDS 1995; 9: 1051-56.

27 Tang AM, Graham NMH, Semba RD, Saah AJ. Association between serum vitamin A and E levels and HIV-1 disease progression. AIDS 1997; 11: 613-20.

28 Pozniak AL, Miller R, Ormerod LP. The treatment of tuberculosis in HIV-infected persons. AIDS 1999; 13: 435-45.

29 Harries AD, Nyirenda TE, Banerjee A, Boeree MJ, Salaniponi FML. Tuberculosis in health care workers in Malawi. Trans R Soc Trop Med Hyg 1999; 93: 32-35.