

District-randomized phased implementation: strengthening the evidence base for cotrimoxazole for HIV-positive tuberculosis patients

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Tuberculosis is a curable disease. Randomized controlled trials since the 1940s have provided a solid basis for the choice of highly effective chemotherapeutic regimens [1]. ‘DOTS cured me – it will cure you too!’ is the theme chosen for World TB day in 2003. Yet in Malawi, whose National Tuberculosis Programme has been following the DOTS strategy since a decade before the term was coined, one in every three patients who starts anti-tuberculosis chemotherapy is dead before the end of the course. The actual cause of death is usually not known, but three-quarters of patients with tuberculosis are also infected with HIV-1, so a range of secondary and opportunistic infections are likely.

Primary and secondary prevention of *Pneumocystis carinii* pneumonia with cotrimoxazole prolonged the lives of many people living with HIV infection, even before the advent of effective antiviral treatments [2]. While *P. carinii* is not a common cause of HIV-related mortality in most African settings, [3–5] cotrimoxazole has broad activity against a range of protozoal and bacterial pathogens that are implicated in morbidity and mortality of Africans living with HIV infection. The results

from two randomized controlled trials of cotrimoxazole in Cote d’Ivoire published in 1999 both showed positive results. In one, mortality was reduced among HIV-positive patients with smear-positive pulmonary tuberculosis [6] while in the other, despite no impact on mortality, hospitalization and morbidity were reduced among people with WHO stage 2 or 3 HIV infection [7]. As a result of these trials, UNAIDS and WHO convened a meeting in March 2000 to review the available evidence. Provisional recommendations were that cotrimoxazole should be offered to all persons with symptomatic HIV disease (stages 2, 3 or 4) as well as those with fewer than 500×10^6 CD4 cells/l [8]. Other placebo-controlled trials were consequently stopped earlier than planned. Inadequate power may therefore explain why no effect on morbidity or mortality could be demonstrated in Senegal [9]. The placebo-controlled trial that had just started in Malawi, with funding from UNAIDS, was also stopped, although such trials continue in neighbouring countries which considered that the rates of resistance to cotrimoxazole among common pathogens were sufficiently high [10] to make it unsafe to generalize the results from Cote d’Ivoire, where resistance rates were rather lower.

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The provisional WHO/UNAIDS recommendations raise the concerns about exacerbation of antimicrobial resistance in the management of pneumonia in children, dysentery and malaria, for which sulphonamides are used as first-line therapy in Malawi [11]. They recommend instituting 'ongoing surveillance for clinical effectiveness of cotrimoxazole prophylaxis for people living with HIV'. Zachariah and colleagues' study is one approach to provide further evidence for the effectiveness of cotrimoxazole prophylaxis for HIV-positive patients with tuberculosis [12]. How robust is this evidence?

Given the ethical impossibility of a placebo-controlled study in Malawi, the investigators have used a historical cohort as a comparison. They have achieved an impressive operational success. Acceptance of an HIV test following counselling was very high in this rural district hospital setting and the organization of the service good enough to ensure that more than 90% of tuberculosis patients underwent testing. That 18 of those 97 who were not tested died before a test could be done and a further six died before the post-test counselling could be done, reflects the challenges faced by health services and tuberculosis programmes in many African districts. The primary outcome, death while still on tuberculosis treatment, seems clear-cut and shows a significant improvement in the recent cohort compared to the historical one. However, as the investigators point out, there are many differences between the management of patients then and now. The National Tuberculosis Programme is continually trying to improve its performance [13] and 'the increase in proportion of patients with smear-positive pulmonary tuberculosis in the intervention group reflects the on-going training and supervision of all tuberculosis programme staff around Malawi in improving the diagnosis of tuberculosis by sputum smear examination' [12]. As a result, a greater number of tuberculosis patients received rifampicin-based treatment in the intensive phase and a shorter total duration of treatment. Unlike the Cote d'Ivoire study in tuberculosis patients, the Malawi study failed to demonstrate a benefit among the sputum smear-positive patients, possibly because a smaller proportion of these were HIV seropositive and received cotrimoxazole. Cotrimoxazole was most beneficial to those tuberculosis patients who were treated with the 'standard' regimen that lasts 12 months and does not include rifampicin. Perhaps the broad antimicrobial spectrum of rifampicin already provides some of the benefits of cotrimoxazole in Malawi [14].

Will those responsible for defining the policy in Malawi, or in other similar settings, now feel confident to recommend the whole-scale introduction of voluntary counselling and testing with cotrimoxazole prophylaxis for HIV positive tuberculosis patients? Given the very high rates of HIV infection, particularly

among sputum smear-negative tuberculosis patients, is it necessary to wait for the institution of voluntary counselling and testing services in all districts? Should we offer cotrimoxazole to all sputum smear-negative tuberculosis patients unless they are known to be HIV seronegative? How confident are we that it is the cotrimoxazole reducing the death rate rather than rifampicin or even the knowledge by health care staff, patient and carer alike of the patients' HIV status? How do we define the 'clinical effectiveness' recommended by WHO and UNAIDS?

Malawi is in a strong position to help define evidence-based policies for the whole region. The National Tuberculosis Programme already provides an effective outcome oriented monitoring system for all tuberculosis patients in the country. Whenever changes in management of tuberculosis patients are envisaged, they are tested in a few pilot districts and then rolled out in a phased approach throughout the country. By including the element of randomization in this approach, the evidence for clinical effectiveness could be greatly strengthened.

Pilot districts in Malawi (both Thyolo, as reported here, but also Karonga) have already demonstrated the feasibility of offering voluntary counselling and testing for tuberculosis patients followed by cotrimoxazole [12]. The results are encouraging and may lead to calls for nationwide implementation. In order to expand the intervention, each year a number of districts will be selected for training and enhanced supervision so that over the next few years, the whole country will be covered. If the districts that are ready to start could be randomly allocated to start either this year or next, Malawi would rapidly and efficiently generate higher quality evidence on which to base policy than that provided by using historical controls.

For interventions believed to be useful, but for which context-relevant, hard evidence is missing, this district-randomized phased implementation strategy avoids the ethical veto of individually randomized trial designs. While patients will still be randomly allocated to control or intervention, this will be done because of the scarcity of capacity to implement new interventions to all districts at once. It will promote equity by making it equally likely that each individual in the districts ready to begin a new programme is as likely as any other to receive the benefit this year rather than next. Should such an approach prove practical, it would also be possible to address many of the important issues facing tuberculosis programmes in the era of HIV in a similar fashion. Should sputum smear-negative patients receive three or four drugs in the intensive phase? Do 6 months' rifampicin-containing regimens reduce mortality and recurrences compared to existing 8-month regimens? Does secondary isonia-

zid prophylaxis reduce the proportion of tuberculosis patients presenting with recurrent disease?

National tuberculosis programmes routinely collect data on the outcome of treatment and perform cohort analyses that would allow comparisons between districts with and without the intervention [15]. A more difficult challenge is how to measure the effectiveness of interventions for which the expected outcome is not included in the routine data. The logistics, training and supervision necessary for many new interventions will often necessitate a phased implementation to cover the country. If systems to measure key outcome indicators at district level can be established early during the planning stages, a district-randomized phased implementation strategy provides an equitable framework to generate high quality evidence for policy makers.

References

1. Fox W, Ellard GA, Mitchison DA. **Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications.** *Int J Tuberc Lung Dis* 1999, **3**(10 Suppl 2):S231-S279.
2. Osmond, D, Charlebois E, Lang W, Shiboski S, Moss A, Nyangulu D, Veen J, Ringdal T. **Changes in AIDS survival time in two San Francisco cohorts of homosexual men, 1983 to 1993.** *JAMA* 1994, **271**:1083-1087.
3. Grant AD, Djomand G, De Cock KM. **Natural history and spectrum of disease in adults with HIV/AIDS in Africa.** *AIDS* 1997, **11**(Suppl B):S43-S54.
4. Lucas SB, Hounnou A, Peacock C, Beaumel A, Djomand G, N'gbichi J-M, et al. **The mortality and pathology of HIV infection in a west African city.** *AIDS* 1993, **7**:1569-1579.
5. Hargreaves NJ, Kadzakumanja O, Phiri S, Lee CH, Tang X, Salaniponi FM, et al. **Pneumocystis carinii pneumonia in patients being registered for smear-negative pulmonary tuberculosis in Malawi.** *Trans R Soc Trop Med Hyg* 2001, **95**:402-408.
6. Wiktor SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Maurice C, 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**:1469-1475.
7. Anglaret X, Chene G, Attia A, Ture S, Lafont S, Combe S, et al. **Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial.** *Cotrimo-CI Study Group.* *Lancet* 1999, **353**:1463-1468.
8. UNAIDS. *Provisional WHO/UNAIDS Secretariat Recommendations on the use of Cotrimoxazole Prophylaxis in Adults and Children Living with HIV/AIDS in Africa.* Geneva: WHO/UNAIDS; 2000.
9. Maynard M, Lievre L, Sow PS, Badiane S, Coulaud JP, Delaporte E, et al. **Primary prevention with cotrimoxazole for HIV-1-infected adults: results of the pilot study in Dakar, Senegal.** *J Acquir Immune Defic Syndr* 2001, **26**:130-136.
10. Mwansa J, Mutela K, Zulu I, Amadi B, Kelly P. **Antimicrobial sensitivity in enterobacteria from AIDS patients, Zambia.** *Emerg Infect Dis* 2002, **8**:92-93.
11. MacArthur J, Stennies GM, Macheso A, Kolczak MS, Green MD, Ali D, et al. **Efficacy of mefloquine and sulfadoxine-pyrimethamine for the treatment of uncomplicated Plasmodium falciparum infection in Machinga District, Malawi, 1998.** *Am J Trop Med Hyg* 2001, **65**:679-684.
12. Zachariah R, Spielmann MPL, Chinji C, Gomani P, Arendt V, Hargreaves NJ, et al. **Voluntary counselling, HIV testing and adjunctive cotrimoxazole reduces mortality in tuberculosis patients in Thyolo, Malawi.** *AIDS* 2003, **17**:LWW to complete at revises.
13. Harries AD, Mbewe LNO, Salaniponi FML, Nyangulu D, Veen J, Ringdal T, et al. **Tuberculosis programme changes and treatment outcomes in patients with smear-positive pulmonary tuberculosis in Blantyre, Malawi.** *Lancet* 1996, **347**:807-809.
14. Nunn P, Brindle R, Carpenter L, Odhiambo J, Wasunna K, Newnham R, et al. **Cohort study of human immunodeficiency virus infection in patients with tuberculosis in Nairobi, Kenya. Analysis of early (6-month) mortality.** *Am Rev Respir Dis* 1992, **146**:849-854.
15. **An expanded DOTS framework for effective tuberculosis control.** *Int J Tuberc Lung Dis* 2002, **6**:378-388.