TUBERCULOSIS AND HIV/AIDS IN SOUTH AFRICA

The Deadly Partnership

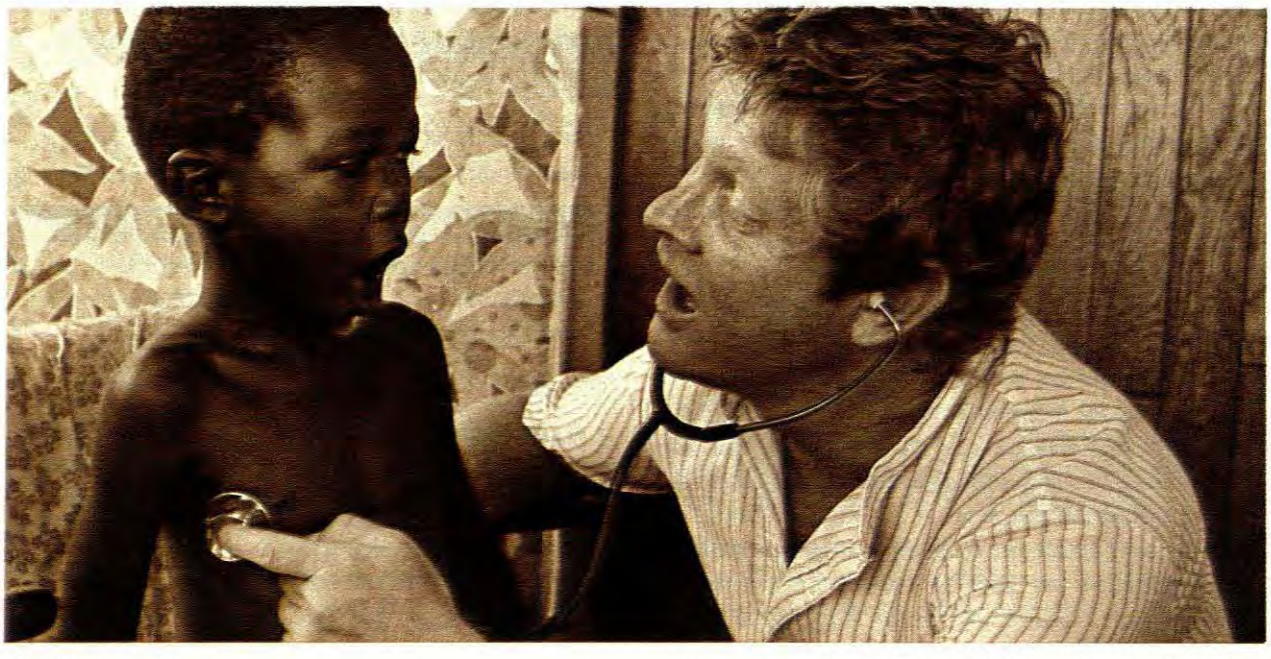
Jean B Nachega, *MD, MPH, DTM&H — Johns Hopkins University Center for Tuberculosis Research, Baltimore, USA, and Perinatal HIV Research Unit, University of the Witwatersrand and Chris Hani Baragwanath Hospital, Johannesburg*
Richard E Chaisson, *MD — Johns Hopkins University Center for Tuberculosis Research, Baltimore, USA*

MAGNITUDE AND KEY DETERMINANTS

Nearly two-thirds of South Africa's population has at some time been infected with *Mycobacterium tuberculosis*. Most people do not develop symptoms and become clinically ill as they have a robust immune response sufficient to contain the organism's replication. Of the 30% of affected people who develop infections, about 5% develop clinical or active disease, located principally in the lung. Well-known South Africans such as Archbishop Desmond Tutu and the former President Nelson Mandela were once afflicted with tuberculosis (TB). South Africa, like the rest of southern Africa, is experiencing concurrent explosive epidemics of HIV and TB. Indeed, TB is the most frequent opportunistic infection, leading to a number of deaths among HIV-infected patients in sub-Saharan Africa.

In 1999, 163 000 cases of TB were reported in South Africa – an incidence of 407 cases/100 000 – one of the highest rates in the world. About 10 000 people die of TB every year in South Africa (Department of Health – unpublished data, July 2000). It is estimated that 4.5 million people in South Africa are infected with HIV and that nearly 1 700 new infections occur every day, with a total of more than 550 000 new infections having occurred in 1999.[1] Among pregnant women attending publicly funded antenatal clinics, the HIV seroprevalence rate was 22% in 1999.[2] In recent years the escalation of the HIV epidemic has been accompanied by soaring TB case rates. The numbers of TB cases reported in South Africa in 1990 and 1994 were 80 400 and 90 200, respectively, compared with 105 000 cases reported in 1997 and 163 000 reported in 1999. In Gauteng it is estimated that 30 - 40% of TB patients are co-infected with HIV (Department of Health – unpublished data).

Epidemiological evidence strongly suggests that reactivation of latent TB infection plays a major role in the burgeoning TB epidemic in South Africa.[3] HIV weakens the cell-mediated immunity and reduces resistance to opportunistic diseases. This leaves patients vulnerable and unable to prevent latent TB infection from developing into active TB disease. HIV-infected individuals with a positive purified protein derivative (PPD) skin test (which identifies latent TB infection) have up to 10% per year risk of developing active TB disease.[4] In addition, the TB epidemic is being fuelled by poverty, increasing migration, an expanding population, lack of resources and multidrug-resistant strains of tuberculosis (MDR-TB). MDR-TB is resistant to both rifampicin and isoniazid, two front-line anti-TB drugs. In South Africa, it is estimated that 2 000 new MDR-TB cases occur every year. The drug regimen to treat one MDR-TB patient costs US$3 600, as opposed to US$36 to treat a non-MDR-TB case; at best only 50% of the MDR patients will be cured.



SOUTH PHOTOGRAPHS - GRAEME WILLIAMS

TABLE I. FEATURES OF CLINICAL TB IN RELATION TO HIV AND IMMUNE SUPPRESSION (ADAPTED FROM ISEMAN MD[3])			
Features of TB	HIV-negative	Early HIV	Advanced HIV (AIDS)
Site involved	Pulmonary, 80% Extrapulmonary, 16% Both, 4%	Intermediate	Pulmonary, 20% Extrapulmonary, 50% Both, 30%
Chest X-ray	50 - 70% typical upper lobe, fibnod; ~50% cavities	Mixed typical and atypical	Atypical: adenopathy, effusions, lower zone and miliary, normal, rare cavitation
Sputum smear positivity (in culture-positive cases)	70 - 80%	50%	30-40%

CLINICAL AND DIAGNOSTIC ASPECTS

The clinical features of TB in HIV-infected patients may be atypical, especially in patients with more advanced immunosuppression, in which case setting, mycobacteraemia and extrapulmonary TB become progressively more common. Unusual features include reduced frequency of cavitation, involvement of the upper lobe in less than 30% as compared with mid-lung involvement and normal chest radiography in 10 - 20% of cases. Involvement of visceral lesions and intra-abdominal adenopathy is also more common. In addition, HIV-infected patients with TB meningitis present more frequently with intracerebral masses and/or tuberculoma. Smears of expectorated or induced sputum, positive for acid-fast bacilli, are found in only 30 - 40% of individuals with advanced HIV infection (Table I).

DIRECTLY OBSERVED THERAPY SHORT COURSE (DOTS)

DOTS was introduced in 1993 by the the World Health Organisation (WHO) as a technical and management strategy to improve global TB control. This strategy has been proved to be cost-effective, and may improve cure rates and also prevent MDR-TB.[6]

The five core elements of a well functioning DOTS programme are:

- government commitment to sustained TB control
- sputum microscopy to diagnose infectious patients
- a standardised course of a cost-effective TB treatment regimen using the best drug combination available
- direct observation of treatment for at least the initial 2 months of therapy
- a monitoring and reporting system to evaluate treatment outcomes in every patient, and
- ongoing evaluation of the performance of the TB control programme as a whole.

The primary goal of the new South African National Tuberculosis Programme (NTP) is the implementation of the DOTS strategy with a goal of 85% case detection and a 70% cure rate. Since the implementation of DOTS in 1997, major advances have been made. At least 50% of the current health districts in South Africa are implementing the DOTS strategy (Department of Health – unpublished data), but there is still a need for greater coverage in order to increase the national cure rate significantly. In addition, about 20% of all TB patients in South Africa are 'treatment interrupters' and are at risk of developing MDR-TB. There is an urgent need to explore the primary barriers to adherence to TB treatment among patients. This information will provide a basis for the development of culturally acceptable and more cost-effective community-based DOTS interventions.

HIV/AIDS AND TB THERAPY

HIV-infected patients respond as well to standard anti-TB therapy as HIV-uninfected patients. Analysis of 6 published prospective studies shows that 6-month TB regimens were associated with a 3 - 9% TB relapse rate (Table II). In the study done in Zaire in which the TB relapse rate was nearly twice as high among HIV-infected patients, it was not clear if the relapses were due to a recurrence or re-infection. In the USPHS multicentre (21 sites) study[10] conducted in the USA, and more recently the study conducted by Sterling and colleagues[12] in Baltimore, DNA fingerprint analysis ruled out the possibility of re-infection since relapse isolates obtained during the relapse matched the initial isolate. In the latter study relapse rates were not significantly higher in HIV-infected patients compared with HIV-uninfected patients (6.4% versus 3.0%, $P = 0.38$). In addition, Connolly and colleagues[11] recently reported results of a South African study conducted in Hlabisa rural district, showing acceptably low relapse rates (6.4 v. 5.5, $P = 1.0$) following successful DOTS using a twice-weekly refampicin regimen, irrespective of HIV status. Current recommendations endorsed by the US Centers for Disease Control and Prevention and the American Thoracic Society are to treat TB in HIV-infected patients with short-course (6-month) therapy. However, a more lengthy regimen (9 months) may be of benefit in patients with delayed conversion of MTB sputum cultures from positive to negative, in cases of delayed clinical response, or in patients with poor adherence to TB treatment.

TABLE II. TB RELAPSE RATE AFTER SHORT-COURSE THERAPY IN HIV-INFECTED PATIENTS			
AUTHOR	LOCATION	RELAPSE HIV+ (%)	RELAPSE HIV– (%)
Perriens *et al.*[7]	Zaire	9.0	5.3
Kassim *et al.*[8]	Cote d'Ivoire	3	3
Chaisson *et al.*[9]	Haiti	5.4	2.7
El-Sadr *et al.*[10]	USA	3.9	N/A
Connolly *et al.*[11]	South Africa	5	5
Sterling *et al.*[12]	USA	6.4	3.0

TB CONTROL IN THE PRESENCE OF HIV

In developing countries, TB control measures have focused on the BCG vaccine, case detection and treatment.[13] Most recent studies have demonstrated that BCG vaccination in childhood does not prevent TB in adults, particularly in those with HIV infection. In addition, a recent decision analysis found that among HIV-infected individuals, preventive therapy would be more effective for TB control than BCG vaccination.[14] There is increasing evidence that even high-quality TB programmes are failing to contain TB in the face of increasing HIV seroprevalence.[15-18] Supervised treatment cures active TB disease in the majority of HIV-infected patients but does not address the reservoir of latent TB infection in HIV-infected individuals in the community. Alternative approaches, including more widespread use of cost-effective TB preventive therapy, are urgently needed.[19]

TB PREVENTIVE THERAPY

Chemoprophylaxis of HIV-uninfected individuals with latent TB infection using isoniazid (INH) reduces the risk of developing active disease by 60 - 90%.[20] Among HIV-infected patients with a positive tuberculin skin tests (TST), prophylaxis involving several regimens has been shown to be effective in preventing TB (Table III). While treatment of latent TB infection in HIV-infected individuals has been the standard of care in the USA for some years, international authorities, including the WHO, have been reluctant to recommend preventive therapy in developing countries.[21] Indeed, a WHO/UNAIDS Special Consultant on TB prevention in HIV-infected people (WHO/UNAIDS Policy Statement, May 1998) endorsed TB prophylaxis for TST +, HIV-infected individuals only as a personal health measure, not as a public policy; thus countries were not encouraged to make organised efforts to provide preventive therapy as a public health intervention.

Lack of international support has been based on a number of concerns, principally that programmes to provide preventive therapy for HIV-infected people may not be feasible in developing countries as clinical services for identifying co-infected patients and ruling out active TB may be lacking. Indeed, the delivery of preventive therapy requires several steps to be taken such as identification of HIV-positive status and targeted tuberculin skin tests to detect dual infection and it is important to exclude active TB. Furthermore, attention must be paid to the availability of drugs and adherence to therapy. Addressing these limitations will go a long way towards integrating efforts to control both TB and HIV. Therefore, widespread voluntary HIV testing and counselling should be promoted in collaboration with all sectors of the community, including the private and public health sectors, pharmaceutical companies, non-governmental organisations and other voluntary groups. Tuberculin skin testing may not be feasible on a large scale, and in such circumstances preventive therapy could be offered to all HIV-infected individuals in whom active TB has been excluded. The ideal and feasible screening procedure to exclude active TB in developing countries also remains an important research question. Prophylaxis for TB may be given under directly observed therapy to improve adherence.

An early operational study of INH prophylaxis in Uganda, for example, found that fewer than 10% of eligible patients actually completed TB prophylaxis with INH.[22] Recent studies have attempted to identify short-course preventive therapy regimens that might promote better adherence, such as 2 - 3 months of rifampicin and pyrazinamide (RIF/PZA) (Table III).

The long-term effectiveness of TB preventive therapy in HIV-infected people in developing countries has also been questioned because of the ongoing risk of re-infection from prevalent TB cases in the community. Indeed, the optimal duration of INH therapy for latent TB in HIV-infected people is unknown, and may differ in developed and developing countries. In the past, clinical trials[29] conducted among HIV-uninfected individuals have suggested that a 12-month course is more effective than a 6-month course in adherent patients, but not in an intent-to-treat analysis since many patients assigned to the 12-month regimen failed to complete more than 6 months of therapy.[29] Both 6- and 12-month regimens were more effective than 3 months of INH, or a placebo. In a retrospective analysis of a controlled clinical trial in Alaskan subjects conducted in the early 1960s, Comstock[30] found that the efficacy of INH therapy increased progressively when analysed at 3, 6 and 9 months, but did not improve further after 9 months. The efficacy of varying durations of INH therapy in HIV-infected patients has not been directly studied. As shown in Table III, Whalen *et al.*[24] found that the incidence of TB was 1.1 per 100 person-years with 6 months of INH in Ugandan patients, while the multinational trial of Gordin *et al.*[27] found a rate of 1.2 per 100 person-years with 12 months of INH. The majority of patients in the latter study, however, only completed 6 months of INH, despite the trial design. Pape and colleagues[23] reported a TB incidence of 1.7 per 100 person-years for Haitian patients treated with INH daily for 12 months, while Halsey and associates[26] reported a rate of 1.7% per year in patients receiving 6 months twice-weekly INH for 6 months. In the Halsey study there were no incident TB cases while patients were taking INH; all cases occurred after preventive therapy was completed. Thus INH therapy could be effective in both latent TB infection and new TB infection resulting from exposure in the community.

Recently Godfrey-Fausset and colleagues[31] reported a study conducted among South African gold miners (in press) showing that in a setting with a high risk of TB infection and high HIV seroprevalence, HIV infection increases the risk of recurrent TB, mainly due to re-infection.[31] Also, according to studies conducted in both Uganda and Zambia, 6 months of INH has no efficacy at 3 years of follow-up. The Ugandan study showed that rifampicin regimens retained 60% efficacy after 3 years, but the Zambian study found no efficacy at 2 years for rifampicin regimens. The situation strongly begs for a clinical trial to resolve this issue and to indicate whether in developing countries with epidemic TB, longer courses of INH prophylaxis may provide additional protection against new TB infections as well as eliminating latent infection. Finally, the cost-effectiveness of TB preventive therapy in developing countries with limited health budgets is also an important issue. However, a recent decision analysis has suggested that provision of preventive therapy to TST-positive, HIV-infected individuals in developing countries not only prolongs life, but saves money as well.[32]

CONCLUSION

The explosion of the HIV/AIDS epidemic is affecting TB control in South Africa disproportionately since HIV-induced immunosuppression has dramatically increased the number of TB cases and has changed the clinical course of TB, making it more difficult to diagnose. Yet among developing countries that have fully implemented DOTS, only a few have achieved 70% detection rate and an 85% successful treatment rate. Moreover, TB case rates continue to escalate in a few developing countries despite successful implementation of the elements of the DOTS strategy. Addressing these challenges will require efforts to increase commitment and resources for TB control, enhanced surveillance, co-ordination between TB and HIV programmes, expansion of the DOTS strategy, evaluation of efficacy trials that may be able to validate the impact of preventive treatment on TB incidence in the community, and finally, operational research that will answer critical programmatic questions such as feasibility and cost-effectiveness in order to help develop public health policies.

TABLE III. TB CHEMOPROPHYLAXIS REGIMENS FOR HIV-POSITIVE AND TST-POSITIVE PATIENTS

AUTHOR	REGIMEN	ANNUAL RATE OF TB (%)	REDUCTION (%)
Pape *et al.*[23]	INH daily x 12 months Vitamin B_6 (placebo)	1.7 10.0	83
Whalen *et al.*[24]	INH daily x 6 months INH/RIF daily x 3 months INH/RIF/PZA daily x 3 months Placebo	1.1 1.3 1.7 3.4	68 60 50
Mwinga *et al.*[25]	INH 2 x/week x 6 months RIF/PZA 2 x/week x 3 months Placebo	2.3 2.7 9.8	77 73
Halsey *et al.*[26]	INH 2 x/week x 6 months RIF/PZA 2 x/week x 2 months	1.7 1.8	N/A
Gordin *et al.*[27]	INH daily x 12 months RIF/PZA daily x 2 months	1.2 1.2	N/A
Hawken *et al.*[28]	INH daily x 6 months Placebo	5.6 8.0	40 (NS)

INH = ioniazid; RIF = rifampicin; PZA = pyrazinamide; N/A = not applicable; NS = statistically not significant ($P > 0.05$).

REFERENCES

1. Department of Health. *Summary Report, National HIV Seroprevalence Survey of Women Attending Antenatal Clinics in South Africa, 1999.* Pretoria: DOH, May 2000.
2. Allen D, Simelela PN, Makubalo L. Epidemiology of HIV/AIDS in South Africa. *Southern African Journal of HIV Medicine* 2000; 1: 9-11.
3. Corbett EL, Churchyard GJ, Clayton T, *et al.* Risk factors for pulmonary mycobacterial disease in South African gold miners. A case-control study. *Am J Respir Crit Care Med* 1999; 159: 94-99.
4. Markowitz N, Hansen NI, Hopewell PC, *et al.* Incidence of tuberculosis in the United States among HIV infected persons. *Ann Intern Med* 1997; 126: 123-132.
5. Iseman MD. *A Clinical Guide to Tuberculosis.* Lippincott Williams and Wilkins, 2000.
6. Kochi A. Tuberculosis control – is DOTS the health breakthrough of the 1990s? *World Health Forum* 1997; 18: 225-232.
7. Perriens JH, St. Louis ME, Mukadi YB, *et al.* Pulmonary tuberculosis in HIV-infected patients in Zaire. A controlled trial of treatment for either 6 or 12 months. *N Engl J Med* 1995; 332:779-784.
8. Kassim S, Sassan-Morokro M, Ackah A, *et al.* Two-year follow-up of persons with HIV-1- and HIV-2-associated pulmonary tuberculosis treated with short-course chemotherapy in West Africa. *AIDS* 1995; 9:1185-1191.
9. Chaisson RE, Clermont HC, Holt EA, *et al.* Six-month supervised intermittent tuberculosis therapy in Haitian patients with and without HIV infection. *Am J Respir Crit Care Med* 1996; 154: 1034-1038.
10. El-Sadr WM, Perlman DC, Matts JP, *et al.* Evaluation of an intensive intermittent-induction regimen and duration of short-course treatment for human immunodeficiency virus-related pulmonary tuberculosis. *Clin Infect Dis* 1998; 26: 1148-1158.
11. Connolly C, Reid A, Davies G, Sturm W, McAdam KP, Wilkinson D. Relapse and mortality among HIV-infected and uninfected patients successfully treated with twice weekly directly observed therapy in rural South Africa. *AIDS* 1999, 13: 1543-1547
12. Sterling TR, Alwood K, Gachuhi R, *et al. AIDS* 1999, 13: 1899-1904.
13. International Union Against Tuberculosis and Lung Disease. *Tuberculosis Guide for Low Income Countries,* 3rd ed. Paris: IUATLD, 1994.
14. Sterling TR, Brehm W, Moore RD, Chaisson RE. Tuberculosis vaccination versus isoniazid preventive therapy: a decision analysis to determine the preferred strategy of tuberculosis prevention in HIV-infected adults in the developing world. *Int J Tuberc Lung Dis* 1999; 3: 248-254.
15. Cantwell MF, Binkin NJ. Impact of HIV on tuberculosis in sub-Saharan Africa: a regional perspective. *Int J Tuberc Lung Dis* 1997; 1: 205-214.
16. Yanai H, Uthaivoravit W, Panich V, *et al.* Rapid increase in HIV-related tuberculosis, Ching Rai, Thailand, 1990-1994. *AIDS* 1996; 10: 527-531.
17. Cantwell MF, Binkin NJ. Tuberculosis in sub-Saharan Africa: a regional assessment of the impact of the human immunodeficiency virus epidemic by National Tuberculosis Control Program quality. *Tuber Lung Dis* 1996; 77: 220-225.
18. Harries AD, Nyong'Onya Mbewe L, Salaniponi FM, *et al.* Tuberculosis programme changes and treatment outcomes in patients with smear-positive pulmonary tuberculosis in Blantyre, Malawi. *Lancet* 1996; 347: 807-809.
19. De Cock KM, Chaisson RE. Can DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection. *Int J Tuberc Lung Dis* 1999; 3: 457-465.
20. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis: a general review. *Adv Tuberc Res* 1969; 17: 28-106.
21. Hawken MP, Muhindi DW. Tuberculosis preventive therapy in HIV-infected persons: feasibility issues in developing countries. *Int J Tuberc Lung Dis* 1999; 3: 646-650.
22. Aisu T, Raviglione ME, Van Prag E, *et al.* Preventive chemotherapy for HIV-associated tuberculosis in Uganda: an operational assessment at a voluntary counselling and testing center. *AIDS* 1995; 9: 267-273.
23. Pape WJ, Jean SS, Ho JL, *et al.* Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. *Lancet* 1993; 342: 268-272.
24. Whalen CC, Johnson JL, Okwera A, *et al.* A trial of three regimens to prevent tuberculosis in Ugandan adults infected with human immunodeficiency virus. *N Engl J Med* 1997; 337: 801-808.
25. Mwinga A, Hosp M, Godfrey-Faussett P, *et al.* Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS* 1998; 12: 2447-2457.
26. Halsey NA, Coberly JS, Desormeaux J, *et al.* Randomized trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. *Lancet* 1998; 351: 786-792.
27. Gordin F, Chaisson RE, Matts JP, *et al.* An international, randomized trial of rifampicin and pyrazinamide versus isoniazid for prevention of tuberculosis in HIV-infected persons. Submitted for publication.
28. Hawken M, Meme HK, Elliot LC, *et al.* Isoniazid preventive therapy for tuberculosis in HIV-infected adults: results of a randomized controlled trial. *AIDS* 1997; 11: 875-882.
29. IUAT Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull World Health Organ* 1982; 60: 555-564.
30. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis* 1999; 10: 847-850.
31. Godfrey-Fausset P, Sonnenberg P, Shearer SC, et al. Tuberculosis control and molecular epidemiolgy in a South African gold-mining community. *Lancet* 2000; 356: 1055.
32. Bell JC, Rose DN, Sacks HS. Tuberculosis preventive therapy for HIV-infected people in sub-Saharan Africa is cost-effective. *AIDS* 1999; 13: 1549-1556.