

## Impact of human immunodeficiency virus on tuberculosis in developing countries

Paul P Nunn, Alison M Elliott, Keith P W J McAdam

Numerous reports have underlined the concern which the resurgence of tuberculosis has created in the industrialised world.<sup>1-6</sup> For the most part these have considered the problem from the perspective of an industrialised country. The control of tuberculosis in developing countries, however, has many facets which need not trouble the health services of a developed nation.<sup>7</sup> This review will therefore concentrate on the problems created by the interaction between the human immunodeficiency virus (HIV) and tuberculosis which, if not specific to developing countries, are at least more serious there. Most of the research work on the effect of HIV on tuberculosis in developing countries comes from studies in Kinshasa, Zaire by the Projet SIDA, in Abidjan, Cote d'Ivoire by Projet Retro-Ci, and the authors' projects in Nairobi, Kenya and Lusaka, Zambia. There is therefore a sub-Saharan African bias in the article, but reference will be made to other developing areas of the world where information is available.

The association of tuberculosis with the immunodeficiency that was later recognised as HIV infection was first recorded among Haitian immigrants to the USA,<sup>8</sup> but it rapidly became clear that tuberculosis was also a major feature of HIV infection in Africa<sup>9-13</sup> and South America.<sup>14</sup> Whilst HIV associated tuberculosis is likely to be containable in northern Europe, the same is not true of developing countries nor, perhaps, of parts of North America.<sup>15</sup> The main reason for this is the degree of overlap of the populations infected with both HIV and *Mycobacterium tuberculosis*,<sup>16</sup> and the lack of resources in the health sector. Throughout the world young adults have the highest prevalence of HIV infection, and infection with *M tuberculosis* is present in about 50% of 15-49 year olds in the developing world. In Europe and North America, however, the annual risk of infection with *M tuberculosis* has been falling for many years, and infection is now largely limited to elderly people<sup>17</sup> and some disadvantaged groups such as the homeless,<sup>15</sup> alcoholics, drug users,<sup>18,19</sup> and immigrants.<sup>20</sup> There is therefore a major difference between industrialised and developing countries, where the annual risk of infection with *M tuberculosis* remains extremely high at over 1% per year in some large surveys<sup>17</sup> and probably even higher in especially poor areas. As a result tuberculosis has never

been adequately controlled, so that whilst the annual incidence of tuberculosis fell to around 10/100 000 in some developed countries, it remained at over 200/100 000 in sub-Saharan Africa<sup>21</sup> before the advent of HIV.

### HIV infection and predisposition for tuberculosis

Until recently it was believed that HIV gave rise to tuberculosis by reactivation of previously acquired tuberculous infection.<sup>22</sup> It is now clear from investigations of outbreaks of tuberculosis in an infectious disease unit in Verona, Italy<sup>23</sup> and in a residential care facility in San Francisco, USA<sup>24</sup> that HIV infected individuals can also rapidly develop disease from recently acquired infection. They may also be more prone to becoming infected initially with *M tuberculosis*. We do not yet know whether previous infection with *M tuberculosis* in such situations would be protective, but the Italian outbreak suggests that this is a possibility.

We do not fully understand the cellular mechanisms underlying the development of tuberculosis. Firstly, however, infection with *M tuberculosis* has to occur. Newly inhaled tubercle bacilli enter the lungs as droplet nuclei where they are engulfed by alveolar macrophages which process the mycobacterial antigens and present them to CD4+ T helper lymphocytes. Little is known of the host factors influencing infection in the human, but in the mouse it is at least partly controlled by genetically mediated innate resistance involving the tissue macrophage.<sup>25</sup> In any case, within one year of infection there is an approximate risk of 5% of tuberculous disease in non-immunocompromised subjects.<sup>26</sup> In a further 5% tuberculosis presents later, presumably following reactivation of latent infection. Latent infections with *M tuberculosis* are probably controlled in the healthy individual by a dynamic interaction between CD4+ helper T lymphocytes and tissue macrophages containing intracellular tubercle bacilli, resulting in granuloma formation. Macrophages are activated to kill intracellular organisms by lymphokines, but whereas most intracellular infections can be inhibited or killed by interferon  $\gamma$  induced activation,<sup>27</sup> *M tuberculosis* in human macrophage systems seems relatively resistant<sup>28</sup> suggesting that other mechanisms

Department of  
Clinical Sciences,  
London School of  
Hygiene and Tropical  
Medicine, Keppel  
Street, London  
WC1E 7HT  
P P Nunn  
A M Elliott  
K P W J McAdam

Reprint requests to:  
Dr P P Nunn, Tuberculosis  
Programme, World Health  
Organisation, CH-1211  
Geneva 27, Switzerland.

are involved. One novel theory is that a class of CD4+ cytotoxic T lymphocytes is involved in the control of *M tuberculosis* latent infections by causing cytolysis of infected macrophages, thus releasing tubercle bacilli and exposing them to further immune attack.<sup>29</sup>

How does HIV affect this process? It is well established that HIV can infect macrophages and upset their function.<sup>30</sup> If mice and men are comparable, impairment of macrophage function may increase susceptibility of HIV infected individuals to infection with *M tuberculosis*. HIV infection is clearly associated with a steady decrease in both numbers and activity of CD4+ lymphocytes, although the mechanisms underlying this progressive loss are not well understood.<sup>31</sup> Opportunistic infections usually occur at less than 200 CD4+ cells/mm<sup>3</sup>. Tuberculosis, however, commonly occurs at higher concentrations,<sup>32</sup> presumably reflecting its greater virulence. The pattern of clinical tuberculosis represents a spectrum from those with high CD4 counts who exhibit granuloma formation, caseation, and cavitation,<sup>33</sup> to those with such poor immunity that uncontrolled bacterial multiplication occurs without granuloma formation, caseation, or cavitation,<sup>34</sup> analagous perhaps to lepromatous leprosy.

#### **Epidemiological determinants of the tuberculosis-HIV interaction**

Regardless of the pathogenic mechanisms, the effect of HIV on the incidence of tuberculosis will be broadly determined by the prevalence of HIV infection, the prevalence of infection with *M tuberculosis*, the proportion of dual infections, and the risk dually infected people have for the development of tuberculosis, either from recently acquired infection or from reactivation.

In most of the developing world HIV is transmitted principally by heterosexual intercourse, although homosexual and bisexual men are at high risk in Brazil<sup>35</sup> and parts of the Caribbean, and use of injected drugs is common in parts of south east Asia.<sup>36</sup> The prevalence of HIV among high risk groups is distressingly high<sup>37</sup> but of uncertain relevance for predicting the incidence of tuberculosis in the general population, although these "core" groups with very high seroprevalence appear to be essential for driving the HIV epidemic.<sup>38</sup> Of greater importance are data obtained from randomised community based surveys among adults of both sexes which are now becoming available, especially from Africa. They give HIV prevalences ranging from 0% for HIV-1 in the Gambia to 23.5% for women in the Rakai district of Uganda.<sup>37</sup> Infection rates are generally higher among women and among urban dwellers. Africa is a very large and heterogeneous place, however, and it cannot be assumed that results from one area can be extrapolated to anywhere else in the continent, let alone to the developing world. Less secure data are available from elsewhere. The Caribbean area seems similar to Africa.<sup>7</sup> In the north east of Brazil only five of 11 830 (0.04%) blood

donors were HIV-1 positive<sup>35</sup> although, as in other countries, prostitutes in Brazil have a much higher prevalence (12% in one study in Rio de Janeiro<sup>39</sup>). Detailed surveys of high risk groups in Asia give HIV seroprevalences ranging from 0% to 63% in drug users in Myanmar.<sup>40</sup> In summary, the World Health Organisation (WHO) has calculated that over nine million adults were infected with HIV in Africa by December 1993, 2.5 million in Central and South America, and two million in south east Asia and the western Pacific area.

In Grzybowski's editorial in *Thorax* the distribution of tuberculous infection was outlined.<sup>41</sup> Across the globe over 1700 million people are infected with *M tuberculosis*, of whom 1400 million live in developing countries. Africa contains only one tenth of the world's tuberculous infected population, but because it has such a high prevalence of HIV infection it is already experiencing a major resurgence of tuberculosis. Living in Asia and the western Pacific area are over 1000 million people infected with *M tuberculosis*, and these areas already account for over five million of the world's eight million cases of tuberculosis per year. Even a low prevalence of HIV infection in this area would be catastrophic.

The relative risk for HIV positive persons developing tuberculosis compared with those who are HIV negative appears to be between six and 100.<sup>4</sup> Among intravenous drug users in New York those dually infected with both HIV and *M tuberculosis* developed tuberculosis at the rate of 7.9% per year compared with 0.3% for those without a previously positive tuberculin test (rate ratio 24.0).<sup>22</sup> This would make HIV the most potent risk factor known for the development of tuberculosis. Only silicosis comes close,<sup>42</sup> but it is much less common. A retrospective analysis in Kinshasa amongst women enrolled in a vertical transmission study<sup>43</sup> found a case rate of 3.1 and 0.12 per 100 person-years among HIV positive and negative women respectively, giving a relative risk of 26. Whilst the authors believed this to be an underestimate owing to under-reporting of cases of tuberculosis, others asserted it was an overestimate since a clinical diagnosis of tuberculosis was used in seven of the 19 "cases" and non-tuberculous pulmonary infections may have been the real cause.<sup>44</sup> In a large cohort of women in Kigali, Rwanda, followed for two years, the minimum risk of tuberculosis among the HIV positive women was 5.0%, giving a rate ratio compared with HIV negative women of 22.9 (95% CI 5.4 to 97.6).<sup>45</sup>

The degree of infectiousness of HIV associated tuberculosis will also affect the ultimate scale of the tuberculosis epidemic. Leaving aside the cases of extrapulmonary tuberculosis associated with HIV infection (see below), contact studies of HIV associated pulmonary tuberculosis suggest that the risk of tuberculous infection, or tuberculosis disease, among household contacts is not increased by the presence of HIV infection in the source.<sup>94,95</sup>

Just what sort of levels of increase in tuberculosis are predicted? Sophisticated mathema-

tical models<sup>46</sup> and back of the envelope calculations<sup>12</sup> come up with similar results: a 6–10 fold increase in urban areas of many developing countries is quite possible before the year 2000. Already by the end of 1989 in Abidjan tuberculosis was the cause of death in 40% of post mortem examinations performed in HIV infected patients dying from pulmonary disease compared with 4% of HIV negative patients.<sup>34</sup> However, the main determinant of the ultimate scale of the tuberculosis epidemic is the annual risk of infection with *M tuberculosis*. Studies are underway in Tanzania to determine if high HIV seroprevalences in a district are associated with local increases in the risk of infection.<sup>47</sup>

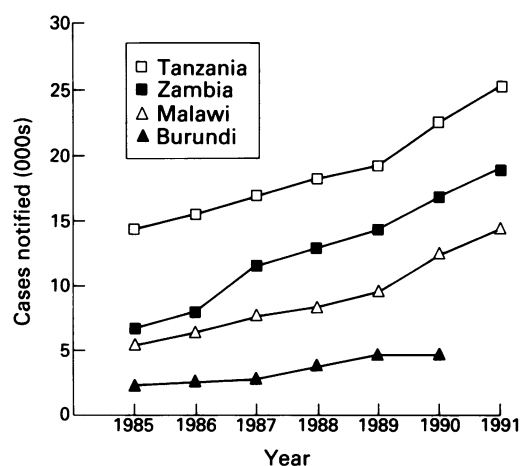
### HIV-2 and tuberculosis

Since the discovery of HIV-2 there has been confusion as to its pathogenicity, and its association with tuberculosis. However, it is now clear that HIV-2 infection is associated with immunosuppression<sup>48</sup> and occurs at a higher prevalence among tuberculosis patients than among blood donors in the Cote d'Ivoire (odds ratio 3.8, 95% confidence interval 2.6 to 5.6).<sup>49</sup> Nonetheless HIV-2 is probably less pathogenic than HIV-1. In the Gambia the ratio of HIV-2 to HIV-1 infection in community surveys is much greater than among AIDS cases presenting to hospital,<sup>50</sup> suggesting that even in countries where HIV-2 is more prevalent it is HIV-1 that is causing most disease.

### Impact of HIV on tuberculosis treatment services

#### PREVALENCE OF HIV AND INCIDENCE OF TUBERCULOSIS

Burundi, Malawi, Tanzania, and Zambia have all experienced significant rises in national annual tuberculosis notification rates since the mid 1980s (figure), as have many other countries.<sup>51,52</sup> Possible reasons for this increase include the introduction of more effective short course regimens with consequent improvements in case finding, better reporting, and increases in numbers of refugees. However, the bulk of it is most likely to be as a result of



Rise in annual notifications of all forms of tuberculosis in four African countries 1985–91 (WHO unpublished data).

HIV infection. Reported increases are very likely to be underestimates: health services in developing countries are not available to the whole population and tuberculosis treatment services may rapidly become saturated. Nevertheless, it is also likely that patients suffering from HIV infection without tuberculosis are increasingly misdiagnosed as having tuberculosis. This is the likely explanation of the disproportionate increase in smear negative cases reported from Malawi. HIV seroprevalence rates among patients with tuberculosis vary according to location, type of referral institution, and site of tuberculosis (table).<sup>51</sup>

#### CLINICAL FEATURES OF HIV ASSOCIATED TUBERCULOSIS

Undue emphasis has been placed on the differences between HIV associated tuberculosis and "normal" tuberculosis in developing countries. Most cases of HIV associated tuberculosis presenting in subSaharan Africa are pulmonary, and a high proportion have a positive sputum smear.<sup>10,11,13</sup> Indeed, nearly half of HIV positive patients with tuberculosis will have no clinical features specifically suggestive of HIV infection.<sup>13</sup> This is of crucial importance in the diagnosis and control of tuberculosis in such countries; current diagnostic tests remain useful, albeit less so (see below), and most patients are infectious, requiring precisely the same urgency for diagnosis and effective treatment as patients without HIV infection. Nevertheless, it is true in Africa, like elsewhere, that patients with HIV associated tuberculosis are more likely to have extrapulmonary disease,<sup>11,53</sup> miliary infiltrates, and non-reactive tuberculin tests<sup>10</sup> than those with tuberculosis and without HIV infection.<sup>11,13</sup> Extrapulmonary tuberculosis is more likely to present to general medical rather than to tuberculosis services, has a high early mortality,<sup>53</sup> and is often undiagnosed before death (A Nelson, unpublished observations). In industrialised countries the clinical features of tuberculosis vary according to the degree of immunosuppression,<sup>32,54,55</sup> and atypical presentations are more commonly found among the

Prevalence of HIV-1 infection among patients with tuberculosis

Location	Year of study	Reference	Institution	Site of tuberculosis	No. (%) of patients tested with HIV		
Africa	Zaire	1985/87	10	Sanatorium	All forms	465 (38%)	
					Pulmonary	287 (33%)	
						Extrapulmonary	46 (48%)
						Suspect	132 (45%)
	Burundi	1986	90	Hospital	All forms	328 (54%)	
	Central African Republic	1986/87	91	Hospital	All forms	72 (54%)	
	Zaire	1987		Clinic	Pulmonary	149 (49%)	
	Zambia	1988	11	Hospital	Pleural	83 (81%)	
					Pericardial	19 (84%)	
				All forms	125 (26%)		
Malawi	1988	92	Hospital	All forms	59 (66%)		
Uganda	1988/89	93	Hospital	All forms	195 (9%)		
Kenya	1989	13	Chest clinic	All forms	196 (27%)		
				Hospital	All forms		
Americas	Brazil	1988	14	Sanatoria	Pulmonary	389 (0.5%)	
					Extrapulmonary	319 (3%)	
						225 (30%)	
Haiti	1988	56	Rural hospital	Pulmonary			

most immunosuppressed patients. The same is probably true of tuberculosis in developing countries, but accurate measures of immune function, such as CD4+ cell counts, are less easily available.

The same is true for radiological features. The classical type of predominantly upper lobe, cavitating, fibrotic disease is still the most usual finding among HIV positive patients in Africa and Haiti,<sup>11 13 56</sup> but variations on this pattern do occur. Just as in Florida tuberculosis with AIDS was originally reported to be without lung cavitation, usually with hilar or mediastinal lymphadenopathy or both, and often with localised pulmonary infiltrates,<sup>57</sup> so too in Africa lower zone disease, thoracic lymphadenopathy, and even normal chest films are more frequently found in HIV positive patients with culture proven pulmonary tuberculosis than in HIV negative patients.<sup>11 13</sup> The distinction between AIDS and HIV infection, so much discussed in developed countries,<sup>3</sup> is often impossible to make in the developing world. The facilities required for diagnosis of AIDS defining infections or malignancies are usually unavailable.

#### BACTERIOLOGY OF HIV ASSOCIATED TUBERCULOSIS

The diagnosis of tuberculosis in developing countries depends heavily on microscopy of the sputum smear. The frequency of infection with *Mycobacterium avium-intracellulare* in AIDS patients in the USA and Europe has cast some doubt on its specificity.<sup>58</sup> However, a number of studies in Africa have made it clear that non-tuberculous mycobacteria are not a significant cause of disease in HIV positive patients diagnosed as "tuberculosis" based on a positive sputum smear,<sup>10 13 59</sup> although they have been found in small numbers of patients in Haiti<sup>60</sup> and in Africans presenting with AIDS in Europe.<sup>61</sup> With regard to sensitivity, a study in Zambia,<sup>11</sup> as well as the Haitian study,<sup>60</sup> reported a rate of concentrated sputum smear positivity of about 63% (95% CI 51 to 75) in HIV positive patients with pulmonary tuberculosis confirmed by culture compared with 82% (72 to 92) in HIV negative patients. Direct measurements of the concentration of viable tubercle bacilli in sputum<sup>62</sup> confirm that HIV positive patients excrete significantly fewer organisms/ml sputum than HIV negative patients with culture confirmed pulmonary tuberculosis.

Considerable concern has arisen about an increase in drug resistant strains of *M tuberculosis* in both HIV infected patients and their medical care providers in the USA.<sup>63</sup> Initial drug resistance has remained around 7% in East Africa for nearly 30 years<sup>64</sup> and, at least in Kenya, there is no evidence that HIV infection is associated with a significant increase in drug resistance.<sup>59</sup> In West and Central Africa, however, primary resistance to isoniazid is reported to be as high as 32%<sup>65</sup> to 37%.<sup>66</sup> A similar situation pertains in Asia, with high rates from Pakistan<sup>67</sup> and Korea,<sup>68</sup> for example, and anecdotal reports of even higher rates of

resistance from the Philippines and parts of India. Although multidrug resistance in association with HIV infection has yet to be reported from developing countries, it is almost certain to become a problem.

#### Treatment regimens

Financial considerations dictate that suboptimal antituberculosis treatment regimens are used in most developing countries. Thus, while treatment based on rifampicin and isoniazid in both the initial and continuation phases has good results in industrialised countries,<sup>69</sup> problems arise when rifampicin is unavailable because the alternatives are either toxic or less effective. Antituberculosis treatment in the poorest countries often consists only of the "standard" regimen of streptomycin (S) for 1–2 months together with isoniazid (H) and thiacetazone (T) for 12–18 months (most commonly, 2STH/10TH). Before the appearance of HIV cure rates of around 80% were obtained in Tanzania and Malawi with the modified short course regimen promoted by the International Union against Tuberculosis and Lung Disease (IUATLD) which consisted of streptomycin, isoniazid, rifampicin (R), and pyrazinamide (Z) for two months, followed by isoniazid and thiacetazone for six months (2SHRZ/6TH).<sup>70</sup> Very few studies have examined the efficacy of this regimen in HIV infected patients. Efficacy needs to be judged by the incidence of adverse effects, tuberculosis specific mortality rates, the time taken for cultures to become negative, and the relapse rate.

#### RESPONSE TO TREATMENT

##### *Adverse effects of antituberculous treatment*

In the late 1980s reports appeared linking HIV infection to an increased incidence of Stevens-Johnson syndrome<sup>71–73</sup> and toxic epidermal necrolysis in patients with tuberculosis. Thiacetazone was thought to be a likely culprit and this has recently been confirmed,<sup>74</sup> although such reactions can occur with other drugs. The implications for treatment policy in developing countries are not straightforward. It is clear that thiacetazone is best avoided, but it is a fact of life that it is also the cheapest antituberculosis agent available and many developing countries will not be able to afford an alternative in the foreseeable future. Studies aimed at identifying those likely to react to the drug may be useful, although in some areas physicians are already refusing to prescribe it and patients are refusing to take it. In the meantime WHO has recommended that thiacetazone-free regimens should be used for all patients known or suspected of being infected with HIV.<sup>75</sup>

##### *Mortality, morbidity, and treatment failure*

In spite of a generally good response to antituberculosis drugs,<sup>69</sup> patients with HIV associated tuberculosis still have a 5–14 fold greater chance of dying during treatment than HIV negative patients.<sup>65 76</sup> This is somewhat para-

doxical, given that the CD4+ T cell counts are relatively high at presentation, at least in San Francisco.<sup>77</sup> The increased mortality is mostly due to other bacterial infections, cutaneous hypersensitivity reactions,<sup>76</sup> and neurological disease with cerebral space occupying lesions observed on computed tomographic scanning. The significance of bacterial infections, usually caused by *Salmonella typhimurium*, other Gram negative rods, and *Streptococcus pneumoniae*, is that they are treatable provided health workers are trained to recognise them, have laboratory facilities to isolate them, and antibiotics to prescribe. Some of the neurological lesions may be due to cerebral toxoplasmosis. Tuberculoma is an unlikely cause when sputum cultures have converted to negative some months previously.

The mortality from conditions other than tuberculosis raises the interesting issue of whether tuberculosis accelerates the course of HIV infection. *M tuberculosis* is a potent activator of T lymphocytes and macrophages, and tuberculosis disease, or even infection, may increase intracellular replication of HIV.<sup>78</sup> The answer to this question must await comparisons of survival or disease progression in HIV infected persons with and without tuberculosis.

With a standard antituberculosis regimen (2STH/10TH) the frequency of persistent positive sputum cultures at one year after the start of therapy<sup>65</sup> was no greater in HIV positive than in HIV negative patients with tuberculosis. In another study using both standard regimens (1STH/11TH) and a modified short course regimen (1SHRZ/1HRZ/6TH) persistent sputum positivity at six months was related to initial drug resistance, and the use of a standard rather than a short course regimen, but not to HIV infection.<sup>59</sup>

Relapse rates among HIV positive patients treated with a standard regimen in Kinshasa were 18/100 patient years of observation compared with 6/100 patient years for HIV negative patients, yielding a threefold greater risk of relapse in HIV positive than HIV negative patients.<sup>65</sup> In Nairobi equivalent interim figures were 17 and 0.5, respectively, with a much higher relative risk of 34.<sup>79</sup> The better result among HIV negative patients in Kenya is most probably the result of active follow up of patients and a far lower level of initial resistance. Poorer compliance among HIV positive patients contributed to the higher relative risk of relapse in Zaire but not in Kenya. However, a history of cutaneous hypersensitivity reaction to thiacetazone during treatment was a strong predictor of recurrent tuberculosis in Kenya. There are many possible explanations for this, including immunosuppression and inadequate treatment. However, in all patients with cutaneous hypersensitivity reaction thiacetazone was changed to ethambutol, together with isoniazid, in the continuation phase. Urgent evaluation of the thiacetazone-free regimens now recommended by the WHO<sup>75</sup> is required.

These results also raise the question of the optimal duration of treatment. In the presence

of HIV the Centers for Disease Control (CDC)<sup>80</sup> recommend treating for a minimum of nine months, or at least six months after culture conversion, provided that both rifampicin and isoniazid are in the regimen. If this or a similar recommendation is established for developing countries, the management of tuberculosis will clearly depend upon HIV status. Routine screening of all tuberculosis patients for HIV is likely to be a major economic, logistical, and political hurdle. In addition, the CDC recommendations do not deal with the situation of rifampicin in the initial phase only, as occurs in the modified short course regimen – for example, 2SHRZ/6TH. Studies are urgently required to determine the effectiveness of such regimens in HIV infected patients since a number of developing countries are considering their introduction to replace the old “standard” treatment. In addition, the effectiveness of maintenance therapy for HIV positive patients successfully completing treatment needs assessment.

### Prevention

General improvement in living standards is probably the most effective measure for tuberculosis control but the least easy to achieve. Prevention of tuberculosis thus depends on case finding and treatment, chemoprophylaxis, and vaccination with the Bacille Calmette-Guerin (BCG) strain of *M bovis*.

### BCG VACCINATION

The effectiveness of BCG vaccination against tuberculosis is in some doubt,<sup>81</sup> quite apart from fears regarding its safety in HIV positive individuals,<sup>82,83</sup> although these concerns are probably unfounded unless HIV related symptoms are already present.<sup>84</sup> In addition, the effectiveness of BCG in the immunocompetent subject clearly varies with geographical location.<sup>85</sup> Its main effect appears to be in the reduction in frequency of disseminated infections with *M tuberculosis*, and reduction in the incidence of the more severe forms of tuberculosis such as miliary disease and tuberculous meningitis in infants and children. Studies are required to assess the effectiveness of BCG in the prevention of disseminated tuberculosis among HIV infected adults.

### CHEMOPROPHYLAXIS

Chemoprophylaxis has been advocated for the prevention of tuberculosis in HIV positive individuals<sup>80,86</sup> and a pilot study from Lusaka suggests daily isoniazid for six months may be effective (D Wadhawan, unpublished observations), especially in those with more advanced HIV infection. Double blind placebo controlled trials are needed, but the logistical and political problems of applying such a policy nationwide in a developing country are likely to prevent it from becoming an important public health measure. It may, however, be applicable in certain situations such as HIV clinics or self referral testing centres. Given

the high annual risk of infection in most of the developing world, and the knowledge that reinfection does occur following completion of antituberculosis therapy, it cannot be assumed that primary or secondary chemoprophylaxis will be successful. Chemoprophylaxis will only prevent those cases resulting from reactivation of latent infection (or from exposure during the period of prophylaxis), and not those acquired by recent infection. It would be very useful to know what proportion of new or recurrent cases are due to reactivation or new infection. DNA fingerprinting using restriction fragment length polymorphism analysis has the capacity to differentiate between these two.

#### CASE FINDING AND TREATMENT

The mainstay of preventive measures remains the breaking of the chain of transmission by case finding, treatment, and case holding.<sup>87</sup> More attention needs to be paid to the reasons why patients fail to attend for treatment when they develop tuberculosis, and why health workers fail to diagnose them when they do. Adherence to treatment is frequently inadequate once treatment has begun and, although usually blamed on patients by health workers, it is not always so. Drug supplies, patient supervision, and health education are often poor. In Africa, especially, increasing the health service coverage is vital. Adjuvant immunotherapy with killed *M vaccae* has been advocated as a way of shortening treatment,<sup>88</sup> but evidence for its efficacy remains elusive. There is room for many kinds of studies aimed at increasing patients' willingness and ability to complete treatment.

As the HIV epidemic massively increases the caseload,<sup>12,46</sup> tuberculosis clinics and hospitals will fill to breaking point. Many hospitals can no longer admit patients routinely for the first month or two of treatment. This may constitute a major loss of opportunity for patient education and result in even poorer compliance. Supervised intermittent chemotherapy for all patients may become impossible, through sheer force of numbers, in those few centres where it has been introduced in the developing world. Totally oral regimens, effective without supervision, need urgent evaluation. New drugs with efficacies similar to isoniazid are desperately needed.

#### Conclusion

In summary, HIV greatly increases an individual's risk of contracting tuberculosis by reactivation or recent infection or both. HIV associated tuberculosis is not more infectious. The efficacy of most diagnostic procedures is compromised by HIV, and antituberculosis drug resistance is associated with HIV infection in the industrialised, but not yet the developed, world. Tuberculosis responds well to optimal treatment, but death from other causes during treatment, and recurrence of tuberculosis, are common with the suboptimal regimens used in most developing countries.

Thiacetazone needs to be removed from treatment regimens owing to its high incidence of toxicity. The duration of antituberculosis treatment required for HIV infected patients needs to be determined. More effective drugs are required urgently, but in the meantime much can be done by the introduction of short course chemotherapy in countries where it is generally unavailable, and by the application of programme guidelines such as those set out by the IUATLD.<sup>89</sup> Better case finding and treatment offer the only real hope of limiting the impact of tuberculosis in developing countries.

The authors would like to thank Professors Hopewell, Murray, and Winkelstein for their critical review of the manuscript. Any errors are ours alone. PN gratefully acknowledges support from the Wellcome Trust, United Kingdom. Ms Ann Pulun typed the manuscript with great care.

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