



## Tuberculosis: 8. The disease in association with HIV infection

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### The case

A 27-year-old counselor from a community-based AIDS agency presents and requests a TB skin test. She is HIV positive and complains of a smoker's cough with no systemic symptoms. She has no known contact with an active case of TB but she knows that, in the past, people who have used the facility have been diagnosed with TB. She has not previously been skin tested.

**M***ycobacterium tuberculosis* infects approximately one-third of the world's population and causes about 3 million deaths each year.<sup>1</sup> At the same time, the HIV pandemic is increasing rapidly in many communities worldwide; more than 30 million people are currently infected, and 1.5 million deaths are estimated to have occurred in 1996. Nearly 14 million people are expected to be infected with both agents by the year 2000.<sup>2</sup> These 2 infections interact in fundamentally important ways, pathophysiologically, clinically and epidemiologically. Although in Canada the overall impact of HIV on tuberculosis (TB) rates has been small,<sup>3</sup> there is evidence that this situation may be changing, especially in certain risk groups.<sup>4</sup> For example, injection drug users have higher rates of co-infection with *M. tuberculosis* and HIV than the general population.<sup>5</sup> In this paper we review the interactions between HIV and TB and outline the approach to screening for and preventing TB, as well as managing active TB, in the presence of HIV infection.

### Interactions between HIV and TB

#### Pathophysiologic interactions

Cell-mediated immunity is critical to an effective host response against infection with *M. tuberculosis*. It is this component of the immune response that is most affected by HIV infection, because the primary target or host cells of the virus are CD4<sup>+</sup> lymphocytes and macrophages. The patient's defence against progression of primary infection with *M. tuberculosis* or reactivation of latent infection is compromised in proportion to his or her degree of immunosuppression related to HIV infection.

A reduction in the cell-mediated immune response may also alter the clinical and radiologic features of TB, which result from the interaction between host and pathogen. For example, the delayed hypersensitivity response, which is the basis for the tuberculin skin test, is affected by declining cell-mediated immunity,<sup>6</sup> and this may make the diagnosis of *M. tuberculosis* infection more difficult.

Finally, each of these infectious agents enhances infection by the other. Not only does HIV infection increase replication of *M. tuberculosis* in the human host, but, conversely, there is also evidence that *M. tuberculosis* infection enhances HIV replication in vivo and in vitro through one or more of several possible mechanisms.<sup>7-9</sup>

#### Clinical interactions

In people with HIV infection, primary *M. tuberculosis* infection is more likely to develop into progressive primary disease.<sup>10-12</sup> In addition, DNA fingerprinting

### Education

### Éducation

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techniques have shown that HIV patients who currently have TB responding to therapy may be reinfected with multidrug-resistant *M. tuberculosis*.<sup>13</sup>

However, the most important interaction, both clinically and epidemiologically, is reactivation of previously acquired "latent" *M. tuberculosis* infection as the patient becomes immunocompromised by the HIV infection. HIV appears to be the most potent known risk factor for reactivation of latent TB. In New York, for example, the risk of active TB was 7.9 per 100 person-years in HIV-infected injection drug users who had a positive result for a tuberculin skin test, a risk 24 times greater than among tuberculin-negative HIV-infected subjects.<sup>12</sup> This close to 10% per annum risk of TB in persons infected with both HIV and TB compares to a 10% lifetime risk of TB in a non HIV infected person infected with TB alone.<sup>14</sup> In addition, molecular epidemiological studies indicate HIV-associated TB to be a significant risk factor for clustering of TB cases due to recent acquisition and progression to disease.<sup>15</sup>

As mentioned earlier, the clinical presentation of TB may be altered in the presence of HIV co-infection.<sup>16,17</sup> *M. tuberculosis*, a more virulent pathogen than many of those leading to opportunistic infections in HIV patients, may cause disease in those with CD4<sup>+</sup> cell counts ranging from normal to profoundly depressed. Extrapulmonary sites are more often involved in HIV-infected patients, particularly in those whose CD4<sup>+</sup> count is markedly depressed. The lymph nodes are the most common extrapulmonary site of tuberculous disease in those with HIV, but several studies have also reported higher rates of TB meningitis, pleural TB and TB pericarditis. TB presenting in unusual forms, such as splenic or pancreatic abscess, has also been reported in HIV-infected patients. Nonetheless, pulmonary TB (the form that is potentially infectious) is present in well over half of HIV-infected TB patients.<sup>17</sup>

The radiologic findings in pulmonary TB may also be altered in the presence of HIV co-infection,<sup>18</sup> to a degree proportional to the degree of immunosuppression.<sup>19</sup> Lower lobe involvement is seen more often, pleural effusion is more common, cavities are less common, and intrathoracic adenopathy in adult TB is observed more frequently than among HIV-seronegative patients. The presence of a normal chest x-ray usually excludes the diagnosis of pulmonary TB but in the presence of symptoms, sputum should be examined for acid fast bacilli,<sup>17</sup> if necessary by sputum induction.

Although the diagnosis of TB in children is often more difficult, particularly in the setting of HIV infection where the tuberculin skin test may be unreliable, HIV also appears to increase the risk of pediatric TB.<sup>20</sup>

## Epidemiologic interactions

The HIV epidemic has had a profound influence on the epidemiology of TB in both poor and wealthy countries, and it is spreading rapidly in parts of the world with high rates of TB infection, such as southern Asia, Southeast Asia and central Europe. TB is the most common cause of death in AIDS patients globally. The World Health Organization has predicted that deaths due to TB will increase in every major region of the world and that 14.2% of TB deaths overall and 29% of those in Africa will be attributable to HIV by the year 2000.<sup>21</sup> For the period 1985 to 1992, AIDS patients in the United States were 59 times more likely than the general population to have TB, and TB patients were 204 times more likely than the general population to have AIDS.<sup>22</sup>

The prevalence of HIV infection may exceed 50% in some groups of TB patients. Many countries, including the US, have experienced sharp increases in the annual incidence of TB, in large part because of HIV. In the US at least, this increase has subsequently been reversed by a large investment in TB control measures.<sup>23</sup>

To date, HIV has not had a major impact on the epidemiology or rates of TB in Canada. There is concern that, as the HIV epidemic spreads to groups with higher rates of *M. tuberculosis* infection, such as injection drug users, aboriginal people and the urban poor, this interaction may become more important here also.<sup>4</sup> Using mathematical modelling, we have shown the potential future impact of this overlap in infections in inner-city Vancouver.<sup>24</sup> On the basis of this model in 1993 we predicted a potential 21-fold increase in smear-positive cases observed in 1995–2000. Although we have noted increasing numbers of HIV-related TB cases, it has not reached that level. This may reflect the model's predictive capacity or alternatively it is due to our aggressive surveillance and chemoprophylaxis policy for this population.

Although some studies have found that TB is less readily transmitted from HIV-infected patients than from HIV-seronegative patients, other studies have found that the infectious risk is similar. Several nosocomial or institutional outbreaks of TB have been reported,<sup>10,11</sup> some involving multidrug-resistant organisms and some affecting staff as well as patients or inmates. There is a much greater risk that infection with *M. tuberculosis* in an HIV-infected individual, as opposed to someone without HIV, will progress to active, and therefore potentially infectious, TB. Hence, more rapid spread of TB, including multidrug-resistant disease, may occur in any population with a high prevalence of HIV infection. This has important implications for infection control in hospitals, prisons and other settings

### Key points

HIV-related tuberculosis (TB) is much less common in Canada than elsewhere in the world, but it is a potentially serious problem in certain populations such as injection drug users, aboriginal people and disadvantaged inner-city populations.

TB and HIV infection interact in fundamentally important ways, pathophysiologically, clinically and epidemiologically.



where HIV infection is prevalent. Delay in diagnosis of such cases will lead to more people progressing to active disease if they are infected with TB. Recommendations have been made to limit such institutional exposures.<sup>14</sup>

## Diagnosis of TB

The diagnosis of active TB in HIV-infected patients is based on an assessment of the likelihood of infection by epidemiologic history and tuberculin testing, a high index of suspicion and recognition of atypical presentations of TB in the presence of HIV, and appropriate use of clinical and laboratory examinations. There are several differences between HIV-infected and uninfected patients with TB that have practical diagnostic implications.

First, a false-negative tuberculin skin test is more likely in an HIV-infected patient and is increasingly likely with increasing immunosuppression.<sup>6</sup>

Second, the radiographic appearance of TB, which usually provides diagnostic information, is nonspecific in HIV-infected patients. Furthermore, unrecognized pulmonary TB poses a serious risk of transmission. Therefore, for any HIV-infected patient with unexplained pulmonary disease, strong consideration should be given to testing respiratory secretions for *M. tuberculosis* and applying respiratory isolation measures until infectious TB is excluded.

Third, some studies have found that sputum smear examination is less sensitive in HIV-infected patients;<sup>25</sup> however, this observation has not been confirmed.<sup>26</sup> When the sputum smear is positive for acid-fast bacilli, the patient should usually be treated for presumptive *M. tuberculosis* disease until the species has been identified.<sup>14</sup> Polymerase chain reaction techniques can help in making this distinction rapidly. Positive blood culture results for *M. tuberculosis*, uncommon in HIV-negative patients with TB, may be diagnostic for disseminated TB in patients with advanced HIV infection.<sup>27</sup> The typical granulomatous histologic features of TB may also be altered, particularly in profoundly immunosuppressed patients. Granulomata may be poorly formed or absent, and there may be greater numbers of organisms.

Although it is important to suspect and diagnose TB in patients with known HIV infection, HIV should also be considered and testing offered to every patient in whom TB is diagnosed.<sup>28</sup> TB is often the sentinel opportunistic infection leading to the diagnosis of HIV infection.

## Prevention of TB

The high risk of active TB in those co-infected with HIV mandates that anyone with known HIV infection and

groups at risk for HIV infection be screened for TB infection by means of regular skin testing with 5 tuberculin units of purified protein derivative. There are no explicit evidence-based recommendations that suggest an optimal time interval, but a pragmatic suggestion would be every 6-12 months.

Two recent randomized controlled trials<sup>29,30</sup> failed to demonstrate any benefit of 6 months of isoniazid prophylaxis in anergic HIV-infected patients at high risk of TB. Anergy testing has little to contribute in making individual decisions about TB chemoprophylaxis.

Before commencing TB prophylaxis in HIV patients, it is particularly important to exclude active disease by performing a clinical assessment, chest radiography and sputum examination (smear for acid-fast bacilli and culture). Although if radiographic results are normal, active disease

is unlikely, the results of sputum culture, especially of induced specimens, are sometimes positive in this setting. Unfortunately, physicians' compliance with these recommendations, although improving, remains suboptimal.<sup>31</sup>

Once active disease has been excluded, 12 months of chemoprophylaxis with isoniazid should be strongly encouraged and supported for all HIV-infected patients with induration of 5 mm or more on tuberculin skin testing. Isoniazid taken daily for this duration significantly reduces progression to active TB and also reduces progression of HIV disease.<sup>3,8,32</sup> Some authors have suggested that isoniazid should be continued indefinitely, particularly in those with a high risk of reinfection, but there is no published evidence to support this recommendation. Three studies have described directly observed intermittent isoniazid therapy in populations at high risk of HIV-related TB, but the efficacy of this regimen has not been established.<sup>33</sup> One recent study<sup>34</sup> found that rifampin and pyrazinamide, given concurrently over 2 months, had efficacy comparable to that of isoniazid given over 6 months; this short-course regimen might facilitate adherence to chemoprophylaxis. Expert advice should be sought in managing the contacts of isoniazid-resistant patients. Baseline testing and regular monitoring of liver function during chemoprophylaxis should follow current guidelines<sup>28</sup> and is particularly important in patients with chronic viral or alcohol-related liver disease.

Fortunately, the prevalence of multidrug-resistant TB is low in Canada,<sup>35</sup> probably less than 1%, and this form of the disease has not been identified as a major problem in case series of HIV-related TB.

In Canada, BCG (bacille Calmette-Guérin) vaccine has a limited role in preventing TB and is not recommended for HIV-infected infants<sup>14</sup> or the infants of HIV-positive mothers. A small number of cases of disseminated BCG have been reported in HIV-infected patients.<sup>36</sup>

### Key points

A patient's defence against progression of primary infection with *Mycobacterium tuberculosis* or reactivation of latent infection is compromised in proportion to the degree of HIV-related immunosuppression.

HIV infection increases replication of *M. tuberculosis* in the human host, and *M. tuberculosis* infection enhances HIV replication.



## Treatment of HIV-related TB

The management of TB is detailed elsewhere in this series, so only key issues specific or critical to the management of HIV-related TB are discussed here.

Therapy for TB can be initiated only after the diagnosis has been considered. Unfortunately, in HIV-related TB, as in TB in the general population, the diagnosis is often delayed because of a failure to think of this disease. As for HIV-negative TB patients, standard therapy with at least 3 first-line drugs — isoniazid, rifampin and pyrazinamide — should be started in all HIV patients in whom active TB is diagnosed or suspected.<sup>14</sup> Although the collection of body fluids for smear and culture is important, this step should not unduly delay initiation of treatment when TB is likely. If there is concern about drug resistance, based on the probable source of the patient's infection, this regimen should be augmented by at least one other drug, usually ethambutol. For patients who have been treated previously for TB, it is critical that at least 2 new drugs be used in the re-treatment regimen until new sensitivities are known. Multidrug-resistant TB is devastating in the context of HIV infection; the mortality rate is high, and there is a greater potential for clustering of cases.<sup>15</sup>

Concurrent treatment for HIV infection and TB is complicated by a high likelihood of drug interactions, particularly between rifampin and the HIV protease inhibitors, which may seriously compromise the effectiveness of one or both therapies. Current guidelines<sup>37,38</sup> outline the therapeutic options, but expert advice should be obtained.

Apart from these interactions, people with HIV-related TB experience more adverse reactions, including cutaneous reactions and hepatotoxicity, the latter perhaps related to high rates of coexisting viral or alcoholic liver disease.

Once the appropriate regimen has been chosen, directly observed therapy (DOTS), considered the “gold standard” by many authorities,<sup>39</sup> is recommended. Major reductions in case rates of TB have been achieved when this strategy has been adopted.<sup>40</sup> Others<sup>41</sup> have argued that selective application of DOTS with attention to other measures, such as greater flexibility of clinic hours to enhance patient acceptance of the therapy, use of incentives, and monitoring of adherence, can lead to high levels of success. For example, we and others<sup>42</sup> have dispensed methadone as an incentive to improve treatment completion rates among injection drug users.

Careful clinical, radiographic and bacteriologic follow-up is required to verify that a satisfactory response has occurred. A critical assessment is the one that takes place about 8 weeks after therapy has been initiated and sensitivities are known.

### Key points

Before commencing chemoprophylaxis, especially in HIV patients, active disease must be excluded.

Chemoprophylaxis with isoniazid for a period of 12 months should be strongly encouraged for all HIV-infected patients with induration of 5 mm or more on tuberculin skin testing. Multidrug short course (8 week) regimens should make chemoprophylaxis a more viable option.

Standard therapy with at least 3 first-line drugs — isoniazid, rifampin and pyrazinamide — should be started in all HIV patients in whom active TB is diagnosed or suspected.

Once the organism has been confirmed to be fully sensitive, treatment can usually be switched to a 2-drug (rifampin and isoniazid) twice-weekly intermittent regimen. This regimen should always be on a directly observed basis. Twice-weekly regimens have been used earlier, but a more cautious approach is suggested for HIV-associated TB. If the response to treatment is slower than expected, and if adherence and drug sensitivity are assured, other causes for failure to respond, including malabsorption, should be sought; in such cases, monitoring of drug levels may be useful. There is conflicting information on the risks and importance of malabsorption of TB drugs in HIV-infected patients.<sup>43,44</sup>

The response to a standard TB treatment regimen, as described here, is similar in HIV-infected and uninfected patients, although the mortality rate is higher in the former because of other complications of HIV infection. In addition, the risk of recurrence of TB in this group has been slightly higher in some studies.<sup>45</sup> Previous US and Canadian recommendations advised that therapy be continued until 6 months after the last positive culture result or a minimum of 9 months. However, good outcomes have now been documented in a number of studies of HIV-infected patients who have undergone standard 6-month treatment regimens.<sup>45,46</sup>

In cases in which either isoniazid or rifampin cannot be used because of drug resistance or intolerance, there appears to be an increased risk of relapse, especially if rifampin is not used. In these situations an extended course of therapy is needed: up to 12 months if isoniazid is not used and 18 months if rifampin is not used. As with TB in patients without HIV, a comprehensive approach to care is required<sup>47</sup> to ensure satisfactory completion of treatment. Although extreme measures, including incarceration, may occasionally be required to protect the public interest, in most cases non-coercive measures have a greater sustained benefit.<sup>48</sup>

## Conclusions

HIV-related TB is much less common in Canada than in many other countries, but it is a potentially serious problem in certain populations such as injection drug users, aboriginal people and disadvantaged inner-city populations. Physicians caring for patients with HIV must have a high index of suspicion for TB, and those treating patients with TB should consider the possibility of HIV. Ongoing surveillance of high-risk populations, as well as liberal use of prophylaxis, is required. In those who develop active TB, careful management and an awareness of the greater risk of side effects and drug interactions mandate careful follow-



up and expert advice. In many of these patients, a high level of treatment adherence may best be achieved with DOTS.

## Case follow-up

The PPD skin test shows 7 mm of induration. A chest x-ray is normal. Because of the cough, sputum induction is carried out and the smear is negative for acid fast bacilli but the culture is positive for *M. tuberculosis*. Treatment for active pulmonary TB is started. This case highlights the importance of excluding the possibility of active TB before initiating treatment for latent tuberculous infection. It also shows the need for community agencies providing services to HIV-infected patients to have an employee screening policy in place to detect tuberculous infection.

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