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## Tuberculosis in AIDS: past or new problems?

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Since the emergence of AIDS, tuberculosis and HIV infection have been intimately connected. The immunodepression resulting from HIV infection increases the risk of tuberculosis progression in co-infected individuals and tuberculosis accelerates the course of HIV infection.<sup>1</sup> In spite of new and effective anti-retroviral therapy, tuberculosis remains a major problem in HIV infected patients. In developing countries protease inhibitors containing anti-retroviral therapy are seldom used and tuberculosis remains the most common life threatening HIV related infection. A major goal in such a setting is to prevent and cure tuberculosis in HIV infected patients.<sup>2</sup> In developed countries protease inhibitors containing anti-retroviral therapy decrease the incidence of tuberculosis which, however, reveals HIV infection in some cases.<sup>3</sup> In these countries the best strategy for treating tuberculosis and HIV infection together remains to be defined.

This editorial reviews the past, present, and future interactions between HIV infection and tuberculosis, focusing on their respective natural histories and treatments.

### What are the changes in the natural history of tuberculosis induced by HIV infection?

IS TUBERCULOSIS MOST FREQUENT IN HIV INFECTED PATIENTS?

Several studies have clearly shown that the incidence of active tuberculosis is increased in HIV infected patients—for example, in two cohort studies of intravenous drug users<sup>4,5</sup> the incidence of tuberculosis disease in patients with tuberculous infection defined by a positive PPD test was much higher in HIV seropositive than in HIV seronegative patients.

There is evidence that this increased incidence of tuberculosis disease in HIV infected patients results from three mechanisms: (1) reactivation of latent tuberculous infection which is suggested by the higher incidence of tuberculosis in HIV infected patients with a positive PPD test<sup>6</sup>; (2) rapid progression of recently acquired tuberculous infection which has been demonstrated by molecular epidemiology during several nosocomial outbreaks<sup>7</sup>; and (3) exo-

genous tuberculous reinfection which has also been shown by molecular analysis in patients with repeatedly positive cultures.<sup>7</sup>

The incidence of tuberculosis is not increased in all HIV infected patients. In a prospective study of pulmonary complications in a cohort of HIV infected patients followed up for 53 months Markowitz *et al*<sup>8</sup> identified two major risk factors for tuberculosis progression: (1) a positive PPD test at baseline or during the study, suggesting a major role for the degree of previous or current exposure to *Mycobacterium tuberculosis*, and (2) a low CD4 count, supporting a role for immunodepression in the development of active tuberculosis. Similarly, in a nested case control study Sudre *et al*<sup>9</sup> found that, in countries with a low prevalence of *M tuberculosis* infection, individuals coming from a country with a high prevalence of tuberculosis infection such as Eastern Europe, Brazil or Africa and with advanced immunodeficiency were significantly at risk for tuberculosis.

ARE SYMPTOMS OR SIGNS OF TUBERCULOSIS DIFFERENT IN HIV INFECTED PATIENTS?

Several studies have shown some differences in radiographic findings of pulmonary tuberculosis between HIV positive and HIV negative patients including a non-apical distribution of infiltrates, infrequent cavitation, and increased frequency of hilar and mediastinal adenopathy and pleural effusion.<sup>10</sup> However, these findings are not observed with the same frequency with different degrees of immunodepression. A recent analysis by Perlman *et al* which pooled the results of American and African series showed that the percentage of cavitation is particularly low and adenopathy is mainly observed in patients with profound immunodepression as indicated by a low CD4 count.<sup>11</sup> A first explanation for such atypical radiological data is that intrathoracic adenopathy or pleural effusion, which classically reflect a primary tuberculosis, result from a greater likelihood of severely immunocompromised patients to develop such primary tuberculosis. In fact, the validity of the relationship between, on the one hand,

intrathoracic adenopathy or pleural effusion and primary tuberculosis and, on the other, upper lobe infiltrates or cavitation and reactivated tuberculosis, has not been systematically evaluated in adults. In a recent study Jones *et al*, using molecular analysis of *M tuberculosis* isolated from patients with tuberculosis, identified a group of patients with a high probability of recent infection and another group with a high probability of reactivated infection, as suspected by identical or different molecular patterns, respectively.<sup>12</sup> Surprisingly, there were no significant differences in the occurrence of adenopathy, pleural effusion, or cavitation between the two groups of patients. In this study mediastinal and/or pleural effusion were significantly more common in HIV infected patients but this difference was also found in HIV infected patients with presumed recent infection and in those with presumed reactivated infection.<sup>12</sup> Finally, mediastinal adenopathy and pleural effusion could reflect not only a high frequency of recent infection, but also tuberculosis dissemination due to ineffective immunity. This last hypothesis is in agreement with the development of massive mediastinal adenopathy, diffuse pulmonary infiltrates, and absence of cavitation in rabbits highly susceptible to tuberculosis.<sup>13</sup>

Likewise, Jones *et al* showed that the frequent dissemination of tuberculosis observed in HIV infected patients and confirmed by extrapulmonary localisation and/or mycobacteraemia is clearly related to the degree of immunodepression.<sup>14</sup> In a recent study by Markowitz *et al* the prevalence of a positive PPD test was similar in HIV positive patients with a CD4 count of  $\geq 600/\text{mm}^3$  and HIV negative controls, but decreased dramatically in HIV positive patients as the CD4 cell count decreased.<sup>8</sup>

#### WHAT ARE THE PRACTICAL CONSEQUENCES OF THESE CHANGES FOR DIAGNOSIS AND TREATMENT OF TUBERCULOSIS IN HIV INFECTED PATIENTS?

Since the incidence of tuberculosis is increased in HIV infected patients, guidelines recommend that all patients with tuberculosis should be tested for HIV infection. In practice the compliance of physicians with this recommendation is incomplete, with some proposing that only patients with easily detectable risk factors for HIV infection should be tested. However, in a recent study by Barnes *et al* of 183 patients admitted to hospital with tuberculosis in Los Angeles, only 37% of the 150 HIV negative patients had no risk factor suggesting a low positive predictive value of specific interview.<sup>15</sup> Moreover, in the same study Barnes *et al* compared the results of specific interviews with those of medical records in the 33 HIV positive patients. With specific interviews only three patients had no risk factor for HIV infection whereas systematic questioning found no risk factor in 17 patients. Clearly, the risk factors related to heterosexual transmission of HIV were inadequately documented, suggesting a low negative predictive value of systematic questioning.<sup>15</sup> HIV testing should therefore be proposed for any patient with tuberculosis.

Since the expression of tuberculosis is frequently atypical in HIV infected patients, a practical problem is to diagnose the infection early in spite of these difficulties. In practice there are two situations. In HIV infected patients with a CD4 count of  $>200/\text{mm}^3$  two kinds of pathogens are usually responsible for lung or pleural diseases: *M tuberculosis* and *Streptococcus pneumoniae* or *Haemophilus influenzae*. Clinical and radiological data of tuberculosis are typical, the PPD test is frequently positive, and positive acid-fast smears in the sputum and typical granulomas are found as frequently as in non-immunocompromised patients.<sup>14</sup> In this situation the diagnosis of tuberculosis is rapidly suspected and confirmed, even in patients with a normal chest radiograph. In contrast, in HIV infected patients with

a CD count of  $<200/\text{mm}^3$  numerous infectious or non-infectious diseases may be the cause of lung disease, pleural disease, intrathoracic adenopathy, and even respiratory symptoms in patients with a normal chest radiograph. Clinical and radiological data of tuberculosis are atypical, the PPD test is usually negative but, if looked for, *M tuberculosis* is frequently found in respiratory specimens and in other specimens such as blood cultures.<sup>14</sup> In this setting tuberculosis may be diagnosed only if systematically suspected.

Since HIV infection depresses the natural immune defences against tuberculosis, another practical problem is to determine whether the usual rifampicin-containing regimens are sufficient to cure tuberculosis and to prevent relapses in such patients. A retrospective study by Small *et al*<sup>16</sup> and a prospective study by Jones *et al*<sup>17</sup> evaluated six month and nine month standard self-administered continuous regimens in developed countries. With these standard regimens the percentages of failures and relapses were very low. Moreover, the failures or relapses were clearly related to non-adherence to the treatment. More recently two prospective studies by Chaisson *et al*<sup>18</sup> and Perriens *et al*<sup>19</sup> evaluated six or 12 month supervised intermittent regimens in developing countries. Chaisson *et al* showed that a six month intermittent regimen was equally effective at curing the disease and preventing relapses in HIV positive and HIV negative patients.<sup>18</sup> Perriens *et al* also found no difference in rates of cure between HIV positive and HIV negative patients with a six month intermittent regimen. However, the recurrence rate was higher in HIV positive patients on six month intermittent treatment than in those on 12 month intermittent treatment, which suggests a minimum limit for duration of treatment.<sup>19</sup> An illustration of this limit is given by the results of a recent trial presented at a recent American Thoracic Society meeting.<sup>20</sup> After an initial phase of eight weeks HIV positive and negative patients with tuberculosis were randomised to receive supervised treatment with either isoniazid and rifampentine once weekly or isoniazid and rifampicin twice weekly. Enrolment of patients in the study was closed due to the high rate of relapses in patients receiving isoniazid and rifampentine once weekly. Moreover, four of the five relapses observed with this regimen were due to rifamycin resistant *M tuberculosis*.

#### What are the changes in the natural history of HIV infection induced by tuberculosis?

##### DOES TUBERCULOSIS ACCELERATE THE COURSE OF HIV INFECTION?

In a retrospective cohort study Whalen *et al* compared the incidence of new opportunistic infections and survival in HIV infected patients with tuberculosis and HIV infected patients without tuberculosis but with a similar degree of immunodepression as determined by similar CD4 cell counts.<sup>21</sup> In HIV infected patients with tuberculosis the incidence of new AIDS defining opportunistic infections was four per 100 person-months compared with 2.8 per 100 person-months in controls. Indeed, patients with tuberculosis tended to develop opportunistic infections at a slightly greater rate than control subjects over the same period. Moreover, a Kaplan-Meier analysis indicated that cases had a shorter survival time than control subjects. Furthermore, in a proportional hazards regression analysis active tuberculosis was associated with an increased risk of death, even taking into account age, intravenous drug use, baseline CD4 count, previous opportunistic infection, and anti-retroviral therapy.<sup>21</sup> A European study by Perneger *et al*<sup>22</sup> gave similar results. If tuberculosis accelerates the course of HIV infection, what are the mechanisms involved? We cannot exclude the possibility that tuberculo-

sis was not the cause but the result of more severe immunodepression, imperfectly reflected by the CD4 count only. One interesting hypothesis is that tuberculosis may increase HIV replication.

#### DOES TUBERCULOSIS INCREASE HIV REPLICATION?

In HIV infected patients with or without pulmonary tuberculosis, none of whom were receiving anti-retroviral treatment, Nakata *et al* investigated the *in vivo* effect on HIV replication of co-infection with *M tuberculosis* using bronchoalveolar lavage (BAL).<sup>23</sup> In patients with pulmonary tuberculosis BAL was performed in segments radiographically involved as well as in segments not involved. The most striking result was the differences in lung viral burden of the patients. Those with tuberculosis had a tenfold increase in the viral burden in diseased segments compared with the viral burden in segments not affected by the disease or with patients without lung disease. These results suggest that local inflammation increases HIV replication. A significant correlation between tumour necrosis factor (TNF)- $\alpha$  concentrations and viral load in the BAL fluid was also reported, with a weaker correlation between IL-6 concentrations and viral load. These observations strongly suggest that *M tuberculosis* stimulates lung cells to produce and release mediators such as cytokines which, in turn, stimulate local HIV replication.<sup>23</sup>

Garrait *et al*<sup>24</sup> investigated the effects of the microenvironment generated *in vivo* by tuberculosis on *in vitro* HIV replication and found that: (1) pleural fluid from HIV negative patients with pleural tuberculosis stimulated HIV replication; (2) the capacity of pleural fluid from subjects with congestive heart failure to stimulate such replication was significantly lower; (3) anti-TNF- $\alpha$  and anti-IL-6 antibodies decreased this induced HIV replication; and (4) unstimulated lymphocytes of HIV negative patients with pleural tuberculosis could be infected with HIV without prior *in vitro* activation. Such results and those of Tanaka *et al* suggest that the microenvironment generated by tuberculosis increases the HIV burden in infected subjects, at least by local production of TNF- $\alpha$  and IL-6. Several other studies have been performed with BAL products of HIV infected patients with pulmonary tuberculosis. Rogers *et al* showed local increased expression of co-receptor CCR5 which is known to be a key for intracellular penetration of HIV.<sup>25</sup> Twigg *et al* demonstrated that BAL lymphocytes from severely immunocompromised co-infected patients produced a mediator facilitating HIV infection of normal macrophages.<sup>26</sup> Finally, Tanaka *et al* found mutations of HIV from lung segments infected with tuberculosis, which probably reflects enhanced rounds of local replication.<sup>23</sup>

#### WHAT ARE THE PRACTICAL CONSEQUENCES OF THESE CHANGES FOR PREVENTION OF TUBERCULOSIS AND MODULATION OF ANTI-RETROVIRAL TREATMENT?

If we consider that tuberculosis increases HIV replication and accelerates the course of HIV infection, treatment should have two goals: to prevent tuberculosis in HIV infected patients and to control HIV replication in patients with tuberculosis.

Several randomised trials of chemoprophylaxis of tuberculosis have been carried out. We know that (a) continuous self-administered prophylaxis with isoniazid (300 mg daily for 6–12 months) is effective in preventing tuberculosis in HIV infected patients with a positive PPD test<sup>5 27 28</sup>; (b) other intermittent partially supervised multidrug prophylaxis administered during a shorter period is as effective as isoniazid in co-infected patients;<sup>29 30</sup> and (c) in developing countries no significant effectiveness is observed with such

prophylaxis compared with placebo in HIV infected patients with a negative PPD test or anergy.<sup>29 31</sup> Moreover, in patients with a positive PPD test, prophylaxis with isoniazid delayed a fatal outcome.<sup>27</sup> Such a beneficial effect indirectly confirms the deleterious role played by tuberculosis in the course of HIV infection. However, it should be noted that this protective effect in patients with a positive PPD test is mainly observed during the period of drug administration. This is not surprising if we consider that any of the prophylactic drugs used can eradicate the whole population of *M tuberculosis* in patients with previous infection or prevent a subsequent exogenous tuberculous reinfection. Consequently, in the study by Hasley *et al*,<sup>29</sup> as in others,<sup>28 30</sup> new cases of tuberculosis were observed very soon after prophylaxis was discontinued.

Finally, if we consider that tuberculosis increases the HIV burden and that protease inhibitors are the most effective drugs against HIV replication, protease inhibitors should be administered in HIV infected patients with active tuberculosis.

#### What are the changes induced by highly effective anti-retroviral therapy in the history of tuberculosis in HIV infected patients?

##### DO HIV PROTEASE INHIBITORS DECREASE THE INCIDENCE OF TUBERCULOSIS IN HIV INFECTED PATIENTS?

In the French clinical epidemiology database of 54 614 HIV positive patients followed up in hospital, Costagliola *et al* compared the incidences of the main opportunistic infections between the first half of 1996 and the second half of 1997.<sup>32</sup> During this period, which corresponds to the early and extensive use of protease inhibitors in France, a dramatic reduction in the incidence of *Pneumocystis*, *Toxoplasma* and cytomegalovirus infections was observed. The incidence of tuberculosis was also reduced, but to a lesser degree (from 11 (1) per 1000 patient years in the first half of 1996 to 5.5 (0.6) in the second half of 1997). Protease inhibitors act at the level of immunodepression but not on the degree of exposure to *M tuberculosis*. It should be noted that in this French cohort, as well as in a German cohort of homosexual men,<sup>33</sup> no major change in the incidence of tuberculosis was observed before 1996 in spite of the use of reverse transcriptase inhibitors, underlying the major role played by protease inhibitors.<sup>32</sup>

##### DOES INITIATION OF HIV PROTEASE INHIBITOR INCREASE SYMPTOMS AND SIGNS OF TUBERCULOSIS?

Race *et al* recently reported five cases of HIV infected patients with a high viral load admitted to hospital with fever, abdominal pain, and lymph node enlargement 6–20 days after starting treatment with indinavir. In all cases biopsy samples of lymph nodes showed an unsuspected infection with *M avium* complex with an intense granulomatous reaction. Four of the five patients had an increased absolute lymphocyte count at admission compared with the baseline count before starting indinavir. In all patients in whom they were measured the absolute number of CD4 T lymphocytes was also increased with indinavir treatment. Immunophenotyping performed in two patients showed that most of these CD4 lymphocytes were memory T cells.<sup>34</sup>

Similar paradoxical worsening was recently reported in patients with AIDS and tuberculosis. Narita reviewed the incidence of paradoxical responses in such patients treated with combination anti-retroviral therapy compared with patients with tuberculosis but without HIV infection and with patients with tuberculosis and HIV infection but not receiving anti-retroviral therapy.<sup>35</sup> Paradoxical responses occurred much more frequently in the first group (36%) than in the other two groups (2% and 7%, respectively).

These paradoxical responses consisted of fevers, cervical and/or intrathoracic lymphadenopathy, a worsening chest radiographic appearance (pulmonary infiltrates, miliary infiltrates, pleural effusions) and/or worsening of extrapulmonary tuberculous lesions (cutaneous and peritoneal). Clearly, these paradoxical responses were temporally more related to the initiation of anti-retroviral therapy (mean (SD) 15 (11) days) than to the initiation of anti-tuberculosis therapy (mean (SD) 109 (72) days), and were associated with an increase in the absolute number of CD4 T lymphocytes and a restoration of PPD reactivity in previously anergic HIV infected patients.<sup>35</sup> Such paradoxical worsening of tuberculosis has been reported by others<sup>36, 37</sup> and we have observed it to be associated with an intense granulomatous reaction (data not shown). These clinical and biological findings could result from a rapid improvement in *M tuberculosis*-specific immunity after combination anti-retroviral therapy. They probably reflect an early increase in memory CD4 T cells which is a composite of initial redistribution of T cells<sup>38</sup> during the first of the three phases of T cell reconstitution demonstrated after highly active anti-retroviral therapy.<sup>39</sup> These findings should be distinguished from the pulmonary granulomatous reaction observed a long time after introduction of protease inhibitors during the last phase of T cell reconstitution.<sup>40</sup>

#### WHAT ARE THE PRACTICAL CONSEQUENCES OF THESE CHANGES FOR SIMULTANEOUS TREATMENT OF AIDS AND TUBERCULOSIS?

Theoretically, if we consider that tuberculosis increases the HIV burden and accelerates the course of HIV infection, protease inhibitors should be administered simultaneously with antituberculous drugs. Conversely, if we consider that rapid immune reconstitution may cause an acute presentation of tuberculosis, protease inhibitors should not be administered at the beginning of specific treatment. Further studies are required to determine if, in patients who have not previously received protease inhibitors, a period of time should elapse between starting antituberculosis treatment and initiation of protease inhibitors.

If protease inhibitors should be given, can they be easily administered? As discussed above, only rifamycin-containing regimens are clearly effective in curing tuberculosis in HIV infected patients. Unfortunately, rifampicin accelerates the metabolism of protease inhibitors and dramatically decreases their plasma levels, resulting in an increased risk of HIV resistance with these drugs. For this reason, rifampicin cannot be given with protease inhibitors. Rifabutin, which is as effective as rifampicin in treating tuberculosis in HIV positive and HIV negative patients,<sup>41-43</sup> produces a less significant decrease in plasma levels of protease inhibitors. In addition, protease inhibitors slow down the metabolism of rifamycin derivatives resulting in increased plasma levels with potentially increased toxicity. Consequently, when administered with a protease inhibitor the dose of rifabutin should be decreased by 50%.

Because of all these uncertainties, official guidelines propose several options for treating tuberculosis in HIV infected patients<sup>44</sup>: (1) treatment with a protease inhibitor to start at the end of a six month period of treatment with a regimen including rifampicin; (2) administration of a protease inhibitor for 18 months with a non-rifamycin containing regimen or administration of a rifampicin containing regimen for six months with a non-protease inhibitor containing anti-retroviral treatment; (3) co-administration of a protease inhibitor containing tri-therapy during the whole period of standard antituberculosis therapy in which rifabutin is substituted for rifampicin. In order to avoid or bypass drug interactions when using the

third treatment option, administration of rifabutin at a dose of 150 mg/day, the protease inhibitor indinavir (or nelfinavir) at a dose of 1000 mg three times daily, and the choice of reverse transcriptase inhibitors must take into account the numerous drug interactions<sup>45</sup> such as those observed with zidovudine and pyrazinamide, zalcitabine and isoniazid, or nevirapine and rifampicin.<sup>46</sup> This last option seems the best with regard to both tuberculosis and HIV infection but remains to be validated by pharmacokinetic studies<sup>47</sup> and clinical trials.

#### Conclusions

HIV infection increases the incidence and modifies the clinical expression of tuberculosis, mainly in patients with severe immunodepression. Tuberculosis increases HIV replication and accelerates the course of HIV infection. There are effective preventive and curative treatments of tuberculosis in HIV infected patients. However, in any one country, their use must take into account the prevalence of tuberculosis, the foreseeable compliance of patients, and the local resources. The best strategy for administration of antituberculous drugs and protease inhibitors in co-infected patients remains to be determined.

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