Evaluation of the status of tuberculosis as part of the clinical case definition of AIDS in India

V S S Attili, V P Singh, M Rai, D V Varma, S Sundar

Aim: To assess HIV associated tuberculosis in a high tuberculosis prevalence setting and its status in the clinical case definition of AIDS.

Methods: All HIV patients attending the infectious disease clinic, Varanasi, India between January 2001 and December 2003 were included in the study. They were stratified into three distinct immunological categories depending on their CD4 levels in accordance to Centers for Disease Control (CDC) classification. Tuberculosis of different organs was defined as detailed below.

Results: Tuberculosis was the commonest opportunistic disease, seen in 163 patients. Of these, 68 had exclusively pulmonary tuberculosis, 55 extrapulmonary disease, and 40 the disseminated form. Pulmonary and extrapulmonary tuberculosis had low positive predictive value (PPV) (51% and 42%) for CD4 levels of <200 when compared with the disseminated form (specificity 87% and PPV 75%). Among 86 patients with radiological evidence of tuberculosis, typical radiological features of post-primary tuberculosis were present in 60 cases (70%). Other features such as effusion (14 patients, 16%) and miliary shadows (12 patients, 14%) were comparatively rare.

Conclusion: Keeping pulmonary and extrapulmonary forms of tuberculosis in AIDS defining illness should be reconsidered. In a similar way tuberculosis in HIV patients from areas endemic with tuberculosis occurs in patients with a wide range of immune status and has a better prognosis than other AIDS defining illnesses. Therefore the inclusion of tuberculosis in clinical case definition of AIDS is not justified.

HIV was identified in 1983 and was shown to be the aetiological agent of AIDS in 1984. With the availability of sensitive and specific diagnostic tests for HIV infection, and for the immune status of the patient, the case definition of AIDS has undergone several revisions. The definition of AIDS was established not for the practical care of the patients but for the surveillance purposes. The Centers for Disease Control and World Health Organisation classifications were the most widely used ones. However, different countries have developed and adopted their own classification systems. In India the National AIDS Control Organisation definition is used for surveillance purposes. It had long been debated to keep the diseases with high prevalence in the clinical case definition of AIDS, which point to a fairly advanced HIV disease. In countries with low prevalence of tuberculosis (TB), it can serve the purpose of representing as an “opportunistic infection”. The role of TB as and opportunistic infection in countries like South Africa was questioned by Badri et al after prospective cohort studies. Therefore we conducted a study to find the pattern of TB in HIV patients and its status in the clinical case definition of AIDS. We also evaluated other clinical diseases for their predictive value of low CD4 counts.

METHODS

Patients

All HIV infected patients attending the infectious diseases (ID) clinic, SS hospital, Varanasi between January 2001 and December 2003 were included in the study. From the total 450 patients who attended the clinic, CD4 counts were available in 375 patients (the remainder either did not consent or data were missing). Informed consent was obtained from all the patients and all the examination findings and investigations were recorded in the ID records. The patients were stratified into three distinct immunological categories deepening on their CD4 levels. CD4 of <200/mm³ was taken as severe immunosuppression, CD4 of >500/mm³ was taken as near normal immune status, and a value in between these was taken as intermediate immune suppression.

CD4 cell estimation

Immunophenotyping of lymphocytes was carried out by FACS count (Becton Dickinson, Singapore (BD)) lymphocytes were stained according to the protocol suggested by the manufacturer. CD4 count was calculated using the formula as suggested in the manual.

HIV serology

HIV status of the patients was confirmed by enzyme linked immunosorbent assay using two different antigens.

Definitions of TB

Pulmonary TB

Diagnosis was confirmed by positive sputum examination for acid fast bacillus (AFB) or characteristic findings on chest radiograph, or both.

Extrapulmonary TB

Diagnosis of tubercular meningitis was based on history of subacute or chronic meningitis, cerebrospinal fluid showing increased protein levels, lymphocytic pleocytosis along with raised adenosine deaminase activities above 7 IU/l with the finding of AFB. In cases with no AFB, patients who responded with therapeutic trial of antitubercular therapy were included as tubercular meningitis. In a similar way abdominal tuberculosis was confirmed by either ascetic fluid examination or suggestive barium studies or by

Abbreviations: TB, tuberculosis; AFB, acid fast bacillus; PPV, positive predictive value
ultrasonographic guided fine needle aspiration cytology from abdominal lymph nodes.

**Lymph node TB**
Diagnosed by the finding of caseation on biopsy or finding of AFB by fine needle aspiration cytology.

**Disseminated TB**
Diagnosed by involvement of two or more organ systems by TB.

**Sample collection and microscopy**
In all patients with productive sputum, samples were collected in wide mouth containers. In those patients with dry cough, sputum was induced by nebulising the patient with normal saline. The samples were stained with the Ziehl-Nielsen stain. In a similar way cerebrospinal fluid, ascetic fluid, and plural fluid were also examined.

**Statistical analysis**
The main characterisation of the association between CD4 counts below 200 and different clinical and radiological presentations was the positive predictive value (PPV). This was compared between different presentation types using the Kruskal-Wallis test on actual CD4 levels, in preference to a less powerful \( \chi^2 \) test. Sensitivity and specificity are not appropriate measures to compare between the three mutually exclusive and exhaustive TB classifications listed in table 1, because sensitivities automatically total 100%, as do complements of specificities. Nevertheless it was judged appropriate to show specificity as well as positive predictive value for disseminated TB in table 3, as comparators for the other presentation types shown.

**RESULTS**
Figure 1 shows the follow up of the patients.
We recruited all patients presenting during 2001–3. We present here cross sectional results based on findings at

![Figure 1](Follow up of the patients.)

![Figure 2](Distribution of TB cases.)
presentation. Follow up was planned, but is incomplete and is unlikely to yield useful information because of poor follow up.

Pulmonary tuberculosis was suspected in 108 patients and 86 of these patients had evidence of tuberculosis by chest radiography (findings include cavity in 22 cases, upper zone infiltrates in 38 cases, miliary shadows in 12 cases, and pleural effusion in 14 cases). In 22 patients, there was a strong clinical suspicion of tuberculosis and AFB in sputum was positive despite normal chest radiograph. In 36 patients there was associated organomegaly and these were diagnosed as disseminated tuberculosis. Eleven patients had hepatosplenomegaly and mesenteric lymphadenopathy or thickened bowel loops. These were included in the category of exclusive abdominal tuberculosis. Surprisingly none of the patients with tubercular lymphadenopathy had active tuberculosis by radiography.

The overall range of TB was pulmonary 68, disseminated 40, and extrapolmonary 55. Table 1 shows the details of the immune status of TB patients according to the various forms of TB. The results show that there are pronounced differences in the immune status of the HIV patients who also had various forms of TB. As the sensitivities and specificities in the immune status of the TB patients according to the various forms of TB reached the optimal figure. The 95% confidence intervals of the CD4 levels in most of these diseases also were around 200 (apart from oral candidiasis, toxoplasmosis, and CCM, and in the last two the difference is attributable to the small number of patients).

As it is known that with decreasing immunity the number of opportunistic infections will increase, we evaluated the CD4 levels of the HIV patients with TB when they had other opportunistic infections. If we compare the predictive value of TB when it was associated with other diseases (for example, oral candidiasis, recurrent herpes zoster, etc.), the results showed that its specificity improved. So it might be considered an opportunistic infection when associated with other diseases (table 4).

### DISCUSSION

Tuberculosis in its different forms is the commonest reported disease in HIV patients in different series published from India. It is also the commonest AIDS defining illness reported by NACO. The pattern and contribution of TB in our study was similar to others. We also analysed the sputum positivity, radiological pattern, risk factors, and effect of TB and immune status on survival.

#### Sputum positivity

The sputum positivity in HIV patients ranged from 15.4% to 85% depending on the immune status of the patients in different series. Chances of AFB isolation were high in patients with mild immunosuppression compared with the advanced disease in the above mentioned studies. In this study, the sputum positivity was 44.2% (comparable to other studies and indirectly implicating comparatively good immunity).

#### Radiological pattern

Radiological lesions reported by various other authors include pulmonary infiltrates (7%–56.3%), cavity (25%–33%), miliary

<table>
<thead>
<tr>
<th>Type of tuberculosis</th>
<th>CD4 &lt; 200 (n = 58)</th>
<th>CD4 200–500 (n = 8)</th>
<th>CD4 &gt; 500 (n = 8)</th>
<th>Total (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary alone</td>
<td>35 (51)</td>
<td>28 (41)</td>
<td>5 (8)</td>
<td>68</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>23 (42)</td>
<td>22 (40)</td>
<td>10 (18)</td>
<td>55</td>
</tr>
<tr>
<td>Tubercular lymphadenopathy</td>
<td>2 (9)</td>
<td>13 (56)</td>
<td>8 (35)</td>
<td>23</td>
</tr>
<tr>
<td>Miliary tuberculosis</td>
<td>13 (62)</td>
<td>7 (33)</td>
<td>1 (5)</td>
<td>21</td>
</tr>
<tr>
<td>Abdominal tuberculosis</td>
<td>8 (73)</td>
<td>2 (18)</td>
<td>1 (9)</td>
<td>11</td>
</tr>
<tr>
<td>Disseminated tuberculosis</td>
<td>30 (75)</td>
<td>8 (20)</td>
<td>2 (5)</td>
<td>40</td>
</tr>
<tr>
<td>Pulmonary TB + TBM</td>
<td>4 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4</td>
</tr>
<tr>
<td>Pulmonary TB + organomegaly</td>
<td>26 (72)</td>
<td>8 (22)</td>
<td>2 (1)</td>
<td>36</td>
</tr>
</tbody>
</table>

Percentages shown in parentheses. Kruskal-Wallis test p = 0.1201.
shadows (6.3%–16.7%), and diffuse infiltrates (12.5%–
13%).\textsuperscript{1, 13, 17–21} (none of them correlated it with immune
status). We found typical radiological features of post-
primary TB—that is, upper zone infiltrates in 38 patients
(44%) and cavitary lesions in 22 patients (26%). Other
features like effusion in 14 patients (16%), miliary shadows
in 12 patients (14%) were rarely seen. Our findings suggested
that cavitary lesions and miliary shadows had better
predictive value compared with the other lesions. The pattern
of pulmonary involvement and the frequency of extrapul-
monary involvement in this study were not different from
other Indian reports.

**Risk factors for TB**

Various studies exist globally, evaluating the risk factors for
development of TB (most of them conducted in countries
with low TB prevalence). In most of them neither age, sex,
nor the mode of transmission of HIV behaved as significant
risk factors for development of TB and the only observed risk
factor was the country of origin and patients from areas of
high prevalence had higher chances of developing TB.\textsuperscript{11–21}

**Effect of TB and immune status on the survival**

We evaluated the effect of TB and immune status on the
survival by analysing various studies. In a study conducted by
Stonburner et al., the authors found that HIV patients with TB
had higher mortality compared with those who did not and
suggested that pulmonary TB be included in the clinical case
definition of AIDS.\textsuperscript{14–18}

Studies by Perronne C et al in France, also had similar
results (note, the difference in CD4 levels of pulmonary and extra-
pulmonary forms of TB were not different in that study).\textsuperscript{25}

However, a few years after these two small studies, a large
prospective study conducted over 17 years on 1000 AIDS
cases at Puerto Rico, found that patients with TB alone had
higher survival compared with those with other AIDS
defining illnesses. They also found that patients with TB
and AIDS with lower CD4 levels had higher mortality

compared with those with higher CD4 levels. This suggests
that immunosuppression is the main reason for the death
rate rather than the mere presence of TB.\textsuperscript{9–10}

In a similar way, a larger cohort of 18 062 US HIV patients
was analysed for validating 1993 revised clinical case
definition of AIDS by CDC. The authors concluded that
“AIDS-defining conditions first occurred in HIV-infected
patients with CD4+ T-lymphocyte counts below 0.20 \(\times 10^9\)/L
(200/microL) for 80% of diagnoses. Similarly, AIDS-defining
diseases occurred at counts below 0.05 \(\times 10^9\)/L for 50% of
diagnoses. Exceptions to both criteria were invasive cervical
cancer and tuberculosis\textsuperscript{17, 27}.

Studies from the developing countries were largely small
hospital based studies. Initially Badri et al found that the
onset of TB in HIV infected patients is associated with an
increased risk of AIDS and death. Although a causal link was
not established as it was an observational study, authors had
the view that prolonged immune activation induced by TB
increased HIV replication and consequent accelerated disease
progression.

But the same author found a different result when he
conducted a prospective cohort study. There he found that
67% of the TB cases occurred at a CD4 level much higher than
200/mm\textsuperscript{3}. And the survival of patients with TB was
comparable to that of other benign illnesses like oral
candidiasis. They also found that survival of patients with
pulmonary and extrapulmonary TB was not different.\textsuperscript{3}

In view of the considerable variability of the results across
the globe, it is advisable to analyse the studies according to
the prevalence of the individual diseases in respective
countries.

In India TB is highly prevalent even in non-HIV patients,
consequently it probably affects HIV patients in any stage of
the disease. In this study TB affected 163 (43%) patients. Of
these patients, 124 patients had TB as the only AIDS defining
illness. The CD4 count in the patients was quite variable,
range from 3 to 610.

We also evaluated the specificity of TB in predicting the
low CD4 levels and the results suggested that pulmonary and
extrapulmonary TB had low specificity (56% and 57%) and
low PPV (51% and 42%) for CD4 levels of <200/mm\textsuperscript{3} when
compared with the disseminated form, which had a
specificity of 87% and positive PPV of 75%. So we conclude
that keeping pulmonary and extrapulmonary forms (espe-
cially lymph nodal as it is the factor responsible for low
positive predictive value) of TB in AIDS defining illness
should be reconsidered.

TB in HIV patients from areas endemic with TB occurs in
patients with a wide range of immune status and has a better
prognosis than other AIDS defining illnesses. Therefore the
inclusion of TB in clinical case definition of AIDS is not
justified. Results of this study also support the views of Badri
et al from South Africa who found that most of the TB
affected patients (67%) had CD4 level of more than 200/mm\textsuperscript{3}.

**Status of tuberculosis as part of the clinical case definition of AIDS**

**Table 3** Specificity and positive predictive value of different diseases in predicting the
CD4 levels of <200/mm\textsuperscript{3}

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of cases</th>
<th>Specificity* (%)</th>
<th>PPV* (%)</th>
<th>Mean*(CD4) (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated tuberculosis</td>
<td>40</td>
<td>87</td>
<td>75</td>
<td>143 (111)</td>
</tr>
<tr>
<td>CNS toxoplasmosis</td>
<td>5</td>
<td>99</td>
<td>80</td>
<td>145 (70)</td>
</tr>
<tr>
<td>PML</td>
<td>3</td>
<td>100</td>
<td>100</td>
<td>127 (18)</td>
</tr>
<tr>
<td>CCM</td>
<td>16</td>
<td>98</td>
<td>81</td>
<td>186 (104)</td>
</tr>
<tr>
<td>PCP</td>
<td>16</td>
<td>97</td>
<td>71</td>
<td>147 (32)</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>81</td>
<td>69</td>
<td>38</td>
<td>237 (141)</td>
</tr>
<tr>
<td>Recurrent herpes zoster</td>
<td>12</td>
<td>97</td>
<td>66</td>
<td>138 (105)</td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>6</td>
<td>99</td>
<td>83</td>
<td>145 (37)</td>
</tr>
</tbody>
</table>

**Table 4** Specificity and positive predictive value of TB
when it is associated with other diseases (for example,
oral candidiasis, recurrent herpes zoster, molluscum
contagiosum)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Specificity* (%)</th>
<th>Positive predictive value* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral candidiasis</td>
<td>96</td>
<td>88</td>
</tr>
<tr>
<td>Recurrent herpes zoster</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>100</td>
<td>94</td>
</tr>
</tbody>
</table>

*All the values were rounded to the nearest whole number.
Limitations of the study:
- Small sample size
- Non-evaluation of the survival data
- Large attrition in the sample
- This study did not investigate the natural history of TB and HIV in India

Explanations/ suggestions:
- As the study was conducted in the Uttar Pradesh state of the India, which contained only 870 AIDS patients in January 2003, a larger study involving all states is required to look for the exact pattern
- As most of the asymptomatic HIV patients do not seek medical attention, and patients might have TB for some time it is difficult to predict the natural history of TB in HIV patients.

CONCLUSION
Retaining pulmonary and extrapulmonary forms (especially lymph nodal as it is the factor responsible for low PPV) of TB in AIDS defining illness should be reconsidered. In a similar way TB in HIV patients from areas endemic with TB occurs in patients with a wide range of immune status and has a better prognosis than other AIDS defining illnesses. Therefore the inclusion of TB in the clinical case definition of AIDS is not justified.

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