

## AIDS and the lung: update 1995 · 2

Series editors: R F Miller, D M Mitchell

### New developments in the pulmonary diseases affecting HIV infected individuals

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Since this topic was last reviewed in *Thorax*<sup>1</sup> a number of developments have occurred and it would seem, therefore, timely to present an updated review. Generally speaking the prognosis for AIDS patients has not improved over the last few years. Despite a massive international investment programme in research into all aspects of HIV infection, the prognosis remains poor with a median survival for HIV positive persons remaining at only 17 months from diagnosis of AIDS in European patients,<sup>2</sup> although years may elapse between infection and development of AIDS. For example, in one study 20% of HIV infected individuals remained asymptomatic 11 years after infection,<sup>3</sup> and recent projections from a cohort study estimate that as many as 25% will survive for 20 years after infection with HIV without developing AIDS.<sup>4</sup> Recent experience with zidovudine and other antiretroviral agents has not supported early enthusiasm; in particular, the results of the Concorde study show that zidovudine, which remains the only widely used antiretroviral agent, is of limited efficacy, at best providing a few additional months of relatively symptom free life.<sup>5</sup> These features mean that respiratory physicians will continue to see infectious and non-infectious pulmonary complications in HIV infected individuals, and in this review recent information on respiratory aspects of HIV infection will be discussed in the hope of facilitating the management of these patients. Pneumocystis pneumonia was discussed in last month's issue of *Thorax*. Here we consider (1) some general features of pulmonary disease in HIV infection that have changed recently; (2) our improved understanding of pulmonary bacterial infection and the importance of upper airway disease including tuberculosis and atypical mycobacterial infection which remain of central importance while viral and fungal infections are of less importance clinically; and (3) non-specific aspects of lung disease and secondary neoplasms in HIV infection. Kaposi's sarcoma will be the subject of the third review in this series.

#### Recent changes in the general features of pulmonary disease in HIV infection

Much emphasis has been placed on pneumocystis pneumonia because it is a severe and

potentially fatal end stage pulmonary complication of AIDS. However, respiratory problems are common in early HIV disease although data remain sparse. In one study a cohort of HIV seropositive persons and a group of individuals at high risk for HIV infection were followed for 18 months.<sup>6</sup> During the observation period 33% reported an upper respiratory infection, 16% had an episode of acute bronchitis, 5% an episode of acute sinusitis, whereas 5% developed bacterial pneumonia and 4% pneumocystis pneumonia. Upper respiratory infections were independent of CD4 helper T lymphocyte counts in peripheral blood whereas both bacterial pneumonia and pneumocystis pneumonia were more common in individuals with low CD4 counts. Bacterial pneumonia was more common in intravenous drug users.

As a result of increased travel and mobility, a good travel history is indispensable to enable an appropriate diagnosis to be made of diseases normally seen in a tropical setting such as malaria, disseminated strongyloidiasis, and histoplasmosis<sup>7</sup> which may affect the lung. Of particular importance is tuberculosis developing in HIV positive patients who have either visited or lived in areas of the world with a high prevalence for tuberculosis.<sup>8</sup>

Pneumocystis pneumonia remains an important and common infection despite the widespread introduction of effective prophylaxis. In a Canadian study 48% of all hospital admissions of patients with AIDS were for pneumocystis pneumonia before the introduction of prophylaxis, falling to 29% after its introduction.<sup>9</sup> In a study from London,<sup>10</sup> similar findings were observed with 68% of all hospital admissions of HIV positive patients with respiratory episodes being for pneumocystis pneumonia before the introduction of prophylaxis, falling to 48% following its introduction. These two studies also showed that the reduction in the number of cases with pneumocystis pneumonia in the western world was counterbalanced by increases in those admitted with other respiratory infections. On the other hand, in subSaharan Africa and other tropical areas where pneumocystis pneumonia is much less common, the most common pulmonary complications in HIV disease are

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tuberculosis and severe respiratory bacterial infections, in particular pneumococcal pneumonia.<sup>7</sup> For example, a recent study from Rwanda showed that, in HIV positive patients with respiratory symptoms requiring bronchoscopy, 23% had tuberculosis, 13% had cryptococcosis, 9% Kaposi's sarcoma, 5% pneumocystis pneumonia, and 38% had a non-specific interstitial pneumonitis.<sup>11</sup>

#### DIAGNOSIS OF PULMONARY DISEASE IN HIV INFECTION

There have been few recent advances in diagnostic techniques for pulmonary disease in HIV although the use of the polymerase chain reaction for detection of pneumocystis pneumonia, as discussed in last month's *Thorax*, shows great promise. The chest radiograph is standard but appearances must be interpreted with caution. Pneumocystis pneumonia generally produces diffuse bilateral infiltrates, but the radiograph may appear normal or show "atypical" changes such as nodular patterns, consolidation, upper or lower lobe changes, or even cavities. Conversely, most other pulmonary diseases in HIV infected individuals can mimic all the appearances of pneumocystis pneumonia. Presumably a partial explanation for this lack of specificity is the inability of the host to mount normal inflammatory reactions. However, this does not mean that the chest radiograph is of no value. The presence of a moderate or large pleural effusion or mediastinal or hilar lymphadenopathy is unusual in pneumocystis pneumonia and suggests other diagnoses such as bacterial infection, tuberculosis, or malignancy (Kaposi's sarcoma or lymphoma).<sup>1</sup>

Aetiological diagnosis of respiratory disease in AIDS continues to rely on early fiberoptic bronchoscopy or induced sputum, where this is available, to obtain peripheral lung secretions. This view has again recently been challenged in a study using a decision analysis model<sup>12</sup> where patients (with typical pneumocystis pneumonia on clinical grounds) who had pneumocystis pneumonia diagnosed by bronchoscopy at presentation had similar mortality and morbidity to patients who were treated empirically for pneumocystis pneumonia for five days, at which time only those who had not responded to treatment underwent bronchoscopy. On the other hand, precise microbiological and histological confirmation of the aetiology of pulmonary disease remains important in some cases, particularly where the incidence of pneumocystis pneumonia has fallen as a result of the widespread use of prophylaxis. In a recent analysis of the results of open lung biopsy in patients with AIDS and respiratory disease where other means of diagnosis had failed<sup>13</sup> a number of unexpected diagnoses were made, including a granulomatous form of pneumocystis pneumonia and bronchiolitis obliterans organising pneumonitis (BOOP), allowing either appropriate specific treatment to be introduced or cessation of inappropriate and potentially toxic treatment.

#### Bacterial infection

The increasing importance of bacterial infection causing respiratory disease continues to be recognised. In HIV infected individuals the incidence of severe pneumonia with bacteraemia caused by *Streptococcus pneumoniae* is high and, indeed, *Str pneumoniae* is one of the most frequently occurring invasive bacterial infections in HIV infected patients. The incidence of bacterial pneumonia in intravenous drug abusers with HIV infection is particularly high.<sup>14</sup> The spectrum of bacterial pathogens causing pneumonia is similar to that of community acquired pneumonia in non-HIV seropositive individuals. Chest radiographic changes are often atypical, resembling pneumocystis pneumonia in nearly 50% of cases. Semiquantitative bacterial cultures from bronchoalveolar lavage fluid provide excellent sensitivity and specificity for diagnosis.<sup>15</sup> Although bacterial pneumonia is rapid and severe in onset, the clinical presentation is similar to that in non-HIV infected patients. Treatment and response to appropriate antibiotics is usually rapid, and the clinical pattern resembles that seen in normal individuals with a similar mortality.<sup>16</sup> Relapse is common, however. The incidence of pneumococcal pneumonia and bacteraemia in HIV infected persons is 9.4 per 1000 patient-years. Bacteraemia is generally more common in HIV seropositive individuals. In one study 82% of pneumococcal isolates from HIV seropositive patients belonged to the 23 pneumococcal serotypes included in currently available pneumococcal vaccines.<sup>17</sup> Other bacterial pathogens that cause pneumonia include *Haemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, *Neisseria meningitidis*, *Rhodococcus* and, in more severely immunosuppressed cases, *Staphylococcus aureus* may be a particular problem. In one study *Staph aureus* was isolated in 23% of respiratory infectious episodes and accounted for pneumonia in 6%. Although the pneumonia was appropriately treated in all cases, the mortality was high at 38%.<sup>18</sup>

*Pseudomonas aeruginosa* infection was thought to be unusual except when associated with severe neutropenia or following cytotoxic drug therapy in patients with AIDS where presentation is usually with acute pneumonia and sepsis. A more indolent and relapsing form of *Pseudomonas* bronchopulmonary infection, somewhat similar to that seen in cystic fibrosis,<sup>19</sup> has recently been described in patients with AIDS and low CD4 counts (mean 25/mm<sup>3</sup>) but without the other risk factors.

In a recent series from North America<sup>20</sup> 27% of all patients admitted to hospital with AIDS had a pleural effusion and 66% of these were due to infection (bacterial 31%, *Pneumocystis*, 15%, tuberculosis 8%, *Nocardia* 3%, *Cryptococcus* 2%, *Mycobacterium avium intracellulare* 2%). In a further 31% non-infective causes were established including hypoalbuminaemia 9%, congestive cardiac failure 5%, and Kaposi's sarcoma 2%. The conclusions of this study were that large effusions were frequently due to tuberculosis or Kaposi's sarcoma and that hypoalbuminaemia was a common cause of

non-infectious effusion in this group of patients. In a series of patients with lobar pneumonia reported from London<sup>21</sup> 49 episodes were identified and bacterial causes were demonstrated in 25; of these 11 had infection with *Str pneumoniae*. Other infectious agents included *Staph aureus*, pneumocystis pneumonia, *Pseudomonas* and *H influenzae*. In seven patients more than one pathogen was identified. The authors concluded that many organisms may cause community acquired pneumonia in HIV disease although *Str pneumoniae* was the most common. Infection with more than one organism should also be considered. A high complication rate was reported with 11 patients developing intrapulmonary cavities or abscesses, 10 pleural effusions, and three empyema.

Vaccination against pneumococcal infection for HIV infected individuals has been recommended in North America.<sup>22</sup> However, a recent study showed that 50% of HIV infected individuals who received standard pneumococcal polysaccharide vaccine (Pneumovax) had an inadequate specific IgG<sub>2</sub> antibody response, IgG<sub>2</sub> being the subclass of IgG known to confer protection against infection by capsulated bacteria.<sup>23</sup>

#### SINUSITIS

Sinusitis occurs in HIV positive individuals with a frequency of 6–16% depending on the clinical and radiological criteria employed.<sup>24–26</sup> It is generally under diagnosed and may present with non-specific symptoms.<sup>26,27</sup> The same bacteria that cause lower respiratory tract disease cause sinusitis with *Str pneumoniae* and *H influenzae* being the most frequently isolated and *Ps aeruginosa* becoming frequent in the late stages of HIV disease.<sup>27</sup> Non-bacterial pathogens occasionally cause sinusitis and these include fungi, *Cryptococcus*, and *Alternaria*.<sup>28,29</sup> Cytomegalovirus may cause sinusitis and normally responds well to treatment with ganciclovir.<sup>30</sup> Sinus infection may be acute, recurrent, asymptomatic or chronic, and the clinical features resemble sinusitis in non-HIV infected individuals. Chronic sinus disease, which may be an incidental finding, is particularly common in patients with a CD4 count of less than 200/mm<sup>3</sup>.<sup>26</sup> Nasal congestion, frontal headache, periorbital and maxillary pain, fever, and post nasal drip may be present and are often associated with respiratory symptoms. Where pain is a major feature sinusitis must be differentiated from meningitis (cryptococcal) and encephalitis (toxoplasmosis).<sup>27</sup> In the posterior oropharynx purulent nasal discharge and lymphoid hypertrophy may be seen. As a result of the underlying immune defect symptoms tend to be diffuse, bilateral, and chronic. Standard radiology is of diagnostic value, particularly if air fluid levels or opacification is observed in sinuses. Computed tomographic scanning and magnetic resonance imaging provide better images with greater diagnostic sensitivity, sinus mucosal thickening being a very common finding.<sup>25,31</sup> Nasal endoscopy and antral puncture remain the final arbiters for a definitive diagnosis.

Treatment of sinusitis in HIV positive patients follows the general principles of treatment of sinusitis with appropriate antibacterial agents, decongestants, and expectorants. As there is a tendency to relapse and for sinusitis to become chronic, it may be necessary to prescribe antibiotics for up to three weeks. Even then, response to treatment may be partial and disappointing.<sup>26</sup> As *Str pneumoniae* and *H influenzae* are the most common pathogens, broad spectrum antibiotics such as amoxycillin, co-trimoxazole, amoxycillin/clavulanic acid or oral cephalosporins should be considered. If *Staph aureus* is isolated flucloxacillin is appropriate, whereas Gram negative or anaerobic infections require appropriate specific treatment with, for example, clindamycin.<sup>32</sup> Surgical drainage may be required for antibiotic resistant disease.

#### HIV AND TUBERCULOSIS

The relationship between tuberculosis and HIV is now well established and has been extensively reviewed.<sup>6,33–35</sup> Tuberculosis differs from the other opportunist infections of AIDS as it is also infectious to normal individuals so that the prevalence of tuberculosis in the general population may be influenced by the prevalence of HIV disease in the same population. Tuberculosis complicating HIV disease is due largely to reactivation,<sup>36</sup> although primary infection and secondary exogenous infection can occur. Tuberculosis in relation to HIV disease in the UK is not a major problem at the moment, occurring in only 5–6% of patients with AIDS.<sup>37</sup> In view of the problems in some African countries and some American cities, however, there are no grounds for complacency. The modest increase in tuberculosis notifications in the general population in the UK is thought to be due to factors other than HIV,<sup>38</sup> although tuberculosis is now being seen increasingly among HIV infected individuals<sup>39</sup> and further increases are likely as a result of the immigration of individuals infected with both HIV and tuberculosis.

Because tuberculosis can develop at any time during the course of HIV disease, an HIV test should be considered for all new cases of tuberculosis in the UK.<sup>34,40</sup> Tuberculosis in HIV infected individuals may be difficult to diagnose as the presentation may be atypical with extrapulmonary features predominating, particularly when the CD4 count is low.<sup>41</sup> However, any presentation of tuberculosis in an HIV seropositive individual, regardless of CD4 count, is regarded as an AIDS defining diagnosis. Traditional diagnostic tests in patients with HIV disease may be unhelpful as the tuberculin test is frequently negative in active disease.<sup>42,43</sup> The chest radiograph may have atypical features<sup>41</sup> (absence of upper zone shadows and cavities) and sputum is more frequently negative than in HIV negative individuals.<sup>37,44</sup> It may also be difficult to distinguish initially between tuberculosis and other mycobacterial infections on immediate staining results, definitive diagnosis depending on the results of the cultures. If acid fast bacilli

are identified on smears from an HIV positive patient, irrespective of CD4 count, it is important that cultures be taken to identify species and potential drug resistance and that treatment is started to cover possible *M tuberculosis* infection pending these results; treatment can be modified later as necessary. Chemotherapy normally provides a good clinical response<sup>45</sup> and standard six month regimens are recommended followed by isoniazid for life to prevent relapse. However, 18% of patients with AIDS and tuberculosis have adverse reactions to medication.<sup>46</sup> In the USA tuberculin testing is recommended for all HIV seropositive persons and isoniazid prophylaxis for all those with positive reactions.<sup>36,47</sup> There is currently no general policy in the UK nor is tuberculin testing a routine procedure yet in most HIV centres. Prophylaxis with isoniazid has now been shown to be effective in HIV disease,<sup>48</sup> but it is not without toxicity. BCG is not recommended in HIV seropositive individuals as disseminated BCG has been reported.<sup>49</sup> BCG is also unlikely to be protective as much clinical tuberculosis in HIV seropositive individuals is due to reactivation. As tuberculosis in HIV positive individuals is infectious,<sup>44,50</sup> contact tracing is extremely important, particularly as HIV seropositive contacts are probably more vulnerable to tuberculosis than seronegative contacts.<sup>51</sup> HIV positive patients with tuberculosis need to be regarded as a health hazard to health care workers, and multidrug-resistant disease has recently been transmitted to a health care worker.<sup>52</sup> Nosocomial transmission of tuberculosis in a cluster of four cases in an HIV care centre in the UK has recently been reported and the strains obtained by culture from the four cases demonstrated identical patterns by restriction fragment length polymorphism analysis.<sup>53</sup>

There has been much concern regarding the emergence of multidrug-resistant strains of tuberculosis in the USA.<sup>54</sup> In New York City 33% of isolates were resistant to one or more drugs, 26% being resistant to isoniazid and 19% to isoniazid and rifampicin. Outbreaks of multidrug-resistant tuberculosis have now been reported in HIV seropositive patients in the USA.<sup>55,56</sup> From restriction fragment length polymorphism analysis it has been shown that, in some cases, multidrug resistance results from exogenous reinfection of patients with advanced AIDS already on treatment for drug sensitive disease.<sup>57</sup> The prognosis for multidrug-resistant tuberculosis occurring in HIV infected individuals is very bad with a median survival of only two months.<sup>56,58-60</sup> Multidrug-resistant tuberculosis in HIV seronegative individuals also carries a poor prognosis.<sup>61</sup> The treatment of multidrug-resistant tuberculosis remains a major challenge.<sup>62</sup> Supervised or directly observed therapy can limit drug resistance but its application and enforcement are ethically problematic.<sup>63</sup> Multidrug resistance in HIV is not the result of a new mechanism but of individual gene mutations, indicating that the problem could be solved by early disease detection and effective treatment.<sup>64</sup>

Experience of multidrug-resistant disease is

greater in the USA where the Centers for Disease Control (CDC)<sup>65</sup> suggest that isoniazid and rifampicin should be used for partially resistant strains in combination with other drugs such as pyrazinamide, ethambutol, and ciprofloxacin. The efficacy of these regimens remains to be determined. So far, multidrug-resistant tuberculosis is not a problem in the UK. The Joint Tuberculosis Committee of the BTS have recently published revised guidelines<sup>66</sup> and these have been discussed in relation to HIV both in the UK and USA.<sup>67</sup>

**MYCOBACTERIUM AVIUM INTRACELLULARE (MAI)**  
Although MAI may cause localised disease, including pneumonitis, disseminated disease is much more common. This may present with fever, sweats, weight loss, diarrhoea, and anaemia, and occurs in 30–50% of all patients with AIDS at some stage. MAI is a ubiquitous organism, being present in water and soil. The portal of entry is thought to be the gut and disseminated disease occurs towards the end of the natural history of HIV infection when the CD4 count is low (<50/mm<sup>3</sup>).<sup>68</sup> Although not solely a pulmonary disease, it is convenient to discuss it here as it may be confused with tuberculosis when acid fast bacilli are identified microscopically in clinical samples and respiratory physicians may be asked to advise on treatment. Disseminated infection with MAI carries a poor prognosis. In one study patients with AIDS and untreated MAI infection had a mean survival of 5.6 months, whereas patients with AIDS without disseminated MAI but matched in all other respects had a mean survival of 10.8 months.<sup>69</sup> Individuals in whom respiratory tract colonisation with MAI occurs tend to develop disseminated disease and have a shorter survival than patients with AIDS without colonisation.<sup>70</sup> MAI is universally resistant to all first line antituberculosis drugs and initial studies using second line agents were disappointing. However, several regimens have now been shown to be successful and these include oral regimens consisting of rifabutin, ethambutol, and clarithromycin, or rifampicin, ethambutol, clofazamine, and ciprofloxacin,<sup>71</sup> or amikacin, ethambutol, rifampicin, and ciprofloxacin.<sup>72</sup> As colonisation inevitably precedes dissemination, there has been considerable interest in the role of prophylactic therapy. Two identical placebo controlled randomised multicentre trials have been completed in which rifabutin (Ansamycin) was used as monotherapy to prevent disseminated MAI infection – that is, by a positive blood culture; 556 patients received 300 mg rifabutin and 580 patients received placebo, and 48 patients in the treated group developed disseminated MAI compared with 102 in the placebo group – a statistically significant difference. There was no difference in mortality between the two groups but symptoms were less common in the treated patients. Patients with a CD4 count of less than 75/mm<sup>3</sup> had improved survival from treatment. Treatment was discontinued in 16% of patients on rifabutin because of toxicity compared with 8% in the placebo group. Overall it was difficult

to correlate rifabutin therapy with definite clinical benefit because of the rate of development of other opportunist infections in both groups of patients and the relatively short study time (mean 218 days).<sup>73</sup> Recent concern with usage of rifabutin as monotherapy for prophylaxis has been expressed on the theoretical grounds that drug resistance could be encouraged where there is a high prevalence of tuberculosis. Even so, prophylactic treatment for MAI with rifabutin in patients with low CD4 counts is widespread in centres in the USA but this is not yet widespread in the UK.

#### OTHER ATYPICAL MYCOBACTERIA

Disseminated infections caused by *M kansasii*, *M xenopi*, *M gordonae*, *M fortuitum*, *M malmoense*, *M chelonae*, and *M haemophilum* may complicate HIV infection but are generally far less common than disseminated MAI. Disseminated infections due to *M genavense* and *M celatum* have recently been described.<sup>74</sup> As with MAI infection, they are regarded as AIDS defining illnesses. Clinical presentation is similar to MAI infection with evidence of pulmonary, intestinal, liver, and bone marrow involvement. In vitro sensitivities of isolates to standard antituberculous drugs are variable. *M kansasii* is the most common of these other atypical mycobacterial infections and response to treatment remains poor. As with MAI infections, combinations of drugs are usually necessary.

#### VIRUSES AND RESPIRATORY DISEASE IN HIV INFECTION

Upper respiratory infections are generally more common in HIV seropositive than seronegative individuals.<sup>6,75</sup> Both herpes simplex and herpes zoster have been implicated in pneumonitis.<sup>76,77</sup> Clinical disease due to cytomegalovirus (most commonly retinitis) eventually occurs in 40% of HIV infected patients.<sup>78</sup> The role of this virus in causing pneumonitis remains controversial. It is a frequent isolate from bronchoalveolar lavage fluid, being found in 30–50% of samples from seropositive persons. However, the clinical course of most episodes of pneumonitis in most patients with AIDS does not seem to be related to the presence or absence of cytomegalovirus and clinical resolution occurs following antimicrobial treatments that are not effective against this virus. However, it does occasionally cause pneumonitis, either when the CD4 count is high or at or near the time of seroconversion following HIV infection.<sup>79</sup>

#### FUNGI

Pulmonary complications due to fungi are being seen increasingly, particularly as disseminated infection late in the disease. Enquiry should be made regarding travel to endemic areas. Pulmonary histoplasmosis with disseminated infection has been described in European patients.<sup>80</sup> *Cryptococcus neoformans* has a world wide distribution and is the most

common cause of meningitis in patients with AIDS. Pulmonary *Cryptococcus* can also occur and a satisfactory treatment response can be expected from fluconazole or itraconazole. In some cases amphotericin B and flucytosine is required. Like pneumocystis pneumonia, cryptococcal infection commonly relapses so that continuing suppressive treatment with fluconazole is required. A rapid diagnosis of cryptococcal infection can be made by determining cryptococcal antigen titres in blood; this can also be measured in bronchoalveolar lavage fluid where a titre of 1:8 or greater indicates the presence of infection. Infection with *Penicillium marneffei* has been described in the UK<sup>10</sup> and disseminated infection has recently been identified as the third most common opportunist infection in HIV infected patients in Thailand. Cough occurred in 50% of cases and 39% had chest radiographic abnormalities. Most recovered following treatment with amphotericin or itraconazole.<sup>81</sup> Disseminated candidiasis is occasionally seen where, generally, response to fluconazole is better than ketoconazole, amphotericin B being reserved for overwhelming infection. Treatment with liposomal amphotericin has the advantage of fewer side effects.<sup>82</sup> Long term use of the triazole drugs for suppression of fungal infections such as candidiasis may be associated with development of drug resistance.<sup>83</sup>

#### Non-specific aspects of lung disease

##### NON-SPECIFIC INTERSTITIAL PNEUMONITIS AND LYMPHOCYTIC INTERSTITIAL PNEUMONITIS

Non-specific interstitial pneumonitis still remains a poorly understood entity and is characterised histologically by diffuse alveolar damage with an interstitial inflammatory infiltrate consisting of chronic inflammatory cells. Macrophages or lymphocytes predominate and plasma cells may also be present.<sup>84</sup> Alveolar septal thickening with alveolar cell hyperplasia may also occur, as may interstitial fibrosis.<sup>85</sup> It is essentially a histological diagnosis lacking any specific aetiological features and requires tissue biopsy samples for the diagnosis to be made. There are no specific radiographic features and, as routine lung biopsy is generally avoided, there is a lack of recent specific information on this disease. In an early report<sup>84</sup> 38% of AIDS patients with episodes of pneumonitis had non-specific interstitial inflammatory changes and diffuse alveolar damage on transbronchial biopsy samples; no pathogens were isolated. In 13 of 41 patients there were no easily identifiable possible causes for the changes seen, but in the other 28 patients possible causes implicated included concomitant pulmonary Kaposi's sarcoma, previous episodes of pneumocystis pneumonia, intravenous drug use, or previous therapeutic drug regimens. In a further early study<sup>86</sup> 24 HIV seropositive individuals who either had an AIDS defining diagnosis but no clinical evidence of lung disease or CD4 counts of less than 200/mm<sup>3</sup> but no chest symptoms underwent bronchoscopy and transbronchial biopsy to detect early *Pneumocystis* infection.

None of the study group had *Pneumocystis* infection but 11 of 23 transbronchial biopsy samples showed non-specific interstitial pneumonitis. All these patients had normal chest radiographs so it would appear that the condition can be either subclinical or present with respiratory illness. Symptoms are usually mild but can resemble pneumocystis pneumonia from which this condition needs to be distinguished. Presentation may be with cough, dyspnoea, or fever. Diagnosis is made by exclusion of *Pneumocystis* infection and definitive diagnosis requires transbronchial or open lung biopsy to obtain histological evidence.<sup>13 87 88</sup> In a radiological study of 105 HIV positive patients presenting with pneumonitis 36 had non-specific interstitial pneumonitis. Eighteen of these had previous respiratory opportunist infections or were intravenous drug users, five pulmonary Kaposi's sarcoma, 20 had abnormal radiographs of which 14 showed interstitial infiltrates ranging from subtle perihilar shadows to gross bilateral infiltrates, four also had pleural effusions and three had alveolar shadowing, one patient had a nodular mass, and 16 patients had normal chest radiographs.<sup>88</sup> The clinical course is generally mild, respiratory failure is unusual, and spontaneous resolution can occur. It has been suggested that corticosteroids may lead to improvement. Lymphocytic interstitial pneumonitis, on the other hand, is usually part of a generalised non-malignant lymphoproliferative condition and is most commonly seen in children and in individuals of Afro-Caribbean descent.<sup>89</sup>

#### BULLOUS LUNG DISEASE

Bullous lung disease and emphysema have been reported in patients with HIV infection. In a retrospective review of 55 patients with AIDS who had had a computed tomographic (CT) scan of the thorax, 23 (42%) had evidence of bullous lung disease and emphysema,<sup>90</sup> which was not evident on the plain chest radiograph. The average age of the patients was 37 years, and changes seen on the CT scan included the presence of bullae or air cysts, vascular destruction, and low attenuation values in the lung fields. Sixteen of the patients had a history of one or more previous respiratory infections, 14 had had pneumocystis pneumonia, and three had no prior history of infectious complications. There were no data on pulmonary function or of  $\alpha_1$ -antitrypsin levels, and smoking and intravenous drug abuse may have been additional confounding features. In a further study<sup>91</sup> four patients who presented with breathlessness and low CD4 counts (mean of  $<100/\text{mm}^3$ ) were found to have bullae on CT scans. None of them had abnormalities on chest radiography. Pulmonary function tests showed hyperinflation with air trapping and a low transfer factor for carbon monoxide, but only minimal airflow obstruction. All were smokers but had normal  $\alpha_1$ -antitrypsin levels. None were intravenous drug users. It would therefore seem possible that bullous lung disease may complicate the clinical course in some patients.

#### Complications of pulmonary diseases in AIDS

**INTERMITTENT POSITIVE PRESSURE VENTILATION**  
Patients requiring intermittent positive pressure ventilation as a result of AIDS related pneumonia have always been reported to have a very bad prognosis<sup>92</sup> and a recent study<sup>93</sup> endorses this view, reporting an 82% mortality. The only survivors were individuals who were intubated shortly after admission at the beginning of their antimicrobial treatment. Patients in respiratory failure requiring mechanical ventilation who are most likely to benefit are those who present with pneumonia and respiratory failure who have not yet had antimicrobial treatment and steroids. Suitable patients therefore would be those with a first episode of pneumocystis pneumonia and no other serious HIV related disease, whereas patients who developed respiratory failure while on treatment are most unlikely to benefit from ventilation.

#### PRIMARY PULMONARY HYPERTENSION AND HEART DISEASE

Primary pulmonary hypertension has been reported in small groups of patients but there are difficulties in distinguishing the additional effects of intravenous drug usage in these patients. In one study six of 74 (8%) HIV infected individuals with cardiopulmonary disease were found to have primary pulmonary hypertension.<sup>94</sup> In a further study 13 patients with primary pulmonary hypertension were identified; 10 were intravenous drug users and three were homosexuals.<sup>95</sup>

Pericardial effusion is the most common cardiac abnormality seen in patients with HIV infection, being found in 72% in one echocardiographic study.<sup>96</sup> They are often subclinical, but occasionally present with tamponade. Frequently no specific cause is found.<sup>97 98</sup> Myocarditis presenting with dilated cardiomyopathy and marantic endocarditis has also been described.<sup>99</sup>

#### PNEUMOTHORAX

Pneumothorax is relatively common in patients with AIDS, occurring in about 2%. It tends to occur spontaneously but may be recurrent and difficult to manage. Pneumothoraces are normally related to active or previous episodes of pneumocystis pneumonia. Aerosolised pentamidine has been implicated.<sup>100</sup> About 95% of pneumothoraces seen in HIV seropositive patients occur in the presence of active pneumocystis pneumonia and 6–9% of patients with pneumonia develop a pneumothorax.<sup>101</sup> In one review of over 100 chest radiographs from patients with pneumocystis pneumonia 10% had cystic areas on the radiograph and 6% had a pneumothorax.<sup>102</sup> In these patients it is particularly advisable to avoid surgery and pleurodesis with tetracycline or doxycycline may be helpful.<sup>103</sup>

#### SECONDARY NEOPLASMS

Kaposi's sarcoma is the most common secondary neoplasm seen in HIV infection and

will be dealt with in a separate article in this review series.

The incidence of other forms of malignancy, in particular non-Hodgkin's lymphoma, is also increased in patients with HIV infection.<sup>104</sup> The incidence of non-Hodgkin's lymphoma is related to the duration of HIV infection. Most of these lymphomas are high grade B lymphocyte derived tumours and the Epstein-Barr virus has been implicated in their development. With increasing loss of T cell immune responses EBV infected B cells proliferate, possibly allowing the activation of oncogenes.<sup>105 106</sup> Intrathoracic involvement by AIDS related lymphoma is generally rare,<sup>106</sup> but in one series of 35 patients 11 had intrathoracic disease.<sup>107</sup> Of these 11 patients eight had pleural effusions, five had interstitial or alveolar shadows or an intrapulmonary mass, and three had hilar or mediastinal lymphadenopathy. Endobronchial lymphoma is extremely rare and only two cases have been reported.<sup>108 109</sup> Both patients had very low CD4 counts and presented with fever, cough, and dyspnoea with wheeze. Tracheal and carinal involvement were seen at bronchoscopic examination and biopsy samples obtained by rigid bronchoscopy were necessary for definitive diagnosis, fibreoptic samples being inadequate. Primary intrathoracic lymphoma without evidence of extrathoracic disease is also extremely rare, only two cases having been reported.<sup>110 111</sup> In one patient rigid bronchoscopy was necessary for diagnosis when fibreoptic biopsies were non-diagnostic. In the second patient diagnosis was only established by left lower lobectomy following a non-diagnostic percutaneous CT guided fine needle biopsy.

Despite several studies it remains unclear whether the incidence of lung cancer is increased in subjects seropositive for HIV. In a study of a large group of 1701 haemophiliacs, observed for several years, no difference was observed in the development of lung cancer between HIV infected (0.09%) and non-infected (0.15%) patients.<sup>112</sup> In a smaller study based on six HIV positive patients with adenocarcinoma of the lung it was estimated that HIV infection carried a 14-fold increased risk for lung cancer. However, this study was not controlled for factors such as age, gender, and smoking habits.<sup>113</sup> In another study of seven HIV positive patients with adenocarcinoma the HIV positive patients presented with more advanced disease, more extensive chest radiographic abnormalities, and more physical signs than the control HIV negative group.<sup>114</sup> In another study of 21 HIV positive patients with lung cancer half were under the age of 40 and all but one were smokers. Eleven patients had adenocarcinoma, six had small cell carcinoma, three squamous cell carcinoma, and one had adenosquamous cell carcinoma.<sup>115</sup> In 19 HIV positive patients with lung cancer of whom 16 were smokers, the HIV positive patients were younger than HIV negative historical control groups with a median age of 47 and had a shorter median survival of three months.<sup>116</sup> Because of problems with ascertainment in these small studies it is not

possible to reach a conclusion but, on the evidence available, it would seem that lung cancer in HIV positive individuals presents at an earlier age, is likely to be more extensive, is strongly associated with smoking, and adenocarcinoma predominates.

### The future

There is now a wealth of clinical information on the various pulmonary diseases that affect the HIV infected individual. Unfortunately therapeutic options remain limited as anti-retroviral treatment at best delays rather than prevents the progressive damage caused by infection with HIV. National programmes in many countries to prevent the spread of HIV by educational means have not been successful and an effective vaccine remains elusive. Thus, clinicians will continue to see patients where the best that can be offered is specific antimicrobial treatment for their infections or chemotherapy for palliation of their secondary neoplasms. Although much has been learnt, there is still much to be explained regarding the spectrum of respiratory disease seen in HIV infected patients. The role of many respiratory pathogens has not been fully determined, nor has the role of HIV itself. This will be the topic of the fourth article in this series.

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