

## Pulmonary infections in the tropics: impact of HIV infection

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Respiratory infections are a major cause of morbidity and mortality in persons living in tropical and developing countries. Although the number and variety of pulmonary pathogens found in tropical areas are enormous, most infections are due to routine viral, bacterial, and mycobacterial organisms. Infection with *Mycobacterium tuberculosis* is particularly common. The World Health Organisation (WHO) estimates that 8-10 million new cases of tuberculosis occur each year worldwide, and over three quarters of these cases are in the tropics.<sup>1</sup>

Infection with the human immunodeficiency virus (HIV) is also common in many tropical countries. In 1992 the WHO estimated that 9-11 million adults, mostly in developing countries, were infected with HIV.<sup>2</sup> Although AIDS is basically the same disease in all parts of the world, the prevalence of microorganisms in an environment governs the patterns of disease encountered. Thus, substantial variation occurs in the combination of diseases that predominate in different areas of the world.<sup>3</sup> Even within a given country, diseases vary depending on whether the population is urban or rural.

The overlap of HIV infection and the many pulmonary pathogens found in the tropics has made pulmonary infections a common manifestation of HIV infection. In a large study from Nairobi, Kenya pulmonary disorders accounted for 28.4% of admissions in HIV-1 seropositive patients compared with 16.5% in seronegative patients.<sup>4</sup> Although the spectrum of disease can be quite broad, most of the pulmonary infections in HIV-1 infected patients are similar to those seen in non-HIV infected individuals. The geographical differences are primarily due to varying frequencies rather than the kinds of infections.<sup>5</sup> In the USA *Pneumocystis carinii* pneumonia and bacterial pneumonia are the most common infectious pulmonary complications of HIV infection.<sup>6</sup> Tuberculosis, though increasing in the USA, is still much less common. On the other hand, in tropical countries where infection with *M tuberculosis* is highly prevalent, tuberculosis and bacterial pneumonia represent the major pulmonary infections (table 1). In a recent study from Burundi, 302 consecutive patients hospitalised for acute respiratory disease were evaluated with fiberoptic bronchoscopy.<sup>7</sup> Of the total, an astonishing 222

patients (73.5%) were HIV-1 seropositive. Tuberculosis and bacterial pneumonias were the most common pulmonary infections and occurred in approximately equal frequency in the HIV-1 seropositive and seronegative groups. Unlike in the USA, *P carinii* pneumonia occurred in only 11 (5%) HIV-1 seropositive patients.

Of all the pulmonary infections encountered in the tropics clearly *M tuberculosis* is one of the most significant pathogens. Data from sub-Saharan Africa and Haiti have shown that between 17% and 66% of tuberculosis cases are HIV-1 seropositive.<sup>2</sup> Moreover, studies of the pulmonary complications of HIV infection in Africa have noted that 50% of seropositive patients presenting with pulmonary symptoms have tuberculosis.<sup>7</sup> The significant impact of HIV on tuberculosis in developing countries will be discussed by Nunn and colleagues in another article in this series. This review will focus on the non-tuberculous pathogens affecting HIV infected patients in tropical and developing nations.

### Bacterial pneumonia

#### PNEUMOCOCCUS

Before the AIDS epidemic community acquired pneumonia was one of the most common causes of admission for acute disease in general hospitals in East Africa, accounting for 9-10% of such admissions.<sup>8,9</sup> Between 1981 and 1983 lobar pneumonia was second only to malaria as a reason for adult admissions at Kasama General Hospital in Northern Zambia.<sup>10</sup> As in the USA, *Streptococcus pneumoniae* has been the most common cause of bacterial pneumonia: in 1976, 20% of patients presenting with pneumonia to Kenyatta National Hospital had pneumococcal bacteraemia.<sup>11</sup>

Data from sub-Saharan Africa have shown that acute bacterial infections are also a leading cause of morbidity and mortality in HIV infected adults. It is estimated that acute bacterial infections account for at least one quarter of medical admissions to one of East Africa's largest hospitals.<sup>12</sup> Moreover, community acquired pneumonia accounts for 17% of admissions to the same hospital.<sup>13</sup> As in the pre-AIDS era, *Str pneumoniae* is still the most common Gram positive organism isolated.<sup>12,14</sup> In a large cohort of lower socioeconomic class

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Table 1 Spectrum of pulmonary infections among HIV-1 infected patients in sub-Saharan Africa\* (values are percentages)

Country	n	PCP	Tuberculosis	Bacterial	Fungal	Other
Zimbabwe**	35	8	12	8	2	7
Burundi	222	11	109	79	1	25
Uganda**	40	0	6	NA	2	NA
Tanzania***	125	0	65	15	0	20

PCP = *Pneumocystis carinii* pneumonia; NA = not available.

\* Studies used bronchoscopy with bronchoalveolar lavage (with or without transbronchial biopsy).

\*\* Patients with smear positive tuberculosis were excluded.

\*\*\* Unpublished data, C Daley.

female prostitutes in Nairobi, Gilks reported that invasive pneumococcal disease was the most frequently encountered serious HIV associated infection, more common than tuberculosis.<sup>15</sup>

Although some studies have not shown a difference in the rate of bacterial pneumonia among HIV-1 seropositive patients,<sup>7,16</sup> recent cohort and case-control studies have shown increased rates of disease among HIV infected individuals.<sup>12,13,15,17</sup> Gilks and colleagues noted that, not only was pneumococcal pneumonia the most common cause of community acquired bacteraemia, but it occurred at a significantly higher rate among HIV seropositive patients.<sup>15</sup> More recently they reported on 145 cases of community acquired pneumonia in Nairobi of which 104 episodes were due to *Str pneumoniae*.<sup>13</sup> Fifty two patients (50%) were HIV-1 positive compared with seven (7%) of controls (trauma victims). Similarly, Pallangyo and coworkers in Dar es Salaam, Tanzania reported that 15 out of 45 patients (33%) with pneumonia were found to be HIV-1 seropositive compared with four (9%) of the control group.<sup>17</sup> Thus clinically defined bacterial pneumonia was significantly associated with HIV-1 seropositivity.

The clinical presentation of pyogenic pneumonia is similar to that seen in HIV-1 seronegative patients. Most patients present with the acute onset of cough and fever.<sup>18</sup> Lobar pneumonia is the most common radiographic presentation;<sup>12,14</sup> all but a single patient with pneumococcal bacteraemia in one study had obvious, radiographically confirmed lobar pneumonia.<sup>12</sup> Bacteraemia is very common among HIV infected patients. Gilks and coworkers evaluated 506 consecutive admissions to Kenyatta National Hospital in Nairobi over a six month period;<sup>12</sup> 26% of the HIV-1 infected patients were bacteraemic compared with 6% of the seronegative group. In a study of community acquired pneumonia from the same investigators, bacteraemia was common in both the HIV-1 seropositive (45 of 52 patients) and seronegative patients (35 of 52).<sup>13</sup>

Response to treatment is usually good and is no different in seropositive and seronegative individuals.<sup>18</sup> Although approximately 10% of patients with lobar pneumonia in the tropics fail to improve with penicillin,<sup>19</sup> this cheap and well tolerated antibiotic is still the drug of choice for community acquired pneumonia, regardless of HIV status, in tropical and developing countries.

The mortality rate has varied significantly between studies.<sup>13,15,17</sup> Among patients with

community acquired pneumonia in Nairobi the mortality rate was higher among HIV-1 seropositive patients (17%) than seronegative individuals (8%).<sup>13</sup> However, among prostitutes in Nairobi with invasive pneumococcal disease there were no deaths reported despite 29 episodes of bacteraemia.<sup>15</sup> There was also no difference in mortality among HIV-1 seropositive and seronegative patients in a study of bacterial infections from Dar es Salaam, Tanzania.<sup>17</sup> The rate of recurrence has been shown to be increased both in the USA and in Kenya.<sup>15</sup> In a study of pneumococcal disease in prostitutes from Nairobi 22% of the patients suffered a recurrence.<sup>15</sup>

#### NOCARDIOSIS

*Nocardia asteroides* is a branching filamentous Gram positive rod which usually produces disease in immunocompromised individuals. The organism is found worldwide in soil and decaying organic matter. In a recent review of the English language literature over 40 cases of nocardiosis had been reported in HIV-1 infected patients,<sup>20</sup> although few cases have been reported from the tropics. In the earliest report of AIDS from Rwanda one of 26 patients was noted to have nocardial pleuropneumonia.<sup>21</sup> Likewise, in Zimbabwe one of 50 patients with interstitial infiltrates was found to have pneumonia due to *N asteroides*.<sup>22</sup> Miliary nocardiosis has also been identified histologically in the lungs of three of 57 AIDS patients who underwent post mortem examination in Uganda, one of 52 in Cote d'Ivoire, and in occasional Zairian patients.<sup>23</sup>

Although nocardiosis is frequently disseminated at presentation, the lung is the most common site of involvement.<sup>20</sup> Symptoms of nocardiosis in HIV-1 infected patients are usually non-specific: most patients present with fever, night sweats, malaise, cough, and weight loss. The chest radiograph is frequently notable for upper lobe, cavitary infiltrates<sup>24</sup> and is thus indistinguishable from tuberculosis.

Definitive diagnosis requires culture of respiratory specimens because blood cultures are rarely positive.<sup>20</sup> Since cultures are unlikely to be available in many areas, the diagnosis should be suspected if the characteristic morphology is seen on Gram stain; filamentous, beaded, branching Gram positive rods. In a review by Javaly and colleagues<sup>20</sup> the Gram stain was suggestive of nocardial infection in 47% of patients. The organism may also stain weakly acid fast. The radiographic presentation, coupled with the fact that the organism can stain acid fast, may cause the disease to be misdiagnosed as tuberculosis. In fact, two such cases were reported from Uganda.<sup>25</sup>

The optimum regimen and duration of therapy for nocardiosis in the setting of HIV-1 infection are not known. Sulphonamides (trimethoprim-sulphamethoxazole) have been the treatment of choice in non-HIV-1 infected patients with nocardiosis.<sup>20</sup> It is likely that these agents will also be effective in HIV-1 infected patients although the high rate of

toxicity to trimethoprim-sulphamethoxazole<sup>26</sup> may limit its use in this population. Other agents with in vitro activity to *N asteroides* include minocycline, some third generation cephalosporins, amikacin, and amoxicillin-clavulanic acid.<sup>20</sup> Some authors recommend treatment for at least 6–12 months and, perhaps, indefinitely since recurrences have been reported.

#### MELIOIDOSIS

Melioidosis is an infection caused by the Gram negative motile bacillus, *Pseudomonas pseudomallei*. The disease is endemic in south east Asia, northern Australia, and West Africa.<sup>27</sup> More than 750 cases of melioidosis have occurred in Thailand during the last decade, and over 75% of the patients were farmers. Patients may present with disseminated disease, cutaneous disease, or isolated pulmonary involvement.

In a recent review from Bangkok 49 cases of melioidosis were noted between 1975 and 1987.<sup>27</sup> Of these patients, 29 had disseminated disease and 20 had localised disease. Almost all of the patients had an underlying immunocompromising condition like diabetes mellitus, collagen vascular disease, or haematological malignancy. Only one of the cases had AIDS. The patient was a 52 year old homosexual man with a CD4 lymphocyte count of 60/mm<sup>3</sup> and left lung infiltrates who presented with recrudescence bacteraemic melioidosis.

The clinical presentation of melioidosis is non-specific so diagnosis requires isolation of the organism.<sup>27</sup> Immunocompromised patients usually present with fever and infiltrates on the chest radiograph. Radiographic presentation is non-specific and may show extensive pneumonia, diffuse infiltrates, abscess formation, or hilar adenopathy. In disseminated disease diagnosis is usually made through culture of blood and/or respiratory specimens.

*Pseudomallei* is usually sensitive in vitro to tetracycline, chloramphenicol, third generation cephalosporins, and trimethoprim-sulphamethoxazole.<sup>28</sup> If the patient is clinically toxic, two antibiotics are usually recommended during the initial 30 days followed by 60–150 days of trimethoprim-sulphamethoxazole alone. In the septicaemic form of disease trimethoprim-sulphamethoxazole and a third generation cephalosporin are recommended. For patients intolerant of trimethoprim-sulphamethoxazole another of the antibiotics listed above should be substituted.

The mortality rate in immunocompromised patients with melioidosis can be substantial, particularly if there is a delay in treatment. In one study from Thailand, of 14 immunocompromised patients with disseminated disease who had a delay in treatment or were treated inappropriately, all but one died.<sup>27</sup> Thus, early diagnosis and institution of combination antibiotic therapy is crucial.

Although melioidosis has been infrequently reported as an HIV related pulmonary complication, it should be pointed out that most HIV infected patients in Thailand are urban

dwellers and that most cases of melioidosis occur in farmers. Thus, the incidence of melioidosis should increase as the HIV epidemic spreads into rural areas.

#### Fungal pneumonia

##### CRYPTOCOCCOSIS

*Cryptococcus neoformans* is a budding encapsulated yeast which is globally distributed. Between 1981 and 1987 the prevalence of cryptococcal infection among AIDS patients in the USA was 5–7% with higher rates in regions of higher prevalence.<sup>29</sup> The prevalence of cryptococcal disease among AIDS patients in Haiti is approximately 13%. In some areas within subSaharan Africa as many as 30% of AIDS patients have cryptococcosis.<sup>30</sup> Although the portal of entry is usually the lung, most patients present with meningitis or disseminated disease: isolated pulmonary involvement is relatively unusual. Of 222 patients evaluated in Bujumbura, Burundi only one patient was diagnosed with cryptococcal pneumonia.<sup>7</sup> Two of 40 patients in a clinical study from Uganda were diagnosed with cryptococcal pneumonia.<sup>31</sup> No cases of pulmonary cryptococcosis were found in a post mortem study from Cote d'Ivoire.<sup>32</sup>

More recently, data from Rwanda suggest that cryptococcal pneumonia is not uncommon, at least in that region.<sup>33,34</sup> Between January 1990 and March 1992 28 HIV-1 seropositive patients were diagnosed with cryptococcal pneumonia. The organism was isolated from sputum, pleural fluid, and bronchoalveolar lavage fluid. The serum cryptococcal antigen was negative in all patients who did not also have an extrapulmonary site of infection.

There are two varieties of *Cr neoformans*: variety *gattii* and variety *neoformans*.<sup>35</sup> Most cases of *Cr neoformans* reported in HIV-1 infected individuals have been of the *neoformans* variety. Variety *gattii* is restricted to geographical areas mainly in tropical and subtropical areas. Since 1987 six cases of variety *gattii* have been reported from Zaire, Rwanda, and Brazil.<sup>35</sup> In one patient from Rwanda the chest radiograph revealed a right lower lung infiltrate as well as right hilar adenopathy. Fibreoptic bronchoscopy was performed when the patient did not improve with penicillin and trimethoprim-sulphamethoxazole. *Cr neoformans* variety *gattii* was isolated from the bronchoalveolar lavage fluid. Cryptococcal antigen was negative in the cerebrospinal fluid and serum.

The treatment of cryptococcosis will depend on the availability of various antifungal agents. The drug of choice in the USA has been amphotericin B, with or without flucytosine.<sup>29</sup> However, these agents are frequently not available in tropical countries. Fluconazole (400–800 mg/day) has been shown to be effective as primary treatment as well as long term maintenance therapy (200–400 mg/day).<sup>29</sup> Taelman and colleagues in Rwanda recently showed that giving itraconazole (200 mg/day) to patients with isolated pulmonary cryptococcosis prevented future dissemination.<sup>34</sup>

**HISTOPLASMOSIS**

*Histoplasma capsulatum* is a dimorphic soil dwelling fungus which is endemic in the Americas. *H. capsulatum*, rare in Africa before the AIDS epidemic, was reported in 1984 in a Zairean subject with symptoms indicative of AIDS.<sup>36</sup> The organism has also been identified in a few lungs in post mortem examination in Zaire. *Histoplasma duboisii* causes African histoplasmosis, a fungal infection occurring mainly in West and Central Africa.<sup>37</sup> Unlike cryptococcosis, which has increased dramatically since 1981, there has been no increase in African histoplasmosis in the Congo. Of 11 cases reported none occurred in an AIDS patient. There have been a few cases reported, however. Carme and colleagues recently reported a 26 year old male from Brazzaville, Congo with disseminated disease.<sup>38</sup> A white heterosexual European patient was reported with African histoplasmosis in 1987,<sup>39,40</sup> and an African child from Guinea Bissau with HIV-2 infection was reported with disseminated disease.<sup>39</sup> Three AIDS patients from Belgium who had lived in Africa developed disseminated *H. duboisii* and one of the three had pulmonary involvement.<sup>41</sup>

Amphotericin B remains the drug of choice for the treatment of histoplasmosis in AIDS.<sup>42</sup> Ketoconazole, with or without a prior course of amphotericin, has been used, but sometimes with disappointing results.<sup>29</sup> After induction therapy patients should be maintained on life-long maintenance therapy with either weekly intravenous amphotericin, oral fluconazole, or itraconazole.

**PARACOCCIDIOIDOMYCOSIS**

Paracoccidioidomycosis is caused by the dimorphic fungus *Paracoccidioides brasiliensis* and is one of the most frequent systemic mycoses in Latin America.<sup>43</sup> The disease may present with cutaneous involvement, pulmonary involvement, or dissemination. Despite its endemicity, there have been only a few cases reported involving HIV-1 infected individuals,<sup>43-46</sup> though some authors feel it is more common but not reported.<sup>43</sup> Most patients have had disseminated disease although some have had pulmonary involvement. The chest radiographs have been notable for diffuse reticulonodular infiltrates, sometimes with hilar adenopathy.<sup>44,45</sup>

Patients have been treated successfully with various regimens including amphotericin B, sulphadiazine, and imidazole compounds.<sup>47</sup> Ketoconazole (200-400 mg/day) has been used successfully to treat paracoccidioidomycosis in normal host. Itraconazole (100 mg/day) appears to be more potent than ketoconazole and studies are underway. The duration of treatment is unknown, but the recommended duration is between six and 18 months. Life-long prophylaxis is necessary and at least two patients have been placed on suppressive therapy with sulphadiazine (1-6 g/day) with good early results.

**PENICILLIUM MARNEFFEI**

*Penicillium marneffeii* is an unusual dimorphic fungus that has been reported to cause disease in both immunocompromised and normal hosts.<sup>48</sup> The fungus is endemic to south east Asia and southern China. In most of the cases reported the disease has presented as a systemic mycoses. A recent review from Thailand documents 21 cases of disseminated *P. marneffeii* in HIV infected patients.<sup>48</sup> One case has also been reported from Zimbabwe.<sup>49</sup>

Of the 21 patients reported from Thailand 11 had a cough as part of their initial presentation.<sup>48</sup> The chest radiograph was abnormal in six patients; three showed diffuse reticulonodular infiltrates, two patients had localised interstitial infiltrates, and one patient had a focal alveolar infiltrate. Diagnosis was usually made from cultures of blood, bone marrow, or skin biopsy.

Amphotericin B is the current treatment of choice and the recommended duration of treatment is 6-8 weeks for a total cumulative dose of 40 mg/kg. However, in the study cited above<sup>48</sup> nine patients were treated with 400 mg itraconazole for eight weeks and six responded well. Six of eight patients treated with amphotericin also responded well. Four patients died before treatment was begun. As with melioidosis, this infection may become more common as HIV moves into rural areas.

**Pneumocystis pneumonia (PCP)**

The taxonomy of *Pneumocystis carinii* is currently in question. Long considered a protozoa, recent data have shown that the organism is more closely related to fungi.<sup>50</sup> Nevertheless *P. carinii* is a ubiquitous organism found in every region of the world<sup>51</sup> and it is the most common infectious pulmonary complication of HIV infection in the USA: PCP develops in 75% of HIV infected patients at some time during the course of their disease.<sup>6</sup>

The frequency of PCP is, however, quite different in tropical countries. In a review of the literature Blaser and Cohn examined the reported frequencies of various HIV related complications and the way in which they differed from region to region and population to population.<sup>52</sup> The frequency of PCP (20%) reported among persons native to the tropics was significantly lower than for persons who had acquired HIV infection through blood borne or sexually transmitted routes in more developed countries. PCP was diagnosed more frequently in developed countries among natives of developed countries (73%) than among natives of the tropics (35%).

The first cases of PCP noted in African patients with AIDS were diagnosed in Europe.<sup>53</sup> Five of 23 AIDS patients reported by Clumeck and colleagues had PCP, three of whom were diagnosed at post mortem examination. PCP has been identified in 14-24% of African patients with AIDS treated in Europe and in 37% of patients with AIDS of African origin in the USA.<sup>5</sup> Whether the exposure to *P. carinii* occurred in Africa or after leaving is not known.

Table 2 Prevalence of *Pneumocystis carinii* pneumonia (PCP) in subSaharan Africa

Country	No. studied	No. (%) with PCP	Reference
Sputum induction:			
Tanzania	83	3 (3.6%)	58
Zambia	27	0	59
BAL/TBB:			
Burundi	222	11 (5%)	7
Congo	45	5 (11%)	57
Tanzania	100	0	16
Uganda	40	0	31
Zimbabwe	37	8 (22%)	49
Necropsy:			
Côte d'Ivoire	53	5 (9%)	32
Uganda	22	0	61
Uganda	57	3 (5%)	23

BAL = bronchoalveolar lavage; TBB = transbronchial biopsy.

Even before the AIDS epidemic cases of neonatal PCP were occasionally reported from the Congo<sup>54</sup> and Uganda.<sup>55</sup> Although cases suggestive of PCP were identified in two of the earliest reports of AIDS in Africa,<sup>21,56</sup> it was not until 1989 that investigators in Zimbabwe documented the first cases of PCP among AIDS patients in Africa.<sup>49</sup> McLeod and coworkers prospectively evaluated HIV-1 infected patients with clinical and radiographic evidence of lung disease. Patients with smear positive tuberculosis were excluded. Thirty seven subjects were evaluated over an 11 month period and fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsies were performed on 35 subjects. Tuberculosis was diagnosed in 12 subjects. *P. carinii* was found in only eight (22%) patients (table 2). More recently investigators in Zimbabwe reported that, of 50 patients with acute interstitial pneumonia, 17 had PCP and 16 had tuberculosis.<sup>22</sup>

Studies from other areas of Africa have reported lower prevalences of PCP ranging from 0% to 11% (table 2).<sup>7,16,31,57</sup> In a study from Mulago Hospital in Kampala, Uganda 40 patients with pulmonary disease were evaluated with fiberoptic bronchoscopy: *P. carinii* was not identified.<sup>31</sup> Nor was PCP noted in a prospective study from Dar es Salaam, Tanzania in which over 100 HIV infected patients with symptoms of pulmonary disease were evaluated.<sup>16</sup> Forty five Congolese AIDS patients at the Brazzaville University Hospital who were smear negative for tuberculosis were evaluated with bronchoscopy.<sup>57</sup> Bronchoalveolar lavage demonstrated *P. carinii* in only five (11%) cases. And finally, in Bujumbura, Burundi only 11 (5%) HIV infected patients were found to have PCP.<sup>7</sup>

Using sputum induction with hypertonic saline investigators in the Iringa district of Tanzania recently reported that three of 83 sputum specimens (3.6%) were positive for *P. carinii*.<sup>58</sup> Mycobacteria were found in 32 patients (38.5%). Of note, two of the three patients with PCP also had pulmonary tuberculosis. Twenty seven HIV seropositive patients with clinical pneumonia and symptoms of two weeks or greater duration were studied in Lusaka, Zambia with sputum induction.<sup>59</sup> Only four of the Zambian patients had something resembling trophozoites on

immunofluorescence, although no cysts were identified.

PCP has also been reported in patients infected with HIV-2.<sup>60</sup> Of 30 patients with HIV-2 infection 17 were found to have AIDS according to the criteria of the Centers for Disease Control. Eight patients with AIDS had respiratory problems: two had pulmonary tuberculosis, another had a non-tuberculous mycobacteria, two had aspergillosis (one also had tuberculosis), two had recurrent episodes of pneumonia without identification of a pathogen, and one had PCP diagnosed at post mortem examination.

Post mortem studies have demonstrated prevalences similar to those reported in clinical studies. Over a six month period in 1989 all deaths on a pulmonary medicine ward in Abidjan, Cote d'Ivoire, West Africa underwent necropsy.<sup>32</sup> Of 473 patients admitted to the hospital ward 38% were HIV-1 positive, 4% were HIV-2 positive, and 14% reacted to both viruses. A total of 100 patients (21%) died. The pathology of 78 necropsies showed, not surprisingly, that the predominant cause of death in the HIV seropositive patients (40%) was disseminated tuberculosis. Pyogenic or bronchopneumonias were the second leading cause of death. PCP was found in only 9% of the HIV infected patients who underwent necropsy. It was also identified in another patient who died of nocardiosis, providing an overall prevalence of 12%. PCP was not found in a limited post mortem series of 22 AIDS patients in Kampala, Uganda, although tuberculosis and cryptococcus were common.<sup>61</sup>

Studies from Haiti have indicated rates of PCP similar to those in subSaharan Africa. Two hundred and twenty nine patients with AIDS were studied between 1979 and 1984 in Haiti.<sup>62</sup> PCP was diagnosed in only 7% of 131 cases compared with 71% of the first 80 AIDS patients seen at the New York Hospital in New York City. Tuberculosis occurred in 31 of 131 (24%), making it the most common pulmonary pathogen.

Data from Latin America have suggested that PCP occurs at a rate intermediate to that seen in Africa and the USA. In Brazil, of 2135 adult patients with AIDS the most common presenting diagnosis was PCP which occurred in 425 cases (20%).<sup>63</sup> Another 265 (12%) cases had PCP plus another infection. The next most common diagnosis was *M. tuberculosis*. In southern Brazil 45% of homosexual urban AIDS patients were diagnosed with PCP.<sup>64</sup>

The clinical and radiographical presentation of PCP appears to be similar among the different regions. However, the frequent occurrence of tuberculosis in developing countries makes differentiation of the two diseases difficult. Clinical features most consistent with a diagnosis of PCP in one study were a respiratory rate of over 40/min.<sup>22</sup> In contrast, coarse reticulonodular infiltrates on the chest radiograph favoured tuberculosis. The treatment of choice is trimethoprim-sulphamethoxazole. Other antipneumocystis agents are often not available in tropical areas.

As noted above, there are wide variations in

the prevalence of PCP throughout the world, and even among different regions of sub-Saharan Africa. The lower rates seen in Africa and Haiti could be related to a number of factors including absence of the organism from the environment, less exposure to the organism, difference in host susceptibility, earlier deaths in AIDS patients due to more pathogenic organisms like *M tuberculosis*, or the lack of diagnostic facilities. It should be clear from the clinical and post mortem studies mentioned above that, when these diagnostic facilities are available, PCP is found much less frequently in sub-Saharan Africa than in North America or Europe.

The organism *P carinii* is not only found in the environment; exposure appears to be similar worldwide. Wakefield and colleagues studied 150 subjects from Gambia and the UK using an ELISA of human immunoglobulin responses to rat derived *P carinii*.<sup>65</sup> The prevalence of significant titres of antibody to *P carinii* steadily increased with age and included more than 70% of both populations by eight years of age. Recently, Smulian and colleagues studied both HIV-1 seropositive and seronegative patients from five different regions of the world.<sup>51</sup> They showed that *P carinii* was highly prevalent in the USA, Haiti, Mexico, Africa, and Korea. The seroprevalence was 82.8% in the three regions studied in Africa (Zaire, Kenya, South Africa). Haiti had the lowest seroprevalence rate at 63.8%. Despite the high *P carinii* seroprevalence rate noted in Kenya, PCP could not be induced in a corticosteroid immunosuppressed mouse model by investigators in Nairobi.<sup>66</sup>

It has also been postulated that AIDS patients in the tropics die before they become immunocompromised enough to develop PCP.<sup>32,59,67</sup> While this may be true, since HIV infected patients in developing nations do not live as long as patients in more developed countries,<sup>63,68</sup> it is not the only answer. Cryptococcal meningitis usually occurs around the same level of immunosuppression and this manifestation of AIDS is quite common in some parts of Africa.<sup>61</sup>

### Parasitic pneumonia

#### STRONGYLOIDIASIS

Despite the many parasitic diseases endemic to tropical and developing nations, very few have been reported to cause pneumonia in HIV infected patients. *Strongyloides stercoralis*, a helminth which is common in many tropical and subtropical areas, has occasionally been reported as the cause of pulmonary disease. The prevalence of this organism in stool samples varies from region to region: USA, 0.4–4.0%; Brazil, 15–82%; Ecuador, 1–16%; sub-Saharan Africa, 26–48%.<sup>69</sup> In a study of 100 AIDS patients from Brazil, 10% had *S stercoralis* isolated from a stool sample.<sup>70</sup> Similarly, in Zambia, of 63 HIV seropositive patients evaluated for chronic diarrhoea 6% had *S stercoralis* isolated: none were isolated from the HIV-1 negative controls.<sup>71</sup>

Despite the prevalence of the helminth in

tropical and temperate countries there have been relatively few cases reported in AIDS patients. There have been several case reports of *S stercoralis* hyperinfection from the USA and Europe,<sup>72,73</sup> countries where the prevalence of strongyloides infection is relatively low. Extraintestinal strongyloides has been infrequently reported from Africa.<sup>56,74</sup> The prevalence of strongyloides infection is also high in south east Asia but no cases have been reported in the English language literature. From Latin America there has been one report each from Guatemala,<sup>75</sup> Brazil,<sup>76</sup> and Mexico.<sup>77</sup> A Colombian man in the USA<sup>78</sup> and a Brazilian in the UK<sup>79</sup> were also diagnosed with the hyperinfection syndrome.

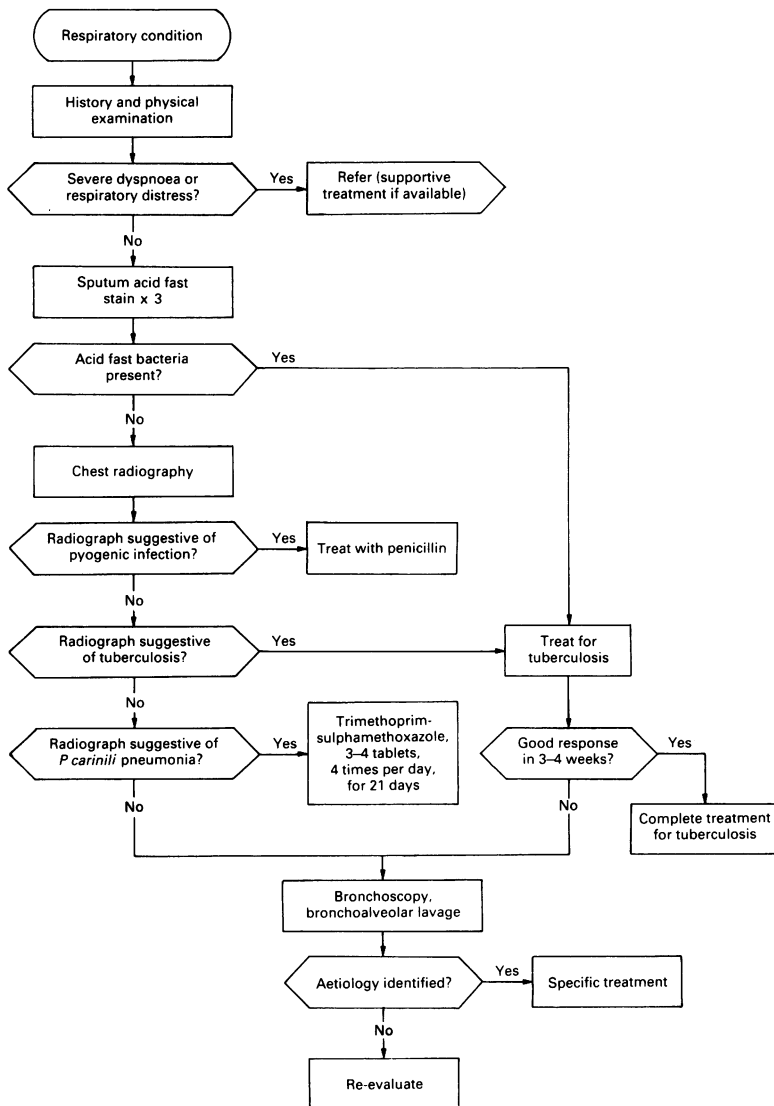
Most patients with hyperinfection present with fever, cough, and shortness of breath. Chest radiographs usually show diffuse infiltrates.<sup>79</sup> The diagnosis has been made by finding the helminth in respiratory specimens and/or stool. Enteric organisms like *E coli* can often be isolated in the blood or cerebrospinal fluid. At least two cases with strongyloides hyperinfection had concomitant PCP.<sup>72,78</sup>

The treatment of choice of strongyloides hyperinfection is thiabendazole, 25 mg/kg twice daily.<sup>79</sup> The duration of treatment in HIV-1 infected patients is unknown. In one review of the literature the only surviving patient was treated for five days with three courses 10 days apart followed by monthly courses of thiabendazole.<sup>79</sup> Most patients have died either directly or indirectly from their infection. Despite the rarity of clinically significant strongyloides infection in HIV infected individuals, it seems prudent to treat any patient who has the helminth isolated in the stool.

### Pleural effusions

Tuberculosis was the predominant cause of pleural effusions in Africa before the AIDS epidemic.<sup>80,81</sup> Limited data suggest that the same is true today among HIV-1 infected patients. An increasing number of pleural effusions were noted over an eight year period in the Department of Internal Medicine of the Centre Hospitalier de Kigali, Rwanda.<sup>82</sup> A total of 127 patients with pleural effusions of undetermined aetiology were enrolled in a prospective study. Pleural tuberculosis was diagnosed in 110 (86%) patients and confirmed histologically and/or bacteriologically in 90 (82%). Of the 90 patients tested for HIV-1 infection, 82 (83%) were positive. This is similar to data from Zambia where tuberculosis patients with pleural effusions were found to be HIV-1 seropositive in 81% of cases.<sup>83</sup>

Only five patients (4%) in the study from Rwanda had a non-tuberculous parapneumonic effusion.<sup>82</sup> *Escherichia coli* and salmonella B were cultured in one of these patients. Malignant effusions were diagnosed in six (5%) of the patients: three with Kaposi's sarcoma and one with lymphoma were HIV-1 seropositive; two with carcinoma were HIV-1 seronegative. In Bujumbura, Burundi radiographically apparent pleural effusions were noted in nine



Simplified algorithm for dealing with respiratory problems in patients with HIV infection. Reproduced from ref. 84 with permission.

of 79 patients with pneumonia: eight HIV-1 seropositive and one seronegative patient.<sup>7</sup> Only two cases of empyema in seropositive patients were reported.

Since most pleural effusions in HIV-1 seropositive persons are caused by tuberculosis, patients should be examined accordingly. Pleural fluid and tissue specimens should be sent for acid fast bacilli smear and culture, if possible. In any patient in whom the diagnosis is in doubt, empirical treatment for tuberculosis should be commenced.

#### Evaluation of HIV infected patients with pulmonary disease

The evaluation of respiratory symptoms in HIV infected patients in the tropics will depend on the diagnostic and laboratory facilities available, as well as the prevalence of specific pathogens in the environment. The WHO has developed a diagnostic algorithm for dealing with respiratory problems in patients with HIV infection (figure).<sup>84</sup> In certain areas where more elaborate diagnostic facilities are available the algorithm can be modified.

Since most patients in tropical and develop-

ing countries will have bacterial pneumonia or tuberculosis, the diagnostic evaluation should focus on these pathogens. As noted in the figure all patients should be evaluated for acid fast bacilli in their sputum. For patients with a clinical and radiographical presentation consistent with bacterial pneumonia, penicillin should be started. If the sputum is smear negative for acid fast bacilli, and the patient is unlikely to have bacterial pneumonia or tuberculosis on clinical grounds, bronchoscopy should be considered to rule out opportunistic infections. Where these facilities are not available, patients should be treated empirically for tuberculosis. In areas where PCP has been documented to occur, empirical treatment with trimethoprim-sulphamethoxazole should also be considered. Although not widely available, the use of sputum induction could be helpful in patients who are not producing sputum spontaneously.

As noted above, since most pleural effusions in HIV infected patients are caused by tuberculosis, pleural fluid and sputum should be examined for the presence of acid fast bacilli. Unless a bacterial empyema is discovered, treatment for tuberculosis should be begun until cultures have returned or the patient has shown clinical improvement.

Because of the lack of diagnostic facilities in many areas of the developing world, more unusual pathogens may be difficult to diagnose. Fortunately, due to the rarity of these infections, sophisticated facilities are seldom needed. For now, physicians caring for HIV infected patients in the tropics or returning from the tropics should be familiar with the more common manifestations of the pulmonary complications of HIV infection. Tuberculosis and bacterial pneumonias are clearly the most frequently encountered pulmonary diseases. However, as the HIV epidemic moves into rural areas the spectrum of disease is likely to change, with some of the more unusual pathogens – for example, melioidosis, *Penicillium* sp – becoming more common. Continued surveillance is therefore necessary so that diagnostic and treatment algorithms can be modified as necessary.

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