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# Pulmonary manifestations of HIV/AIDS in the tropics

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The impact of the worldwide AIDS epidemic is felt most heavily in the developing world. Of the estimated 36.1 million people infected with HIV approximately 90% live in tropical regions of sub-Saharan Africa, Southeast Asia, and Latin America [1]. Despite this fact, the focus of most AIDS research has been in Northern, industrialized countries where the spectrum of opportunistic infections is different from that seen in the tropics [2]. The most dramatic differences are seen in the pulmonary manifestations of HIV. Opportunistic pathogens such as *Pneumocystitis carinii* and atypical mycobacteria, which play a significant role in North America and Europe, contribute far less to clinical morbidity and mortality in tropical regions than the more virulent organisms *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* [3]. Other pathogens and malignancies contribute to pulmonary disease in HIV-infected populations in the tropics. Diagnostic difficulties and low research priority given to these entities likely contribute to an underestimation of their significance.

## Tuberculosis

### *Epidemiology*

Dual epidemics of AIDS and tuberculosis (TB) are concentrated in tropical regions. One third of the worldwide HIV-infected population is co-infected with *M tuberculosis* [4]. As indicated in Table 1, 80% of all new TB cases annually occur in 23 countries located in Southeast Asia, the Western Pacific, and Africa [5]. It is estimated that 8% of patients diagnosed with active TB are co-infected with HIV (Table 2) [6]. In some African countries as many as 70% of individuals with TB are also HIV infected [7]. Contrary to the trend in industrialized countries, the total number of new TB cases continues to rise and is expected to increase most dramatically in regions most devastated by HIV [5].

HIV infection alters the epidemiology of TB by promoting the progression from latent to active disease in co-infected individuals. HIV is the most important risk factor for reactivation of latent TB to active disease. The annual risk of developing TB in a co-infected individual ranges from 5% to 15% [7]. Additionally, the transmission of tubercle bacilli to the general population is facilitated by the development of TB in patients who develop TB as a result of HIV infection [8]. TB infection has been associated with increased levels of cellular activation markers, which lead to increases in HIV viral load and lower CD4 lymphocyte cell count [9]. The exacerbated immune dysfunction in co-infected individuals results in higher overall death rates [10].

### *Diagnosis*

The sensitivity of traditional diagnostic modalities such as tuberculin skin testing, chest radiography, and sputum smear analysis is diminished with progression of immune dysfunction [10]. This makes

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Table 1
Estimated incidence of tuberculosis: 23 high-burden countries, 1999

| | | | Number estimated | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | All cases | | Smear-positive changes | | | |
| | Country (ranked by burden) | Population (1000s) | Thousands | Rate per 100,000 pop | Thousands | Rate per 100,000 pop | Cumulative incidence (%) | Change in rank 1997 to 1999[a] |
| 1 | India | 998,056 | 1847 | 185 | 827 | 83 | 22 | 0 |
| 2 | China | 1,266,838 | 1300 | 103 | 584 | 46 | 37 | 0 |
| 3 | Indonesia | 209,255 | 590 | 282 | 265 | 127 | 44 | 0 |
| 4 | Nigeria | 108,945 | 327 | 301 | 142 | 130 | 48 | 2 |
| 5 | Bangladesh | 126,947 | 306 | 241 | 138 | 108 | 52 | − 1 |
| 6 | Pakistan | 152,331 | 269 | 177 | 121 | 79 | 55 | − 1 |
| 7 | Philippines | 74,454 | 234 | 314 | 105 | 141 | 58 | 0 |
| 8 | Ethiopia | 61,095 | 228 | 373 | 96 | 157 | 61 | 1 |
| 9 | South Africa | 39,900 | 197 | 495 | 80 | 201 | 63 | − 1 |
| 10 | Russian Federation | 147,196 | 181 | 123 | 81 | 55 | 65 | 1 |
| 11 | DR Congo | 50,335 | 151 | 301 | 65 | 130 | 67 | 1 |
| 12 | Vietnam | 78,705 | 149 | 189 | 67 | 85 | 69 | − 2 |
| 13 | Kenya | 29,549 | 123 | 417 | 51 | 173 | 70 | 2 |
| 14 | Brazil | 167,988 | 118 | 70 | 53 | 31 | 72 | − 1 |
| 15 | UR Tanzania | 32,793 | 112 | 340 | 47 | 145 | 73 | − 1 |
| 16 | Thailand | 60,856 | 86 | 141 | 38 | 62 | 74 | 0 |
| 17 | Mozambique | 19,286 | 79 | 407 | 33 | 169 | 75 | 9 |
| 18 | Myanmar | 45,059 | 76 | 169 | 34 | 76 | 76 | − 1 |
| 19 | Uganda | 21,143 | 72 | 343 | 31 | 146 | 77 | 0 |
| 20 | Afghanistan | 21,923 | 71 | 325 | 32 | 146 | 77 | − 2 |
| 21 | Zimbabwe | 11,529 | 65 | 562 | 26 | 226 | 78 | 0 |
| 22 | Cambodia | 10,945 | 61 | 560 | 27 | 251 | 79 | 0 |
| 23 | Peru | 25,230 | 58 | 228 | 26 | 102 | 80 | − 3 |
| | Total, 23 high-burden Countries | 3,760,358 | 6700 | 178 | 2969 | 79 | 80 | |
| | Global total | 5,975,045 | 8417 | 141 | 3724 | 62 | 100 | |

The global tuberculosis burden is concentrated in tropical countries.
*From* Anonymous. Global tuberculosis control. WHO report, 2001. Geneva: World Health Organization, 2001; with permission.
[a] Change in rank resulting from re-estimation of incidence. A positive value indicates that a country has moved up the table.

diagnosis of both latent and active TB more difficult among those co-infected with HIV.

Despite the high risk for reactivation, the diagnosis of latent TB is not generally emphasized in developing countries. Traditionally, the emphasis in resource-poor settings has been the detection of active cases among people presenting to health authorities with suggestive symptoms (eg, chronic cough) [4,11]. Some authorities have argued that intensified screening efforts in populations with high HIV prevalence would help to interrupt further transmission by maximizing opportunities to treat infectious cases [4,12,13].

*Treatment*

The treatment of TB is equally efficacious in HIV-infected and non–HIV-infected individuals. Several series of patients co-infected with HIV and drug-susceptible TB show an excellent response to antituberculosis treatment when regimens containing isoniazid and rifampin are used [14]. Reports from Africa suggest that regimens containing thiacetazone are less potent than those containing rifampin [10]. In developing countries, increased rates of adverse reactions, especially Stevens-Johnson syndrome, have been described in association with thiacetazone. For this reason, thiacetazone is not recommended for use in areas where there is a high prevalence of HIV infection [14]. Rifamycin-containing regimens are more effective than non–rifamycin-containing regimens, allowing a shorter duration of therapy with more tolerable drugs and producing lower rates of treatment failure and relapse [15,16].

The optimal duration of treatment for HIV-related TB with a rifamycin-containing regimen remains

Table 2
Estimates of tuberculosis burden by WHO region, 1997

| WHO region | MTB/HIV Co-infection | HIV-positive TB cases |
|---|---|---|
| Africa | 7,302,000 | 515,000 |
| The Americas | 510,000 | 25,000 |
| Eastern Mediterranean | 107,000 | 16,000 |
| Europe | 84,000 | 10,000 |
| Southeast Asia | 2,364,000 | 64,000 |
| Western Pacific | 307,000 | 9,000 |
| Total | 10,675,000 | 640,000 |

TB = tuberculosis; WHO = World Health Organization
*Data from* Dye C, Scheele S, Dolin P, et al. Concensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Report. JAMA 1999;282: 677–86.

controversial [15]. In a study from Zaire, the cure rate of a 6-month regimen was equivalent in HIV-infected and uninfected patients; however, the administration of isoniazid plus rifampin for an additional 6 months was associated with a decreased rate of apparent relapse [14,17]. Current recommendations from the Centers for Disease Control (CDC) in the United States are 6 months of therapy for most patients and 9 months of therapy for those with ongoing clinical signs or with a positive culture after 2 months of therapy [15,18].

The advent of highly active antiretroviral therapy (HAART) has dramatically improved the clinical outcome of HIV infection, decreasing death and opportunistic infections by 60% to 90% [19]. The initiation of HAART prior to the completion of antituberculosis therapy improves the survival of patients co-infected with HIV [20]. A recent study in South Africa demonstrated that treatment with antiretroviral therapy significantly reduces the incidence of TB, even in communities in which TB rates are among the highest in the world. In fact, the use of HAART may be a powerful strategy for the control of HIV-associated TB [21,22]. The success of the directly observed therapy short course (DOTS) strategy for treating TB could serve as a model for implementing HAART in developing countries [23].

Because of possible drug interactions, dose adjustments may be necessary when HAART is administered with rifamycin-based regimens for the treatment of TB. Rifampin is a potent cytochrome P450 inducer that can cause enhanced drug metabolism in patients and may lead to sub-therapeutic levels of many protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [18,21,24]. The CDC recommends the use of rifampin in limited situations in patients on HAART regimens, including (1) efavirenz (600 to 800 mg) and two nucleoside reverse transcriptase inhibitor (NRTIs), (2) ritonavir and two NRTIs, and (3) combination of the two protease inhibitors ritonavir and saquinavir (at a dose of 400 mg twice daily of both drugs) [21,24]. The CDC also recommends the use of rifabutin, a less potent inducer of cytochrome P450, as a substitute for rifampin for TB patients on HAART [18,22]. Although it is expensive and not readily available in most tropical countries, rifabutin potentially allows for more treatment options in patients receiving HAART. Recommendations regarding dose adjustments of rifabutin are listed in Table 3. HAART is often started after the completion of 1 to 2 months of antituberculosis therapy to minimize drug toxicities and paradoxical reactions [15]. A recent CDC study suggests that once or twice weekly therapy including isoniazid and a rifamycin increases the risk for acquired rifamycin resistance among TB patients with advanced HIV. Until data become available, CDC recommends that persons with HIV-TB and CD4 cell counts $<100/mm^3$ should not be treated with highly intermittent (ie, once or twice weekly) regimens. These patients should receive daily therapy during the intensive phase and three doses a week during the continuation phase. In this group of patients, CDC recommends directly observed therapy [103].

### *Latent tuberculosis*

Given the high incidence of TB reactivation among patients co-infected with HIV, some researchers have advocated efforts to target and effectively treat latent infection [11]. In most developing countries, however, limited resources could potentially hinder efforts to treat all targeted individuals. This potential limitation has prompted efforts to identify shorter, simplified alternatives to the standard 9-month regimen of isoniazid (INH). Data derived from studies performed in Africa and North and South America support the conclusion that a 2-month regimen of rifampin and pyrazinamide is similarly efficacious to a 9-month regimen of isoniazid in preventing TB progression in HIV-infected, PPD-positive adults [25,26]. Though the short course regimen was well tolerated in HIV-infected individuals [25–27], recent reports of fatal hepatotoxicity amongst non-HIV-infected individuals highlight the need for caution [28]. Additional studies

Table 3
Recommended doses of rifabutin and antiretroviral drugs in combined therapy

| Antiretroviral regimen | Rifabutin dose | Antiretroviral dose adjustment |
|---|---|---|
| Protease inhibitor regimens | | |
| Nelfinavir, indinavir, or amprenavir (+2 nucleosides[a]) | Decrease to 150 mg if rifabutin is given daily; use 300 mg for intermittent therapy[b] | Nelfinavir; use 1250 mg q 12 h<br>Indinavir; consider increase to 1000 mg q 8 h[c]<br>Amprenavir; no change |
| Saquinavir (+2 nucleosides) | 300 mg daily or intermittent | Consider increase to 1600 mg q 8 h |
| Ritonavir (+2 nucleosides, other protease inhibitors, and/or nonnucleosides) | Decrease to 150 mg twice weekly[c] | None |
| Lopinavir/ritonavir (+2 nucleosides and/or a nonnucleoside reverse-transcriptase inhibitor) | Decrease to 150 mg twice weekly | None |
| Nonnucleoside reverse-transcriptase inhibitor regimens | | |
| Efavirenz (+2 nucleosides) | Increase rifabutin to 450–600 mg, either daily or twice weekly | None |
| Nevirapine (+2 nucleosides) | Use 300 mg, either daily or intermittently | None |
| Nucleoside regimens | | |
| Dual or triple nucleoside (eg, zidovudine, lamivudine, and abacavir) | Use 300 mg, either daily or intermittently | None[d] |

*Data from* Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. Am J Respir Crit Care Med 2001;164:7–12.

[a] Hydroxyurea is not recommended, since netropenia is a side effect of both rifabutin and hydroxyurea.

[b] Intermittent; twice- or trice-weekly directly administered therapy.

[c] With this rifabutin dose reduction, it is advisable to have the care provider administering directly observed therapy check adherence with ritonavir-based antiretroviral therapy.

[d] Rifampin decreases concentrations of zidovudine and probably abacavir. The clinical relevance of these changes is unclear, but it seems prudent to use rifabutin with triple-nucleoside therapy.

are needed to determine the optimal duration of treatment for latent TB infection.

## Bacterial pneumonias

### *Pneumococcal pneumonia*

Pneumococcal pneumonia is a leading HIV-related problem in both industrialized and developing countries. In developing regions, however, pneumococcus tends to be more clinically significant than the major opportunistic pathogens commonly seen in the industrialized world. This discrepancy is partially explained by the high background presence of the pneumococcus in poverty stricken, overcrowed, and unsanitary environments [2–4].

Irrespective of HIV status, the most common reason for hospital admission secondary to pneumococcal infection is acute community-acquired pneumonia, which is defined as acute cough, fever lasting >1 month, and clinical signs of consolidation [29,30]. Data from a cohort study of predominantly HIV-1-infected female sex workers in Nairobi, Kenya did, however, reveal a wide spectrum of HIV-related pneumococcal diseases. While 56% of cases were pneumonia, sinusitis was seen in 30% of cases and occult bacteremia in the absence of pneumonia was seen in 11% of cases [31]. Other African studies have shown higher nasopharyngeal carriage rates in HIV-infected adults (21% to 25%) versus comparable non-HIV-infected controls (12% to 14%) [29]. This difference might be partially responsible for the high risk of developing invasive pneumococcal disease in patients who are co-infected with HIV. The annual rate of invasive disease amongst the Nairobi cohort was 4.25% [31].

Successful treatment of HIV-related pneumococcal infection requires timely diagnosis and administration of appropriate therapy. Low mortality rates

have been reported under optimal study conditions when appropriate treatment with standard regimens is instituted [32]. When presentation is delayed and pulmonary disease is well established, however, mortality may be twice that seen in patients with pneumococcal pneumonia who are not HIV infected. Mortality rates in excess of 15% have been reported in hospitalized young African adults with underlying HIV infection [3].

High rates of morbidity and mortality in developing countries have prompted calls for the use of pneumococcal vaccination in HIV-infected individuals, which is standard practice in North America and Europe. A prospective study of 1392 HIV-1–infected adults in Entebbe, Uganda, however, found the 23-valent pneumococcal polysaccharide vaccine to be ineffective, prompting researchers to question its benefit [32].

*Pneumocystitis carinii pneumonia*

Fungal-related *P carinii* pneumonia (PCP) is found in every region of the world. Despite its ubiquitous nature, PCP is a less frequent cause of opportunistic disease in tropical regions than the industrialized world [2,33,34]. Data from the CDC indicate that in the United States from 1992 to 1997 PCP was the first opportunistic infection to occur in 36% of patients, and it was the most common opportunistic infection that occurred among persons who had died of AIDS [35]. Various studies in Africa, on the other hand, have reported PCP prevalence ranging from 0% to 11% [33]. Data from Haiti indicate similarly low rates; one study reported PCP in 7% of 131 cases [36].

Definitive diagnosis of PCP often requires access to specialized equipment and personnel, which are likely unavailable in resource-poor environments. Additionally, distinguishing between PCP and disseminated TB on clinical and radiographic grounds can be difficult. One study in Zimbabwe did note the presence of a respiratory rate of greater than 40 breaths/minute to be a powerful bedside predictor of PCP in 64 HIV-infected patients hospitalized with acute diffuse pneumonia [37].

The current standard regimen for primary prophylaxis against PCP in the United States is with the relatively inexpensive drug combination trimethoprim–sulfamethoxale (TMP–SMX) taken three times a week. This regimen is generally initiated when CD4 lymphocyte cell counts fall below 200/mm$^3$ or when patients show evidence of oral candidiasis. While adverse reactions are common, TMP–SMX is more effective than alternative, more expensive agents such as dapsone, pyrimethamine, atovaquone, or aerosilezed pentamidine. TMP–SMX has the additional advantage of providing protection against toxoplasmosis and bacterial respiratory and enteric pathogens [38]. The first treatment option for active disease is 21 days of TMP–SMX and steroids in either oral or intravenous form, depending on the severity of the illness. Alternative treatment regimens employ dapsone plus trimethoprim, clidamycin plus primaquine, atovaquone, or aerosolized pentamidine.

*Nocardiosis*

Nocardia are filamentous, gram-positive, weakly acid-fast rods found worldwide in soil and decaying organic matter. Infection most frequently occurs in immunocompromised hosts. Accurate prevalence data in tropical regions are obscured by variability in study design as well as a clinical, radiographic, and histologic presentation that is often similar to that of TB [33,39,40]. An autopsy study of HIV-positive cadavers in West Africa revealed that 10 of 247 (4%) had nocardiosis of the lung while 87 (35%) had pulmonary TB, yielding a ratio of 1:9 [39]. A prospective study in South Africa, by contrast, calculated 90 cases of pulmonary TB for each norcardial infection in HIV-infected individuals [41].

Although nocardiosis can involve any organ and is frequently disseminated at presentation, the most common site of involvement is the lung [42]. Symptoms in HIV-infected individuals are often nonspecific and can include cough, dyspnea, fever, night sweats, and weight loss [33,40,43]. Chest radiographs frequently reveal upper lobe and cavitary infiltrates [33]. Isolation of the slow-growing nocardia organisms is difficult; detection rates using conventional methods for aerobic respiratory pathogens have reportedly been as low as 15% [41]. Additionally, because the organism can stain acid fast, misdiagnosis is a possibility, especially in regions with high TB prevalence [39–41]. Physicians in tropical regions should maintain a high index of suspicion for nocardiosis, especially in patients who do not respond to antituberculosis medication.

Once diagnosed, nocardial infection is potentially treatable with a number of oral antimicrobial agents. While treatment with sulphonamides such as TMP–SMX for up to 12 months is standard, resistant strains have been reported [41]. Other agents with in vitro activity against nocardia include minocycline, amikacin, and some third-generation cephalosporins [33].

*Melioidosis*

Melioidosis is an infection caused by *Pseudomonas pseudomallei*, a gram-negative, motile bacillus found endemically in Southeast Asia, Northern Australia, and West Africa. Most reported cases are from rural Thailand and involve farmers. Conditions associated with diminished cellular immunity, including AIDS, have been associated with disseminated disease. Patients might also present with localized infection of the pulmonary parenchyma, pleura, or soft tissue [44]. Association between melioidosis and HIV infection has not been found in endemic urban areas [45].

Clinical presentation depends upon the site of infection. Pulmonary involvement ranges from isolated areas of pneumonitis to extensive pneumonia, pulmonary hemorrhage, abscess formation, pleural disease, and hilar adenopathy [44]. The organism can be isolated from blood and sputum specimens and is usually sensitive to TMP–SMX, tetracyclines, chloramphenicol, and third-generation cephalosporins. Early double antibiotic coverage is recommended in the first 30 days of treatment and can be extended with a single agent for up to 6 to 9 months depending on disease severity. Less severe localized forms can be treated adequately with 1 to 2 months of therapy [44].

*Rhodococcus equi infection*

*Rhodococcus equi* is a pleomorphic, gram-positive rod that can cause suppurative bronchopneumonia in horses, calves, swine, and sheep. The organism is a soil saprophyte and is ubiquitous in nature [46]. Human infections have been described in Uganda and Zimbabwe [47,48]. Cavitary pneumonia is the most common reported presentation of *R equi* in HIV-infected individuals, occurring in up to 90% of cases. Extrapulmonary forms such as localized lymphadenopathy and chronic febrile diarrhea have, however, been reported. *R equi* is a facultative, intracellular pathogen that causes granuloma formation that can progress to caseating necrosis, mimicking both TB and nocardiosis [49]. Although *R equi* grows well on routine culture media it can resemble common diphtheroids and might be erroneously discarded [47]. *R equi* is susceptible to several antibiotics. Eryhromycin and rifampin are recommended for treatment of severely ill patients. Vancomycin can be used in patients who have erythromycin intolerance. Penicillin and other β–lactams are not recommended [49]. Treatment is usually recommended for 4 to 6 weeks. Because mortality rates of 50% have been reported in HIV-infected individuals, surgical resection should be considered in patients with localized disease who are refractory to antibiotic treatment [50].

**Non-tuberculosis mycobacterial diseases**

Disseminated *Mycobacterium avium* complex (MAC) infection is the most common systemic bacterial infection in HIV-infected persons [14]. The frequency of MAC infections in tropical areas is, however, much lower than in industrialized Northern countries [34,51]. An international survey of HIV-infected individuals with CD4 lymphocyte counts $< 200/mm^3$ revealed that the rates of disseminated MAC in Trinidad and Kenya are 2.4% and 2.6%, respectively. The same study found that rates in the Northern hemisphere ranged from 10.5% to 21.6% [51]. A separate study of 50 cases of advanced HIV disease in Uganda detected no cases of MAC bacteremia. Reported infection rates in Mexico (5% to 6%), Brazil (2%), and Guinea-Bissau (8%) are similarly low [34,51,52].

The risk of developing MAC rises with severe cell-mediated immunodeficiency. Eventually all untreated HIV-infected individuals will develop disseminated MAC disease [53]. It has been postulated that many AIDS patients in Africa do not survive long enough for MAC infection to be develop, however [34]. Symptoms of disseminated MAC are non-specific and can include fever, fatigue, weight loss, night sweats, and chronic diarrhea. Hepatosplenomegaly and mediastinal lymphadenopathy are common. Frequently occurring laboratory abnormalities are elevated alkaline phosphatase levels and leukopenia. Localized disease, including endobronchial lesions, isolated pulmonary parenchymal disease, and terminal ileitis is less common, though it can be present in those with less advanced immunodeficiency [14]. In such instances the organism can be isolated from respiratory or gastrointestinal specimens. Mycobacterial blood cultures are usually diagnostic in cases of MAC dissemination.

First-line therapy for MAC includes a combination of a new macrolide, rifabutin, and ethambutol. Long-term treatment is standard. Other rifamycins and clofazimine are therapeutic alternatives [14]. Besides MAC, many other non-tuberculous mycobacteria of undetermined clinical significance have been infrequently reported in association with HIV infection [54]. Combination treatment options for these non-tuberculous, non-MAC mycobacteria vary according to the organism [14].

## Fungal respiratory infections

### *Cryptococcosis*

*Cryptococcus neoformans* is a budding, encapsulated yeast found worldwide in bird droppings, decaying fruit, and soil. With the advent of AIDS, cryptococcosis has become increasingly common. Prevalence data indicate rates of infection as high as 30% in areas of Western Africa, 13% in Haiti, and 10% in Thailand [33,55]. While the disease is acquired by inhalation and the primary site of involvement is the lung, the organism has a predilection for CNS tissue. Up to 90% of cases exhibit meningeal involvement [56]. Presentation is nonspecific, however, and up to half of patients will exhibit some respiratory symptoms including minimally productive cough, dyspnea, and chest pain. Cyptococcal infection should be considered in HIV-infected individuals presenting with fever, subacute headache, and respiratory symptoms. Radiographic findings are equally nonspecific and can include diffuse interstitial infiltrates in a pattern similar to that seen in PCP and localized interstitial, alveolar, or nodular involvement [57]. Serum cryptococcal antigen is highly sensitive and specific. Bronchoalveolar lavage will often show organisms on direct smears or by culture, though negative studies cannot be used to exclude infection. Treatment regimens continue to evolve and will likely depend on antifungal agent availability. Standard regimens include induction therapy with intravenous Amphotericin B with or without flucytosine in patients who are severely ill and the less toxic oral agent fluconazole in patients who are less severely ill. Following successful induction, patients with AIDS require lifetime maintenance therapy with fluconazole to prevent disease relapse.

### *Histoplasmosis*

*Histoplama capsulatum* is a thermal, dimorphic fungus found in soil that is enriched by bird or bat droppings. The organism is found in both temperate and tropical climates worldwide with endemic areas concentrated along river valleys. Based on skin test surveys, prevalence among the general population in areas of Central and South America can be as high as 40%. While Southeast Asian and African populations are also endemically affected, prevalence rates tend to be much lower [58]. *Histoplasma capsulatum var duboisii* is a variant found only in Africa, mainly in Western and Central regions of the continent [33].

While this infection is almost always self-limited in normal hosts, patients with AIDS are at risk for uncontrolled progressive dissemination due to impaired T-cell response. The most common mechanism of infection is primary infection, though some cases probably result from reactivation of latent disease [57]. Subacute onset of fever accompanied by weight loss are the most frequent presenting symptoms. With disease progression respiratory symptoms such as cough and dyspnea become evident in more than half of cases. While chest radiographs often show diffuse nodular infiltrates, they can be normal at time of first evaluation. Isolation of organisms from any involved tissue is diagnostic. Brochoalveolar lavage often shows organisms on direct smears or by culture, though a negative result cannot rule out infection. Standard treatment includes Amphotericin B to achieve a cumulative dose of 10 to 15 mg/kg followed by indefinite suppressive treatment with itraconazole 200 mg daily.

### *Paracoccidiomycosis*

Paracoccidiomycosis, a systemic mycosis found in Central and South America, is caused by *Paracoccdioides brasiliensis*. The organism is endemic in hot, sub-tropical regions and, as the name suggests, it is most prevalent in Brazil, which accounts for 60% of all reported cases [57]. Despite wide areas of endemicity, cases associated with HIV infection have rarely been reported [59,60]. The illness is often aggressive. Following inhalation of infectious microconidia, progressive dissemination occurs in individuals with AIDS. Most patients will exhibit cough productive of purulent sputum and dyspnea. Bulky cervical adenopathy, uncommonly seen in most endemic mycoses, is frequently present. Skin, lymph nodes, bone, and meninges are also frequently involved. Chest radiographs may show reticulonodular infiltrates and hilar adenopathy [33,57]. Stains of respiratory specimens show a characteristic morphologic budding pattern and are of high diagnostic yield. Skin biopsy is another simple and sensitive diagnostic approach. Standard treatment in immunocompetent patients is with itraconazole 200 mg for 6 months. Induction regimens for patients with AIDS are not established, though lifelong suppression with itraconazole is advised.

### *Penicilliosis*

*Penicillium marneffei* is a dimorphic fungus endemic to Southeastern Asia and Southern China. While disease has been reported in both healthy and

immunocompromised hosts, penicilliosis has a more rapid onset and a more severe clinical picture when associated with HIV infection [55]. Clinical features are generally nonspecific and can be limited to high fever with few localizing symptoms. More frequently, patients will have accompanying cough and generalized papular skin lesions [57]. A review of 21 cases of disseminated *P marneffei* in HIV-infected individuals from Thailand noted chest radiographic abnormalities in only six patients; three showed diffuse reticulonodular infiltration, and three showed a more localized pattern [61]. Diagnosis can be established from blood, bone marrow, or skin biopsy specimens. Initial treatment is with Amphotericin B or itraconazole. Indefinite suppression with daily itraconazole is recommended to prevent relapse [62].

## Parasitic infections

### *Strongyloidiasis*

Of the many parasitic illnesses found in tropical regions few have been reported to cause pulmonary disease in HIV-infected patients [33]. *Strongyloides stercoralis*, an intestinal nematode found in tropical and subtropical regions worldwide, can cause fatal extraintestinal disease in immunocompromised hosts. Despite wide regional areas of co-endemicity, systemic strongyloidiasis in patients with HIV infection has rarely been reported. Given the ability of the helminth to persist asymptomatically for decades, however, any patient with AIDS who has lived in an endemic area is potentially at risk for developing systemic disease. In addition to gastrointestinal symptoms, many patients with hyperinfection will exhibit cough and shortness of breath. Chest radiographs usually show diffuse infiltrates [63]. Diagnosis is established by isolating the helminth from respiratory and stool specimens. Treatment with thiabendazole 25 mg/kg twice daily for 7 to 10 days is recommended.

## Viral respiratory infections

### *Primary HIV infection of the lung*

The clinical effects of respiratory viral infections in HIV-infected individuals are poorly defined. Studies performed in industrial countries suggest that primary HIV infection can cause clinically significant pulmonary diseases such as lymphocytic alveolitis, non-specific interstitial pneumonitis, and HIV-related lymphoid interstitial pneumonitis, an entity mainly affecting children [64]. The clinical presentation of lymphocytic alveolitis can include dyspnea on exertion or cough. One third of affected individuals will exhibit only chest radiological abnormalities, and another third will have reduced diffusion capacity or a wide alveolar–arterial gradient [65]. There are virtually no data regarding these conditions in tropical areas.

### *Secondary pulmonary viral infection*

Secondary pulmonary viral infections that may complicate HIV infection include herpes virus infections such as cytomegalovirus (CMV) pneumonitis, herpes simplex virus (HSV) pneumonitis and tracheobronchitis, varicella zoster virus (VZV) pneumonitis, Epstein-Barr virus (EBV) pulmonary infection, and the recently described herpes virus 6 (HHV-6), which has been associated with Kaposi's sarcoma (KS). Other pulmonary viral infections have been reported in the setting of HIV infections. With the exception of CMV, measles, and HSV there is little published information regarding HIV-infected patients in the tropics who are co-infected with these viruses [2,64,66–70].

#### *Cytomegalovirus*

Data regarding the prevalence of CMV in HIV-infected populations vary according to study design and definitions of CMV infection and disease. A large autopsy study of patients who died with HIV infection in sub-Saharan Africa (Abidjan) revealed a CMV disease rate of 18%. The cause of death was felt to be associated with CMV in 2% of the study subjects [69]. Cases of generalized CMV infection and CMV pneumonia have also been reported from Zaire [66]. CMV disease was found in 3% of AIDS patients in Brazil [71]. Reported infection rates amongst AIDS patients in Mexico range from 35% to 69% [71–73]. In Thailand CMV disease was found in $<1\%$ of individuals with AIDS [74,75]. A hospital-based clinic site survey from different countries within the Asia–Pacific region reported the prevalence of CMV disease in AIDS patients ranging from 0.9% in India to 37.2% in Indonesia [55]. Gancyclovir and foscarnet remain front line agents for the treatment of CMV.

#### *Herpes zoster*

Herpes zoster is quite common in adult patients with AIDS in the tropics. A history of shingles is reported by more than 10% of patients with AIDS in

Africa [76]. Although herpes zoster tends to develop early in HIV disease and recurrence is common, the actual prevalence of pulmonary HSV co-infections is unclear [2]. The drug of choice for HSV infections is still acyclovir, although new agents are now available.

*Measles*

Measles has only recently been surpassed by HIV as the leading viral cause of mortality worldwide [69]. The course of measles is exacerbated by HIV and a mortality rate of up to 40% has been described in co-infected children and adults. Giant cell pneumonitis is the main complication and cause of death in these patients. Fatal subacute measles encephalitis has also been described. Viatmin A in malnourished individuals and ribavarin are thought to be helpful in reducing the severity of illness, although solid data are lacking. Post-exposure prophylaxis with immunoglobulin is recommended in symptomatic HIV-infected patients. Unfortunately, however, this therapeutic option is probably not financially viable in most underdeveloped countries. Given the potential severity of disease—despite controversy regarding the efficacy and safety of vaccination in HIV-infected symptomatic children—the WHO recommends measles vaccination in all children in developing countries regardless of HIV infection or symptom status [2].

## Neoplastic pulmonary diseases

Among the neoplasms associated with HIV infection, KS, non-Hodgkin's lymphoma (NHL), and perhaps primary lung cancer can affect the respiratory system [77–79]. For a more extensive discussion of the epidemiology, pathogenesis, clinical manifestations, radiological features, diagnosis, and treatment of these neoplasms the authors refer to excellent published reviews [78,79].

*Kaposi's sarcoma*

KS has become one of the leading malignancies in many parts of sub-Saharan Africa in the AIDS era [66–70,80,82]. A longitudinal survey initiated prior to the HIV epidemic estimated the incidence of KS in some sub-Saharan regions to be as high as the incidence of colon cancer in much of Western Europe. The study found a 20-fold increase in the occurrence of KS in Uganda and Zimbabwe since the beginning of the AIDS epidemic [83].

The prevalence of KS in AIDS patients varies widely in different tropical regions. In Latin America, for instance, prevalence data range from 6% in Brazil to as high as 47% in Mexico [71–73,84]. Reports from the Asia–Pacific region are equally varied, ranging from 0.1% in Thailand to 5.5% in Hong Kong, 11.6% in Indonesia, and 28.6% in Australia [55].

Pulmonary KS is responsible for approximately one third of the episodes of respiratory disease requiring evaluation in patients with known KS [85]. Intrathoracic involvement can include parenchymal disease, endobronchial lesions, pleural disease, and adenopathy [79]. Clinical signs of pulmonary involvement include cough with or without hemoptysis, pleuritic chest pain, dyspnea, and wheezing [77]. Common radiographic patterns include focal or diffuse interstitial infiltrates with perihilar predominance and ill-defined nodular infiltrates. Both patterns can be associated with unilateral or bilateral pleural effusions [79]. Although described previously, large, mediastinal adenopathy is unusual in pulmonary KS [77,79]. Bronchoscopic biopsies, bronchiolar lavage, and thoracocenthesis have low diagnostic yield. Direct visualization of characteristic "cherry-red" plaques by bronchoscope is diagnostic, however, and can be helpful in ruling out the possibility other neoplasms or opportunistic infections [77,79].

Though there is little information regarding patient response to treatment in tropical areas, pulmonary KS was associated with a poor prognosis in industrialized countries in the pre-HAART era. Combination chemotherapy including etoposide, vinca alkaloids, bleomycin, anthracyclines, doxorubicin, and daunorubicin as well as single-agent liposomal anthracyclines have shown treatment responses ranging between 25% and 43% [79,86,87].

*Non-Hodgkin's lymphoma*

HIV infection has been associated with a significantly increased risk of NHL in Uganda [80,81]. The incidence of NHL has doubled in this area from the 1960s to the 1990s [80]. While an association between Non-Hodgkin's and Burkitt's lymphoma in Central Africa has been made, the overall incidence is similar to that seen in Western countries [83,88]. Early death from other AIDS-associated illnesses is postulated to contribute to low incidence in Southern Africa [80,89]. NHL in association with AIDS has been infrequently reported in Latin America [34]. Series from the Asia-Pacific region reveal AIDS related NHL incidence ranging from 0.7% in Thailand to 10.6% in Australia [55].

Pulmonary involvement in AIDS has been described in up to one third of NHL cases [90–92]. The

most common radiological presentations are multiple nodular opacities and diffuse interstitial parenchymal involvement [90–92]. As in KS, significant intrathoracic adenopathy is rarely described [77]. Pleural effusions, often without parenchymal involvement, are common [91,93]. Thoracocenthesis fluid analysis and pleural and lung biopsies can be diagnostic [79]. Concurrent HIV infection is associated with high mortality [94]. While multiple therapeutic protocols have been attempted, they have met with limited success and are associated with a high frequency of secondary infections [78,95].

*Lung cancer*

Lung cancer is rarely reported in AIDS case series from Asian, Latin American, and African countries [34,55,80,81]. While concurrent HIV infection has been associated with increased lung cancer frequency, younger age at presentation, and a more aggressive clinical course [96–100], a direct causal relationship has not been established [96,101].

## Idiopathic pulmonary processes

Interstitial inflammatory pneumonitic processes—including a group of lymphoproliferative diseases—have been described in patients with AIDS. The most frequently described disorders are lymphoid interstitial pneumonitis, non-specific insterstitis pneumonitis, and diffuse infiltrative lymphocytosis [77,102]. There is little published information regarding these interstitial inflammatory pneumonitic disorders associated with HIV infection in tropical regions.

## Summary

The most significant pulmonary opportunistic infections in the tropics are TB and pneumococcal pneumonia. Guidelines for the diagnosis and management of these and other pulmonary manifestations of HIV are discussed. Ultimately, unless concerted efforts are made to treat underlying HIV infection in regions most devastated by AIDS, the impact of these diseases will continue to grow.

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