Title: Pulmonary Infections in HIV-Infected Patients: An Update in the 21st Century

Running title: Pulmonary infections in HIV-infected patients

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Abstract

From the first descriptions of HIV/AIDS, the lung has been the site most frequently affected by the disease. Most patients develop a pulmonary complication during the history of HIV infection, mainly of infectious etiology.

Since earlier studies, important changes in the epidemiology of HIV-related pulmonary infections have occurred. Overall, prescription of *Pneumocystis jirovecii* prophylaxis and the introduction of highly active antiretroviral therapy (HAART), are the main causes. Currently the most frequent diagnosis in developed countries is bacterial pneumonia, especially pneumococcal pneumonia; the second most frequent cause is *Pneumocystis* pneumonia and the third cause is tuberculosis. However, in Africa, tuberculosis could be the most common pulmonary complication of HIV. Pulmonary infections remain one of the most important causes of morbidity and mortality in these patients, and remain the first cause of hospital admission in the HAART era. Achieving an etiologic diagnosis of pulmonary infection in these patients is important due to its prognostic consequences.
IMPORTANCE OF THE PROBLEM

The first published reports of acquired immunodeficiency syndrome (AIDS) appeared in 1981, when five homosexual men in Los Angeles were diagnosed with Pneumocystis carinii (currently Pneumocystis jiroveci) pneumonia [1]. Since then, HIV infection has become a pandemic and remains one of the most important global health problems of the 21st century [2]. The number of persons living with HIV is increasing worldwide because of ongoing accumulation of new infections (even at a reduced rate) with longer survival times; there were 33.3 million people living with HIV worldwide at the end of 2009 compared with 26.2 million in 1999—a 27% increase [2].

Combination therapy with multiple agents against the HIV virus, known as highly active antiretroviral therapy (HAART) became widely used between 1996 and 1997 in developed countries. As a result, the incidence of opportunistic infections has decreased and HIV-infected persons have increased their life expectancy [3,4]. However, this has not uniformly occurred worldwide, because antiretroviral therapy (ART) is not yet available to millions of HIV persons, mainly in resource limited countries. Moreover, a significant percentage of patients in developed countries are not receiving HAART because they have a delayed HIV diagnosis (which means an advanced stage of disease at diagnosis) or they are not in active care despite the availability of HAART [5,6].

From the first descriptions of HIV/AIDS, the respiratory tract has been the site most frequently affected by the disease; according to results of autopsy findings, the lung was affected with an incidence ranging from 100% in the early period of the epidemic to 70% in the HAART era [7,8,9,10,11]. Up to 70% of HIV patients have a pulmonary complication during the evolution of the disease, mainly of infectious etiology [11]. Lower-respiratory-tract infections are 25-fold more common in patients
with HIV than in the general community, occurring at rates up to 90 cases per 1000 person/years [12]. Currently, pulmonary infections—not only AIDS-related opportunistic infections—remain a leading cause of morbidity and mortality and one of the most frequent cause of hospital admission in HIV infected people all over the world [13]. An incidence of 20-25 episodes per 100 hospitals admission/years has been observed [14,15]. These numbers give an idea of the magnitude of the problem of pulmonary infections in HIV patients. Moreover, it has been suggested that *Pneumocystis* pneumonia (PCP), tuberculosis and bacterial pneumonia are associated with a significantly worse subsequent HIV disease course, even a permanent decline in pulmonary function [16,17,18,19], although not all studies agree with these findings [20].

**EPIDEMIOLOGY OF PULMONARY INFECTIONS IN HIV-INFECTED PATIENTS**

Few studies have systematically described the full spectrum of HIV-associated pulmonary infections [14,21,22,24]. Most investigators have focused on pneumonias of specific etiologies. Therefore, there is no consensus on any diagnostic algorithm of pulmonary infections in HIV patients. The diagnostic decision should be different depending on the epidemiological features in a specific geographic area [23]. Thus, the incidence of tuberculosis in HIV patients ranges considerably in different geographical areas, depending on the prevalence of disease in the general population. In Africa, tuberculosis could be the most common pulmonary complication of HIV, followed by community-acquired pneumonia [23,24]. On the other hand, PCP is uncommon in Africa, although the incidence seems to be increasing [23, 25,26]. It remains speculative whether this trend denotes a true increase in the prevalence of PCP or whether the early reports underestimated the actual prevalence [25]. In Western Europe, in the 90’s, PCP
was the commonest AIDS-defining illness, whereas pulmonary tuberculosis was more common in Eastern Europe. Within Western Europe, tuberculosis remains more common in the south than in the north [27]. Endemic fungi are common in HIV patients who live in endemic areas, but are exceptional in patients that have never resided in or traveled to endemic regions [28].

The epidemiology of pulmonary infections in HIV has notably changed in the last decades. There have been several reasons to explain these changes. General prescription of PCP primary prophylaxis since 1989 is one of the main causes, and the use of HAART since 1996 is other underlying explanation. After PCP prophylaxis, the incidence of *Pneumocystis* infection did greatly decrease in USA and Europe. Additionally, some studies have suggested that prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) could have decreased the incidence of bacterial infections in HIV patients with less than 200 lymphocytes CD4/mm3; however, not all studies agree with this statement [29,30]. Following the introduction of HAART, the relative incidence of etiologies of HIV-associated pulmonary infections has changed, with bacterial pneumonia replacing PCP as the most frequently encountered cause of these infections [30,31]. Nevertheless, the influence of HAART on the incidence and prognosis of pulmonary diseases, mainly on non-opportunistic infections and malignancies, remains not well known.

The risk for the development of each infection is strongly influenced by the degree of immunosuppression, patient’s demographic characteristics, the place of current or previous residence, and whether they are using prophylaxis against common HIV-associated infections [28]. Genetic factors are probably important but have been less precisely defined.
Bacterial pneumonia is currently the most frequent cause of pulmonary infections in HIV-infected patients, followed by PCP and tuberculosis with different incidences depending on the geographical area (Table 1) [14,15,32]. In addition, endemic fungi, parasites and viruses contribute substantially to the burden of pulmonary disease in patients infected with HIV worldwide.

**Bacterial pneumonia**

Currently, bacterial pneumonia is the most frequent infection in HIV-infected patients, as well as the most common admission diagnosis [14,15,33]. HIV infection is associated with a greater than tenfold increased incidence of bacterial pneumonia [12,18].

Intravenous drugs and smoking are *risk factors* for the development of bacterial pneumonia in this group of patients [29,34,33,35]. Smoking is associated with a two- to fivefold increase in the risk [18,33]. Other risk factors include older age, detectable HIV viral load, and previous recurrent pneumonia [35]. Bacterial pneumonia can occur throughout the all course of HIV infection, but the incidence increases as CD4 cell numbers decline [21,29,33]. Eighty percent of cases of bacterial pneumonia occur with a CD4 count lower than 400 CD4/mm³, and recurrent pneumonia with less than 300 CD4/mm³. The CDC added recurrent bacterial pneumonia as an AIDS-defining condition in 1992. Median of CD4 lymphocyte count in cases of bacterial pneumonia is 200 cells/mm³, significantly higher than median of CD4 lymphocyte in tuberculosis or PCP [14]. Moreover, median of HIV viral load is lower in bacterial pneumonia than in
tuberculosis or PCP [14]. Recently it has been demonstrated that the control of viral load has a significant impact on the development of bacterial pneumonia [33].

Relatively few reports have characterized the impact of HAART on bacterial pneumonia [27]. Several observational studies have shown that HAART would be associated with a decrease in the rate of incidence of bacterial pneumonias [36,37]. In patients with less than 200 CD4/mm3, this decline could be most important [37]. Moreover, the greatest impact of HAART would be on decreasing nosocomial infections rather than community-acquired infections [38]. Data from a randomized trial of continuous versus intermittent ART showed that the risk of pneumonia was significantly higher among patients treated with intermittent treatment [33]. In this study, ART reduced the risk of bacterial pneumonia, even for persons with CD4 cell counts of 500 or more [33]. However, the relative percentage of bacterial pneumonias as cause of pulmonary infiltrates would have increased in last years whilst the percentage of opportunistic infections would have diminished [14,15].

As in the general population, *S. pneumoniae* is the most common bacterial cause of community-acquired pneumonia among HIV-infected adults, implicated in approximately 20% of all bacterial pneumonias (40% of those for which a specific diagnosis is made) [12]. There are conflicting data as to whether the incidence of invasive pneumococcal disease per se has declined during the post-HAART era. It is of note the increased rate of bacteremia complicating pneumococcal pneumonia among HIV infected people (more than 50% in some studies), and the high rates of recurrent pneumococcal pneumonia (10-25%) [39].

Data regarding the effectiveness of pneumococcal vaccination in HIV-positive patients is still controversial [13,12]. A clinical trial of pneumococcal polysaccharide vaccine paradoxically determined that an increased risk of pneumonia was associated
with vaccination [40,41]. However, several observational studies have reported benefits from vaccination with the 23-valent pneumococcal polysaccharide vaccine in HIV infected adults [42,43,44,45,46,47]. Studies have also shown that vaccination is associated with a lower risk of pneumococcal bacteremia [45,48]. Most HIV specialists believe that the potential benefit of pneumococcal vaccination outweighs the risk. In 1999 the Centre for Disease Control (CDC) and the Infectious Disease Society of America (IDSA) guidelines recommended that a single dose of polysaccharide vaccine should be given as soon as possible after the diagnosis of HIV infection to adults who have a CD4 T cell count higher than 200 cells/mm$^3$ and who have not had one during the previous five years [49]. HIV-infected adults who have a CD4+ count of $<200$ cells/$\mu$L can be offered pneumococcal polysaccharide vaccine. Clinical evidence has not confirmed efficacy in this group, but there is some evidence of benefit in those who also start HAART [45]. Revaccination can be considered for persons who were initially immunized when their CD4+ counts were $<200$ cells/$\mu$L and whose CD4+ counts have increased to $>200$ cells/$\mu$L in response to ART [50]. The duration of the protective effect of primary pneumococcal vaccination in HIV-infected patients is unknown. Although no evidence confirms clinical benefit from revaccination, it may be considered every 5 years [50]. Despite these recommendations, pneumococcal polysaccharide vaccine has been underused in HIV-infected adults. A clinical trial evaluating a 9-valent pneumococcal conjugate vaccine in children showed beneficial effects by reducing the incidence of a first episode of invasive disease caused by serotypes included in the vaccine [51]. Additional, there was a strong effect on reduction of virus-associated pneumonias. In a recent clinical trial, the 7-valent pneumococcal conjugate vaccine has shown to protect HIV-infected adults from recurrent pneumococcal infection caused by vaccine serotypes or serotype 6A [52].
*Haemophilus influenzae* account for 10-15% of cases of bacterial pneumonia with etiologic diagnosis [14,15,53]. The epidemiological and clinical characteristics of pneumonia caused by *H. influenza* in this group of patients has been described [53]. It affects mainly patients with advanced HIV disease, and a subacute clinical presentation has been observed in about 30% of cases. More than a half of patients have bilateral lung infiltrates.

In contrast to the noninfected population, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are both reported as community-acquired pathogens with an increased frequency in persons with HIV infection [54,55].

*S. aureus* is the third most frequent cause of bacterial pneumonia [14,15]. Infection drug users can develop right-sided tricuspid valvular *S. aureus* endocarditis with septic pulmonary emboli (small, peripheral, circular lesions that may cavitate with time). Most of affected patients have no history of antecedent valvular damage.

Although *P. aeruginosa* was frequently found as etiologic agent of bacterial pneumonia in early studies [29], currently only a few episodes are caused by this microorganism [14,15]. In early studies performed in the pre-HAART era, there was a higher incidence of nosocomial pneumonia and *P. aeruginosa* was a frequent microorganism in these cases [56]. Moreover, community-acquired bronchopulmonary infecions due to *P. aeruginosa* in patients with a very advanced immunosupression state (typically < 50 CD4 lymphocytes/ml) have been described. After the introduction of HAART, patients remain in this state for a shorter period of time, and hospitalization of HIV patients has decreased. Consequently, infections caused by these microorganisms have also declined.

*Legionella* infection is uncommon, but some studies suggest that it occurs up to forty times more frequently in patients with AIDS than in the general population [57].
Some authors have described a worse prognosis in HIV patients with *Legionella* pneumonia, with higher number of complications; however, other studies have showed few significant differences [57].

Other uncommon infections include *Rhodococcus* and *Nocardia*. *Rhodococcus equi* can cause pulmonary infection in patients with HIV infection, generally in the setting of advanced immunosuppression. *R. equi* pneumonia is characterized by an indolent course with fever, cough, and cavitary infiltrates, mimicking tuberculosis. Treatment is based upon antimicrobial sensitivity testing. Although *nocardiosis* is not very common in HIV-infected patients (0.2-2% of patients) due –at least in part- to prophylaxis with TMP-SMX, the incidence is approximately 140-fold greater in these patients than in general population, particularly in those with CD4 count <100 cells/mm³ [58]. Radiographic findings of lung involvement include single or multiple nodules or masses (with or without cavitation), interstitial infiltrates, lobar consolidation, and pleural effusions. Nocardiosis has frequently been misdiagnosed initially as tuberculosis (since upper lobe involvement is common and *Nocardia* spp. are weakly acid-fast), invasive fungal disease, and malignancy. Because of the propensity for *Nocardia* spp. to cause central nervous system infection, brain imaging should be performed in all patients with pulmonary nocardiosis. Sulfonamides are the most common drugs used for treatment [59].

Pneumonia due to *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* appears to be relatively uncommon in patients with HIV infection, although the role of these pathogens has not been studied systematically.

The *clinical presentation* of bacterial pneumonia in the HIV-seropositive patients is usually similar to that of patients not infected with HIV. Bacteremia is frequently associated with bacterial pneumonia. The most common chest
roentgenographic manifestation is unilateral segmental or lobar consolidation, although diffuse reticulonodular infiltrates and patchy lobar infiltrates may also be identified. A subset of persons with *H. influenzae* pneumonia presents with bilateral infiltrates that are indistinguishable from PCP. On the other hand, pneumonia due to *P. aeruginosa* or *S. aureus* is often associated with cavitation.

**Treatment.** Initial antibiotic regimen will be directed at the most common pathogens. Treatment is similar to that of patients with the same diagnosis without HIV infection.

**Pneumocystis pneumonia**

*Pneumocystis* pneumonia (PCP) is caused by *P. jirovecii*, a ubiquitous organism that is classified as a fungus but that also shares biologic characteristics with protozoa. Whereas the primary mode of transmission of *P. jirovecii* is uncertain, there are increasing data supporting the possibility of airborne transmission of this microorganism [60,61]. That would support the recommendation to avoid placement of an immunocompromised patient in the same room with a patient with PCP [60]. *Pneumocystis* may colonize the respiratory tract in the absence of clinical signs or symptoms of infection; although the clinical significance of colonization is not well understood, patients who are colonized with *Pneumocystis* could serve as a pathogen reservoir [62].

Early studies in the United States showed PCP as the most frequent cause of pulmonary infections (accounting for 85% of cases) and the first cause of hospital admission in HIV patients [7,63]. It was estimated than 75% of these patients would develop PCP during their lifetime [64]. The rate of PCP greatly decreased in developed
countries as a result of *P. jiroveci* primary prophylaxis in 1987 and, more recently, the widespread administration of HAART [65,66,67]. Despite this decrease, PCP remains the most common AIDS defining indicator condition and the most frequent opportunistic infection in North-America and Europe [27]. Nevertheless, *P. jirovecii* pneumonia still occurs in persons who are not receiving neither HAART nor anti-PCP prophylaxis; a significant percentage of these patients (up to 50%) are not known to be infected with HIV [68]. This situation emphasizes the importance of performing an early diagnosis of HIV infection, especially in patients at risk [5,68].

*Pneumocystis* pneumonia develops mainly in patients whose CD4 cell count is less than 200 cells/ml. The median CD4 count is 20 cells/mm3, and the plasma viral load of HIV is usually >10,000 copies/ml [14].

HIV-infected persons with PCP generally have a more sub-acute course and longer duration of symptoms than other immunocompromised patients. The clinical presentation consists of fever, gradually increasing nonproductive cough and dysnea for a few weeks, bilateral interstitial infiltrates and high alveolar-arterial gradients. The most common findings on physical examination are fever, tachypnea, and inspiratory crackles, but physical examination of the chest is unremarkable in approximately 50%.

*Chest radiographs* are initially normal in up to one-fourth of patients with PCP. The chest radiograph typically demonstrates perihilar infiltrates in mild disease, and bilateral, symmetrical interstitial infiltrates emanating from the hila in a butterfly pattern in severe disease [69]. Less frequently, PCP may present with unilateral or asymmetrical opacities. Thin-walled cysts or pneumatoceles are seen in 10-20% of cases. Pneumothorax can occur; in fact, suspicion of PCP should raise when pneumothorax is observed in a patient with HIV infection. Cavitation, intrathoracic adenopathy, and pleural effusion are uncommon; their presence might indicate an
alternative diagnosis. High resolution computed tomography (HRCT) has a high sensitivity for PCP (100%) and a specificity of 89% [70,71]. A negative HRCT may allow exclusion of PCP.

The most common abnormal laboratory value associated with PCP in HIV-infected patients is an elevated lactate dehydrogenase level (LDH), present in 90% of patients and with a prognostic significance [72]. However, elevated LDH level may occur with other pulmonary diseases, especially mycobacterial and fungal infections. Recently, low levels of plasma S-adenosylmethionine showed to be sensitive and specific indicators of PCP; in addition, the levels increased with successful treatment of PCP [73]. More recently, high levels of blood (1→3)-β-D-glucan have demonstrated a good correlation with HIV-related PCP, although the precise role of this test will have to be defined [74]. Although PCP can be suspected based upon clinical and radiological findings, the diagnosis should usually be confirmed.

Specific diagnosis of PCP requires microscopic visualization of the characteristic cysts and/or trophic forms on stained respiratory specimens. It is usually performed by bronchoalveolar lavage (BAL), induced sputum, and in rare occasions lung biopsy [13]. Bronchoscopy with BAL is the preferred diagnostic procedure for PCP, with reported sensitivity of 90%-98%. The most rapid and least invasive method of diagnosis is by analysis of sputum induced by the inhalation of hypertonic saline. While the specificity of this method approaches 100%, the sensitivity ranges from 55% to 92% [75]. This variability is specially related to the skills of the team inducing the sputum [76]. Several PCR assays have been developed for the diagnosis of PCP, and have been tested on BAL, induced sputum, and non-invasive oral wash specimens [77]. In general, PCR assays have been more sensitive but less specific for diagnosis of PCP than traditional microscopic methods. Currently, PCR-based tests are not in widespread use. Treatment
can be initiated before making a definitive diagnosis because organisms persist in clinical specimens for days or weeks after effective therapy is initiated [78].

TMP-SMX remains the drug of choice for the treatment and prevention of this infection, but the best choice of alternative agents has not yet been established. The occurrence of PCP in patients who are compliant with TMP-SMX prophylaxis is highly unusual, but it is relatively more common in patients receiving other prophylaxis strategies. The recommended duration of therapy for PCP is 21 days, and, following the completion of therapy, patients should be immediately started on PCP prophylaxis [50]. Corticosteroids given in conjunction with anti-Pneumocystis therapy decrease the mortality associated with severe PCP, particularly in patients with abnormalities in oxygen exchange at the time of presentation (PO2 < 70 mmHg or an arterial-alveolar oxygen pressure difference > 35 mmHg). [50,79]. Certain strains of P. jiroveci have mutations in the dihydropteroate synthase (DHPS) gene, an essential enzyme that is inhibited by sulfonamides. The DHPS mutation is associated with the use and duration of TMP-SMX prophylaxis, but it is not related to a possible failure of TMP-SMX treatment and a worst prognosis [68,80,81,82]. Once immunologic response is documented and sustained with the use of HAART (CD4 cells count increase above 200 cells/ml for at least three months), PCP prophylaxis may be discontinued [50,83]. Recently, an observational study has suggested that discontinuation of prophylaxis may be safe in patients with CD4 counts of 101-200 cells/ml and suppressed viral load [84]. Alternative regimens of treatment and prevention of PCP can be reviewed in the most recent guidelines of CDC/IDSA [50] (it can be acceded in the web site: http://AIDSinfo.nih.gov).
**Tuberculosis and other mycobacteriosis**

The coincidence of *tuberculosis* and HIV epidemics has created a devastating international public health crisis. At least one-third of HIV-infected persons worldwide are infected with *M. tuberculosis*, and HIV infection is—in global terms—the largest risk factor for developing tuberculosis disease [85]. Additionally, tuberculosis is a leading cause of death for people living with HIV in low- and middle-income countries [86]. HIV-infected persons have a substantially greater risk of progressing from latent tuberculosis infection to active tuberculosis compared with persons without HIV infection [87,88]. The use of HAART has been found to be associated with a notable reduction in the risk of tuberculosis, but incidence rates remain higher than in the general population [89,90,91,92]. In a study of patients initiating HAART over a follow-up of 4.5 years, the risk of tuberculosis only diminished when the CD4 threshold was >500/mm3 [93].

Africa is experiencing the worst tuberculosis epidemic since the advent of antibiotics, with rates increasing sharply in the past two decades [86,94,95]. On the contrary, in the USA and Western Europe a decline in the incidence of tuberculosis in HIV-infected patients has been observed in the last decades; however, remarkable regional differences are founded in Europe, with rates four to seven times higher in southwest Europe than in other European regions [96, 97].

Tuberculosis can occur at any stage of HIV disease, but as the CD4 cell count declines, the incidence of tuberculosis increases. Persons at risk for increased exposure include residents and employees of healthcare facilities, prisons, and homeless shelters; the disease can be found at high rates among intravenous drug users.
Clinical manifestations depend largely on the level of immunosuppression. In persons whose CD4 cell count is above 350-400 cells/mm³, the clinical presentation is similar to that in persons without HIV infection. Typically, these persons have disease that is limited to the lungs and they present with a reactivation tuberculosis radiographic pattern (upper lung zone fibronodular infiltrates with or without cavitation). Persons whose CD4 cell count is below 200 cells/mm³ often present with a primary tuberculosis pattern (middle and lower lung zone infiltrates, lymph node enlargement or a milliary pattern); cavitation is less common, and the chest radiograph may also be normal. Patients with advanced immunosuppression have more often extrapulmonary and disseminated tuberculosis. Subclinical tuberculosis is increasingly recognized. In fact, there is a subpopulation of individuals with HIV with culture-positive pulmonary tuberculosis who are completely asymptomatic [92].

The most important diagnostic tests for tuberculosis are repeated expectorated sputum samples for smear and culture; three samples should be collected, preferably early in the morning on different days; in some studies, two specimens collected on the same day would give similar results [85]. Sputum induction by nebulisation of hypertonic saline is also a useful method on patients unable to produce expectorated sputum or if sputum is smear-negative. In patients with low CD4 counts (especially <100 cells/mm³) disseminated tuberculosis is common, and cultures of blood and urine have a good yield. Cultures on selective media remains the most sensitive method for detecting *M. tuberculosis* in clinical specimens. Testing for susceptibility to first-line agents should be performed on all isolates. Nucleic acid amplification testing amplify the quantity of *M. tuberculosis* DNA in diagnostic specimens, and is useful for rapid identification of the microorganism. The sensitivity of this tests compared with culture is approximately 95% in patients with a positive acid-fast bacilli smear, but in persons
with acid-fast bacilli smear-negative sputum or extrapulmonary disease, nucleic acid amplification tests have lower sensitivity and negative predictive value, and should be used and interpreted with caution [98]. Specificity is very high (greater than 95%). The appropriate use of these tests has yet to be completely determined. Recently, the assay GeneXpert MTB/RIF -an automated nucleic acid amplification test- have shown to provide a sensitive detection of tuberculosis and rifampicin resistance directly from sputum in less than 2 hours [99]. This test can speed the diagnosis, control and treatment of multidrug-resistant tuberculosis.

The principles of tuberculosis treatment in HIV-infected individuals are the same as those in HIV-negative individuals [50]. However, treatment of tuberculosis can be complicated by drug interactions and overlapping toxicities when therapy for both HIV and tuberculosis is concomitantly administered. Rifamycins (mainly rifampin, but also rifabutin) induce hepatic CYP3A4 enzymes that can accelerate metabolism of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) leading to subtherapeutic levels of these antiretroviral drugs. Rifampin should not be used in patients on PI-based regimens; although rifampin lowers levels of both the NNRTIs –efavirenz and nevirapine-, the former is less affected. Rifabutin is an alternative to rifampin that can be administered with PIs or NNRTIs with appropriate dose adjustments. Recent studies suggest that rifampin plays a key role in the treatment of HIV-associated tuberculosis: recurrence rates are 2-4 times higher when rifampin is not included in the continuation phase (after the 2 first months of therapy) [85,100]. Probably, rifampin-based tuberculosis treatment with efavirenz-based ART is the preferred treatment approach for HIV-associated tuberculosis [101]. Regarding the optimal timing of starting ART in these patients, several clinical trials have demonstrated the clinical benefit of initiating ART during tuberculosis therapy, rather
than at later time intervals [102,103,104,105]. Early HAART (initiated during the first two weeks) reduced the HIV disease progression and death among HIV-infected HAART-naïve patients with tuberculosis and a CD4 cell count of <50 cells/mm³. In patients with CD4+ T cells >50 cells/mm³, HAART can be started within the eight weeks after the onset of tuberculosis treatment. HAART never should be delayed until after the completion of the tuberculosis therapy, at least for patients with CD4+ T-cells counts equal to or lower than 500 cells/mm³ [102]. The risk of IRIS was higher among patients who initiate ART at earlier time points, but there were no deaths related specifically to IRIS. A clinical trial showed that 1-month of prednisone reduced the incidence of IRIS in patients with pulmonary tuberculosis who started HAART at the same time of tuberculosis treatment [106]. World Health Organization (WHO) guidelines recommend that -irrespective of CD4 cell counts- patients coinfected with HIV and tuberculosis should be started on antiretroviral as soon as tuberculosis therapy is tolerated [107]. More detailed information on treatment of tuberculosis in HIV patients and management of drug interactions can be reviewed in the most recent guidelines of CDC/IDSA [50, 108] (it can be accessed in the website: http://www.cdc.gov/tb/publications/guidelines/HIV_AIDS.htm).

In developed settings, all persons should be tested for latent tuberculosis infection at the time of HIV diagnosis, and they should be treated if they have a positive diagnostic test for latent tuberculosis infection, no evidence of active tuberculosis and no prior history of treatment for active or latent tuberculosis [50]. The tuberculin skin test has been the usual method to determine latent tuberculosis infection; recently, the development of interferon-gamma release assays has been an important advance in the diagnosis of latent tuberculosis infection. However, sensitivity of interferon-gamma release assays could be diminished by HIV infection [109,110]; lower CD4 counts have
been associated with higher rates of indeterminate results of these assays [109]. Recent WHO guidelines for prevention of tuberculosis in HIV-infected patients in resource limited settings, recommend that persons living with HIV should be screened for tuberculosis with a clinical algorithm; those patients who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active tuberculosis and should be offered treatment of latent infection [111]. Performing a tuberculin skin test would be no a requirement for initiating treatment of latent infection [111]. Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for 9 months; a recently published clinical trial shows that a 12-weeks-course of isoniazid plus rifamycin may be an effective alternative [112].

Pulmonary infections due to *Mycobacterium species other than tuberculosis* are also seen with increased frequency in HIV-infected persons. Infections with at least 12 different mycobacteria have been reported; the most common is *Mycobacterium avium* complex (MAC). Infections with MAC are seen mainly in the United States and are rare in Africa. MAC infection predominantly occurs in patients with CD4 cell counts of <50/ml. The most common presentation is disseminated disease. The chest x-ray is abnormal in approximately 25% of patients; the most common pattern is a bilateral, lower lobe infiltrate suggestive of miliary spread; alveolar or nodular infiltrates, and hilar and/or mediastinal adenopathy can also occur. The finding of two consecutive sputum samples positive for MAC is highly suggestive of pulmonary infection. Therapy consists of a macrolide, usually clarithromycin, with ethambutol [50]. A third drug from among rifabutin, ciprofloxacin, or amikacin can be added in patients with extensive disease. It is possible to discontinue therapy in patients with sustained suppression of HIV replication and CD4 cell counts >100/ml for > 6 months.
In a study in an endemic area in southern Europe, mycobacteriosis were the third cause of pulmonary infiltrates in HIV patients [15]. This high rate, together with the frequent association of mycobacteriosis with other pulmonary infections, supports the performance of routine *Mycobacterium* cultures in all HIV patients with pulmonary infiltrates in endemic areas [15].

**Fungal infections (other than PCP)**

Some studies suggest a decline in the incidence of *endemic fungal infections* since the introduction of HAART; that is difficult to demonstrate, as the incidence of these infections has not been fully determined [50,113]. The three major endemic fungi are *Histoplasma capsulatum*, *Coccidioides inmitis* and *Blastomyces dermatitidis*. They are acquired by inhalation. These diseases can represent primary infection caused by exogenous exposure or reactivation of a latent focus. Infections in patients who reside outside endemic regions generally represent reactivation of latent foci of infection from previous residence in these areas [114]. Reactivation may occur even years after moving to other geographic areas. Endemic areas include the southwestern United States, Northern Mexico, and parts of Central and South America.

Histoplasmosis is the most common endemic mycosis in HIV patients. Most cases of disseminated histoplasmosis and coccidioidomycosis occurs with CD4 lymphocyte counts \( \leq 100 \) cells/mm\(^3\), but focal pneumonia is most common in those with a CD4 cell count \( > 250 \) cells/mm\(^3\). Blastomycosis is an uncommon, but serious complication in HIV-infected persons. All of these endemic fungal infections have a wide spectrum of manifestations in HIV-infected patients with frequent lung involvement. Treatment is based on amphotericin B and triazoles [50,115].
Discontinuing suppressive azole therapy appears to be safe for patients with histoplasmosis who had received \( \geq 1 \) year of itraconazole therapy, had negative blood cultures, *Histoplasma* serum antigen < 2 units, CD4 cell count >150/mm³, and have been on HAART for 6 months [50,116]. In patients with focal coccidioidal pneumonia who have responded to antifungal therapy, are receiving ART and have a CD4 count cell >250 cells/mm³ it would be possible to discontinue secondary prophylaxis after 12 months of therapy. However, in patients with diffuse pulmonary disease or disseminated coccidioidomycosis, therapy should be continued indefinitely. Patients receiving ART who have had a CD4 cell count of >150 cells/mm³ for at least 6 months can discontinue itraconazole therapy for blastomycosis after a minimum of one year [50].

Penicilliosis marneffei (penicilliosis) is endemic in Southeast Asia, southern China, and more recently in India. Penicilliosis is an important cause of morbidity and mortality in HIV-infected patients living in endemic areas or who have had travel-related exposure to this organism; the use of HAART has led to a significant decline of its incidence. The majority of cases are observed in patients who have CD4⁺ counts of <100 cells/\( \mu \)L. Patients commonly present disseminated disease, and the respiratory system is commonly involved (reflecting the probable inhalational route of acquisition).

The recommended treatment is amphotericin B followed by oral itraconazole. All patients who successfully complete treatment for penicilliosis should be administered secondary prophylaxis with oral itraconazole. Discontinuing secondary prophylaxis for penicilliosis is recommended for patients who receive ART and have CD4⁺ count >100 cells/mm³ for \( \geq 6 \) months [50].

When *cryptococcosis* occurs in HIV-infected persons, disseminated disease is common and most patients present with meningitis. The lungs are the portal of infection
and the second most clinically relevant site of infection, after the central nervous system. The number of cryptococcosis cases has declined significantly in developed countries after the introduction of HAART [117]. The presentation of pulmonary cryptococcosis in HIV-infected persons appears to be more acute than in other hosts. The severity of symptoms and extent of dissemination are inversely proportional to the CD4 lymphocyte count; most symptomatic cases occur in patients with less than 100/mm3. Cryptococcal pneumonia in HIV patients most commonly presents with diffuse bilateral interstitial infiltrates that often mimics PCP [118]. In addition, unilateral interstitial infiltrate, focal consolidation, nodules, cavitation, pleural effusion and hilar adenopathy have been reported [118]. Culture of expectorated sputum samples can be positive, but higher yields are obtained using bronchoscopic sampling. The serum cryptococcal antigen is positive in patients with disseminated cryptoccocosis, but can be negative in patients with isolated pulmonary disease. Evaluation of patients with pulmonary cryptoccoccosis should include investigation for disseminated infection with serum and cerebrospinal fluid cryptoccocal antigen testing as well as blood and cerebrospinal fluid cultures [119]. Up to 75% of patients with HIV-associated cryptoccoccosis have positive blood cultures.

The recommended treatment is amphotericin B deoxycholate combined with flucytosine for ≥ 2 weeks followed by fluconazol. Secondary prophylaxis can be discontinued when there is a sustained increase (eg, longer than six months) of CD4 lymphocyte counts ≥ 200 cells/mm3 after HAART [50].

Invasive aspergillosis is a relatively uncommon infection in patients with AIDS, with an overall incidence of approximately 1% in the earlier years of HIV epidemic [120]. The infection is less common after the advent of HAART [121,122]. Aspergillosis most often occur in patients who have CD4 cell counts < 100 /mm3. Risk
factors for the development of invasive disease are neutropenia and corticosteroid use, but are often absent. The lung is the most common site of *Aspergillus* infection and two forms of pulmonary disease have been described in HIV-infected patients: invasive pulmonary disease, which accounts for more than 80% of cases, and tracheobronchial disease. The chest radiograph might demonstrate a diffuse, focal, or cavitary infiltrate in patients with invasive pneumonia; the “halo” and the “air-crescent” sign on computed tomographic (CT) of the lung are suggestive of invasive disease. Several forms of thracheobronchitis have been described: obstructive bronchial aspergillosis, ulcerative tracheobronchitis, and pseudomembranous tracheobronchitis; the chest radiograph may be normal or may reveal areas of atelectasis or parenchimal infiltration [120]. The diagnosis of definite invasive aspergillosis require the detection of *Aspergillus* in cultures and histological evidence of tissue invasion; *Aspergillus* is ubiquitous, and its presence in nasopharyngeal secretions, sputum and BAL fluid may represent contamination or colonization. Newer tests based on circulating fungal antigen (mainly the serum galactomannan antigen) have been employed to diagnose aspergillosis, but they have not been formally evaluated in patients with HIV infection. Treatment of aspergillosis in the HIV-infected population has not been examined systematically, but currently, voriconazole is considered the drug of choice for the treatment of invasive aspergillosis [123]. Lipid formulations of amphotericin B, echinocandins and posaconazol are alternatives. The length of therapy is not established but should continue at least until the CD4 count is > 200 cells/mm3 and there is evidence of clinical response [50]. No data are available to establish a recommendation of therapy among patients who have successfully completed an initial course of treatment [50].

**Viral infections**
Respiratory viruses might contribute to pulmonary complications in HIV-infected patients, although information on the causes, risk factors, and outcomes of respiratory viral infection in these patients is very scarce [124,125,126]. Moreover, the respective role of each agent could vary according to the population and the season studied [124,127,128]. Influenza is a common cause of respiratory illness in adults with HIV, although HAART seems to have reduced the number of patients treated for influenza in hospital [124,129]. People with HIV are usually considered at increased risk from serious influenza-related complications, mostly based on studies carried out in the pre-HAART era [130]. However, recent studies have showed that HIV patients well controlled on HAART with pandemic influenza virus AH1N1 infection had a similar clinical outcome to that of non-HIV patients [131,132]. Yearly influenza vaccination for adults infected with HIV is recommended by the CDC and the IDSA, although this recommendation has not received universal support [50]. The only clinical trial showed a 20% absolute reduction in the risk of respiratory symptoms and 100% protection against laboratory-confirmed symptomatic influenza among HIV-infected patients receiving influenza vaccine compared with those receiving placebo [133]. Two systematic reviews concluded that influenza vaccination of adults infected with HIV might be effective despite variable antibody responses [134,135]. Anyway, more information is needed to confirm how effective and safe vaccination is in these patients, particularly among those with very low CD4 counts [129]. Recently, the role of human metapneumovirus virus infection in adults with HIV infection has been described [126].

The clinical significance of cytomegalovirus (CMV) as a pulmonary pathogen in HIV-infected patients is often unclear. Retinitis and gastrointestinal disease are the most common manifestations, but pneumonitis is infrequent. CMV as a sole cause of pneumonia is not common until the CD4 cell count less than 50 cells/mm3. A particular
problem is posed by the coexistence of CMV with other pathogens found in BAL fluid, particularly *P. jiroveci*. Up to now, the role of CMV in this coexistence is not clear. Criteria for establishing that CMV is the cause of pneumonia are difficult to establish. A diagnosis of CMV pneumonitis could be made in the setting of pulmonary interstitial infiltrates, identification of CMV inclusion bodies and specific cytopathic changes in the lungs, and the absence of other pathogens that are more commonly associated with pneumonitis in this population.

**Parasitic infections**

Parasitic infections result in substantial morbidity and mortality among HIV patients worldwide. Responsible organisms include *Toxoplasmas gondii*, *Strongyloides stercoralis*, *Cryptosporidium* and *Microsporidium*.

*T. gondii* is the most frequent parasitic pneumonia seen in persons with HIV infection. Although encephalitis is overwhelmingly the most common manifestation of *T. gondii*, pneumonitis has become its second most common presentation [136,137]. Active pulmonary toxoplasmosis does not usually occur until the CD4 count falls below 100 cells/mm³. Pulmonary toxoplasmosis may be clinically indistinguishable from PCP, tuberculosis, cryptococcosis, or histoplasmosis. The chest radiograph usually reveals bilateral infiltrates, either fine reticulonodular infiltrates indistinguishable from PCP or coarser nodular pattern similar to that seen with tuberculosis or fungal pneumonias. Most cases of *T. gondii* disease are due to reactivation of latent infection. Consequently, almost all persons with toxoplasmosis have a positive serum *Toxoplasma* IgG antibody. Its absence makes the diagnosis of *Toxoplasma* pneumonia unlikely. The diagnosis of pulmonary toxoplasmosis is usually established by bronchoscopy with BAL, but its sensitivity and specificity are unknown.
There are a few case reports of pulmonary disease due to \textit{S. stercoralis, Cryptosporidium} and \textit{Microsporidium}, which occur in the setting of disseminated infection.

\textbf{Polimicrobial etiology}

Pulmonary infections with more than one pathogen are common in HIV infected patients, particularly in cases of advanced immunosuppression. In a study, the rate of polimicrobial infections was about 9\% of all pulmonary infiltrates [14]. Several studies have shown that frequently any of the etiologic microorganisms identified was not initially suspected [14,138]. This underlines the importance of achieving an etiologic diagnosis.

\textbf{DIAGNOSIS OF PULMONARY INFECTIONS IN PATIENTS WITH HIV INFECTION}

There is no consensus on a diagnostic algorithm of pulmonary infections in HIV patients. Some investigators have recommended an empiric approach based on clinical features and local epidemiology. They have also suggested that diagnostic techniques should be only considered for patients in whom empiric therapy fails [23]. Other authors think that the aim should be always to achieve an etiologic diagnosis by means of non-invasive specimens initially, followed by invasive techniques if these specimens are non-diagnostic [139]. A study showed that not having an etiologic diagnosis was associated with increased mortality [14]. In this way, it is important to remember that while it is always appealing to make a single diagnosis and initiate therapy, multiple simultaneous processes are common in HIV patients, particularly in those with a lower CD4 count [14,97]. The occurrence of multiple simultaneous infections can delay and
complicate appropriate therapy. Additionally, it must be taken into account that the differential diagnosis of pulmonary infiltrates in HIV patients includes both infectious and noninfectious conditions.

The initial approach to the diagnosis of pulmonary infections in HIV-infected patients begins with an adequate clinical history and physical examination. Since the differential diagnosis is broad, historical clues may be useful in narrowing the possibilities, and selecting initial empiric therapy.

**Clinical assessment**

The **history** should include information on:

- Current and previous employments, hobbies and habits (risk of *R. equi* in horse breeders, *C. neoformans* in spelunkers and pigeon breeders).
- Residence in or travel to regions prevalent for tuberculosis or endemic fungi.
- Assessment of any possible exposure to active tuberculosis.
- Use of intravenous drugs.
- Prolonged duration of neutropenia (higher risk for gram-negative infection or *Aspergillus*)
- History of prior infections and antimicrobial exposure (risk of reactivation of old infections when CD4 cell count decreases and higher risk for organisms with resistance to antimicrobials used previously).
- Current use of opportunistic infection prophylaxis
- History and current use of ART.
- More recent CD4 cell count (see below).

The presenting complains and the tempo and duration of these complains should be obtained.
The physical examination should look for signs suggesting extrapulmonary or disseminated disease that may tie together the respiratory complaints and pulmonary findings. The skin can show manifestations of pulmonary-associated bacterial, fungal, or viral infections. Examination of the fundus and optic disc may suggest the presence of viral (CMV), fungal, or mycobacterial infection (mainly tuberculosis).

**CD4 count**

The sequence of pulmonary complications occurring in HIV-infected persons parallels the depletion of CD4 lymphocytes. As a result, the CD4 count provides information about the pulmonary diseases to which the patient is susceptible. However, the CD4-T lymphocyte count measured during the acute stage of infections should not be used to determine the stage of HIV disease, as decreases in the CD4 cell count have been noted in various infections [140].

Bacterial pneumonia (especially *S. pneumoniae*) and tuberculosis can occur early in the course of HIV infection, when the CD4 count is > 500 cells/mm³, although both appear more frequently as immune function declines.

PCP and other fungal disease (cryptococcosis and endemic fungal infections, usually disseminated), disseminated non-tuberculous mycobacterioses with pulmonary involvement, toxoplasmosis, and CMV infections generally occur when the CD4 counts are below 200 cells/mm³.

**Imaging studies**

Plain *chest radiography* is an appropriate initial imaging study for an HIV-infected patient with suspected pulmonary infection. Any new abnormalities, including
pulmonary infiltrates, pleural effusions and/or intrathoracic adenopathy, should be pursued for a definite diagnosis. Certain radiographic patterns as well as time of appearance and rate of progression can assist in the initial diagnosis (Table 2 and Figure 1) [141].

**Chest CT** scans have become an important part of the diagnostic evaluation of HIV patients with suspect of pulmonary infections since they are more sensitive than plain chest radiographs in the detection of early interstitial lung disease, lymphadenopathy, and nodules.

**Specific diagnostic tests**

The high overall yield of the microbiological analysis of spontaneously expectorated *sputum sample* (more than fifty percent) in HIV-infected patients with pulmonary infiltrates is worth mentioning [14]. In the case of bacterial pneumonia the yield of sputum culture ranges from 35% to 60% [14,142]. Additionally, its availability and ease of performance highlight the usefulness of this technique [142]. Moreover, it should be considered the need for performing systematically sputum cultures for mycobacteria in these patients.

**Induced sputum** is not superior to a good expectorated sample for diagnosing pulmonary tuberculosis, but it is helpful in patients who are suspected to have tuberculosis and are unable to produce sputum [143,144]. Induced sputum, if positive, is diagnostic for PCP. The value of sputum induction in the setting of other pulmonary infections is unknown.

The diagnostic yield of *blood cultures* is high in bacterial pneumonias (mainly pneumococcal and *H. influenzae* pneumonias) among HIV-infected persons. Additionally, cultures of blood for *H. capsulatum* and mycobacteria may provide a
definitive diagnosis; the frequency of positive results is inversely related to the CD4 count [145].

**Antigen and antibody testing** are generally of little value in the diagnosis of acute infections in the HIV-infected host. Notable exceptions include assays designed to detect *Histoplasma* polysaccharide antigen and cryptococcal antigen. *Histoplasma* antigen can be detected in the urine of 90% of patients with disseminated infections, and in 75% of those with diffuse acute pulmonary histoplasmosis [146]. The sensitivity is highest when urine and serum are tested. The serum cryptococcal antigen is less likely to be positive in localized cryptococcal pneumonia compared to disseminated cryptococcosis. The assay has excellent specificity. *Histoplasma* and cryptococcal antigen may also be helpful in evaluating response or therapy.

Another non-invasive test that probably has an important diagnostic role is the detection of pneumococcal antigen in urine. There are no specific studies in HIV-infected patients, but the good results obtained in the general population suggest a probable usefulness in this group.

The absence of diagnosis of atypical pneumonias (different from *Legionella pneumophila*) in different series suggests that the routine serologic analysis for diagnosis of these etiologic agents is probably not necessary in the majority of cases.

Because of its high yield and low complication rate, **fiberoptic bronchoscopy** remains the procedure of choice for diagnosing many pulmonary diseases in HIV-infected patients. In a study this test achieved the etiologic diagnosis in 56% of cases of pulmonary infiltrates [14]. The infections most commonly diagnosed using bronchoscopy include infections caused by *P. jirovecii*, mycobacterial, fungal, and viral pathogens. Fiberoptic bronchoscopy is rarely performed in HIV-infected patients for the diagnosis of bacterial pneumonia. In these cases, to circumvent contamination from the
upper airways, a double lumen catheter system or a protected BAL is recommended. Semi-quantitative cultures of the collected specimens should be performed. Any antibiotic usage before the bronchoscopic procedure markedly decreases its sensitivity.

*Transthoracic needle aspiration using CT guidance* has a high yield in diagnosing the cause of peripheral nodules and localized infiltrates; the yield is much lower in patients with diffuse disease.

*Surgical lung biopsy*, performed by means of thoracotomy or video-assisted thoracoscopic surgery, remains the procedure with the greatest sensitivity in the diagnosis of parenchymal lung disease.

**Diagnostic algorithm**

A possible diagnostic algorithm for HIV-infected patients with pulmonary infiltrates is shown in Figure 1. However, more studies are needed in order to establish the best diagnostic algorithm for these patients, which should take into account geographic differences in epidemiology.

**ANTIRETROVIRAL THERAPY IN THE MANAGEMENT OF HIV-INFECTED PATIENTS WITH PULMONARY INFECTIONS**

*Initiation of ART in ART-naïve patients with a pulmonary infection*

Clinicians treating HIV-infected patients often have to consider when to initiate ART in ART-naïve persons with a recently diagnosed pulmonary infection. Initiation of early ART is associated with the risk of immune reconstitution inflammatory syndrome (IRIS), drug interactions, and a high pill burden, but deferral risks advancing immunosuppression and mortality. Initiation of ART in patients with tuberculosis has been discussed above (in the ‘Tuberculosis and other mycobacteriosis’ section). A
recent clinical trial of when to initiate ART for patients with active opportunistic infections (excluding tuberculosis) showed that early initiation (within 14 days of starting therapy for the opportunistic infection) reduced death or AIDS progression by 50% compared with beginning ART after the completion of opportunistic infection treatment [147]. The most common entry opportunistic infection in this trial was PCP (63%), followed by bacterial infections (12%). It was concluded that additional studies are required for other infections [147]. Actually, a more recent study cautions that very early administration of ART in patients with criptococcal meningitis (within 72 hours after diagnosis) can be associated with increased mortality [148]. Based on these data, and according to current guidelines, it can be recommend for most patients with pulmonary opportunistic infections that ART should be initiated within approximately two weeks after initiation of infection treatment [50,149,150,151]. In patients with pulmonary cryptocooccosis and meningitis, a short delay may be considered before initiating ART treatment [150]. Consideration must be given to the potential for drug interactions among therapies for opportunistic infections and ART.

**Management in patients with pulmonary infections receiving ART**

When the infection occurs within 12 weeks of starting ART, many cases can represent unmasking IRISs; treatment of the infection should be started and ART should be continued [50]. When the infection occurs > 12 weeks after initiation of ART despite complete virologic suppression, therapy for the infection should be initiated and ART should be continued; if the CD4+ responses has been suboptimal, modification of the ART regimen could be considered [50]. When the infection occurs in the setting of virologic failure, infection therapy should be started, and the ART regimen should be modified to achieve better virologic control [50].
INTENSIVE CARE OF HIV-INFECTED PATIENTS WITH PULMONARY INFECTIONS

Since the beginning of AIDS epidemic, respiratory failure has been the most common indication for intensive care unit (ICU) admission among patients with HIV infection [152]. In the early years of the HIV pandemic, respiratory failure due to PCP was by far the most common disorder that prompted ICU admission and outcomes were uniformly dismal [153,154]. ICU care was perceived as futile by physicians. Since then, the proportion of ICU admissions caused by respiratory failure has declined, but respiratory failure remains the most common indication for ICU admission in the current era of HAART [152,155]; bacterial pneumonia and PCP are the leading causes of acute respiratory failure, but the proportion of PCP has decreased [155,156,157]. Survival for critically ill HIV-infected patients continues to improve in the current era and could be comparable to the overall survival in non-HIV ICU patients [155,158]. Consequently, clinicians should no longer consider HIV infection as the driving factor for determining outcome in patients with HIV infection and respiratory failure [159,160].

PROGNOSIS OF HIV-INFECTED PATIENTS WITH PULMONARY INFECTIONS

Overall studies analyzing prognostic factors of pulmonary infections in HIV patients are scarce. In a pre-HAART series of patients with pulmonary infections requiring ICU admission, PCP and mechanical ventilation were associated with higher mortality [153]. A study of patients with HIV infection and pulmonary infiltrates showed that not having an etiologic diagnosis was independently associated with higher
mortality [14]. This is a factor of special concern, since it focuses on the need for an improvement in the diagnostic yield of techniques and optimizing the diagnostic algorithm.

Most investigations have focused on PCP, and a mortality of 10% to 30% has been reported [14,15,68,161]. There has been little change in mortality over the past 20 years [14,161]. The degree of hypoxemia at presentation is strongly related to the prognosis of PCP: the case fatality rate is of less than 10% in patients with mild to moderate disease, whereas is above 20% in patients with marked abnormalities in gas exchange [162,163]. Others factors include older age, presence of comorbidities, malnourishment, injection drug use, prior episodes of PCP, high lactate dehydrogenase levels, marked neutrophilia in BAL, low hemoglobin level and high bilirubin level at hospital admission, the presence of cytomegalovirus in bronchoalveolar lavage fluid, and CD4 count < 50 cells/mm³ [14,68,161,164]. Improved survival has been described in the era of HAART among the subgroup of patients with severe PCP admitted to the ICU. Whether improved outcome is attributable to the direct effects of HAART or to general improvements in ICU care (in particular, protective ventilator strategies) remains unclear [161].

Previous studies have indicated a variable mortality (5%-30%) for HIV-associated bacterial pneumonia, although most of them range from 10% to 15% [12,14,29]. The rate of associated mortality in a post-HAART series was lower than previously reported (3.4%), which could be related to a lower incidence of pneumonia due to enterobacteriaceae and *P. aeruginosa* (associated with a higher mortality in previous studies) and a greater percentage of patients with higher levels of CD4 counts [14,15]. Described predicting factors of higher mortality are a Karnofsky score less or equal than 50, neutropenia, a CD4 cell count < 100 cells/mm³, pO2 < 70 mmHg, the
presence of shock, and radiographic progression of disease [165,166]. In many studies, rates of bacterial pneumonia associated mortality are not increased in HIV-infected patients compared with those in control subjects [12,167]. However, these case-fatality proportions are difficult to compare since pneumonia in the absence of HIV infection often occurs in adults significantly older than those with HIV infection and with different comorbidities. Actually, results of different studies do not agree in this issue, and two recent studies showed bacterial pneumonia increased mortality risk in HIV-infected versus HIV-uninfected patients [19,168].
References


55. Levine SJ, White DA, Fels AO. The incidence and significance of Staphylococcus aureus in respiratory cultures from patients infected with the human immunodeficiency virus. Am Rev Respir Dis 1990; 141: 89-93


Table 1. Etiology of pulmonary infections in HIV-infected patients

<table>
<thead>
<tr>
<th>Etiology*</th>
<th>Cumulate incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious etiology</strong></td>
<td>97% of pulmonary infiltrates with diagnosis</td>
</tr>
<tr>
<td>- **Bacterial pneumonia (BP)****:</td>
<td>60% (of PI of infectious etiology)</td>
</tr>
<tr>
<td>- Neumococo (% of BP)</td>
<td>70% (of BP)</td>
</tr>
<tr>
<td>- <em>Haemophilus influenzae</em></td>
<td>10%</td>
</tr>
<tr>
<td>- <em>Staphylococcus aureus</em></td>
<td>9%</td>
</tr>
<tr>
<td>- <em>Legionella pneumophyla</em></td>
<td>6%</td>
</tr>
<tr>
<td>- GNB</td>
<td>5%</td>
</tr>
<tr>
<td>- <strong>Pneumocystis jirovecii pneumonia</strong></td>
<td>20% (of PI of infectious etiology)</td>
</tr>
<tr>
<td>- <strong>Mycobacteriosis</strong></td>
<td>18% (of PI of infectious etiology)</td>
</tr>
<tr>
<td>- <em>Mycobacterium tuberculosis</em></td>
<td>80% (of mycobacteriosis)</td>
</tr>
<tr>
<td>- <em>M. kansasii, MAC, M. fortuitum, M. xenopi</em></td>
<td>20%</td>
</tr>
<tr>
<td>- <strong>Virus</strong></td>
<td>5% (of PI of infectious etiology)</td>
</tr>
<tr>
<td>- Cytomegalovirus</td>
<td></td>
</tr>
<tr>
<td>- Influenza virus</td>
<td></td>
</tr>
<tr>
<td>- Parainfluenza virus</td>
<td></td>
</tr>
<tr>
<td>- Respiratory syncytial virus</td>
<td></td>
</tr>
<tr>
<td>- <strong>Fungus</strong></td>
<td>2%</td>
</tr>
<tr>
<td>- <em>Cryptococcus</em></td>
<td></td>
</tr>
<tr>
<td>- <em>Aspergillus fumigatus</em></td>
<td></td>
</tr>
<tr>
<td>- Endemic fungal infections</td>
<td></td>
</tr>
<tr>
<td>- <strong>Parasite</strong></td>
<td>0.5%</td>
</tr>
<tr>
<td>- <em>Toxoplamas gondii</em></td>
<td></td>
</tr>
<tr>
<td>- <em>Strongyloides stercoralis</em></td>
<td></td>
</tr>
<tr>
<td>- <strong>Multiple organisms</strong></td>
<td>7%</td>
</tr>
<tr>
<td>- <strong>Other</strong>: bronchiectasis, pulmonary abscess</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Noninfectious etiology</strong></td>
<td>3% of PI with diagnosis</td>
</tr>
<tr>
<td>- Pulmonary edema</td>
<td></td>
</tr>
<tr>
<td>- Lung cancer</td>
<td></td>
</tr>
<tr>
<td>- Other</td>
<td></td>
</tr>
</tbody>
</table>

* Incidence of different etiologies can change in different geographical areas. Results in this table are based on our series (references 10, 11, 23)

**Percentage of each microorganism causing bacterial pneumonia is estimated among cases of bacterial pneumonia with identification of etiology

GNB= Gram-negative bacillus; MAC= Mycobacterium avium complex; PI= pulmonary infiltrates
Table 2. Common radiographic appearances of pulmonary infections in HIV patients

<table>
<thead>
<tr>
<th>Chest radiograph or CT</th>
<th>Acute onset</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal consolidation</td>
<td>Any organism, but especially pyogenic bacteria</td>
<td>Mycobacteriosis</td>
</tr>
<tr>
<td></td>
<td><em>Legionella</em></td>
<td><em>Nocardia</em></td>
</tr>
<tr>
<td></td>
<td><em>Legionella</em></td>
<td>Fungi (aspergilosis, endemic fungal infections, cryptoccocosis)</td>
</tr>
<tr>
<td>Diffuse interstitial infiltrate</td>
<td><em>Pneumocystis jiroveci</em></td>
<td>Mycobacteria</td>
</tr>
<tr>
<td></td>
<td>Bacteria, especially <em>Haemophilus influenza</em></td>
<td>Fungal pneumonia, especially cryptoccoccal</td>
</tr>
<tr>
<td></td>
<td>Virus (Influenza, CMV)</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CMV</td>
</tr>
<tr>
<td>Nodules</td>
<td>Tuberculosis</td>
<td><em>Nocardia</em></td>
</tr>
<tr>
<td></td>
<td>Fungi (cryptococosis, aspergilosis)</td>
<td>Fungi</td>
</tr>
<tr>
<td></td>
<td>Bacteria</td>
<td></td>
</tr>
<tr>
<td>Adenopathy</td>
<td>Tuberculosis</td>
<td>Mycobacteriosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endemic fungal infections</td>
</tr>
<tr>
<td>Cavitary infiltrate</td>
<td>Tuberculosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em> (IDU)</td>
<td>Mycobacteriosis</td>
</tr>
<tr>
<td></td>
<td>Fungi</td>
<td><em>Nocardia</em></td>
</tr>
<tr>
<td></td>
<td>Anaerobes</td>
<td>Fungi</td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
<td><em>Rhodococcus equi</em></td>
</tr>
<tr>
<td></td>
<td><em>Legionella</em></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Pyogenic bacteria</td>
<td>Fungi</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td><em>Nocardia</em></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td><em>P. jiroveci</em></td>
<td></td>
</tr>
</tbody>
</table>

CMV = citomegalovirus; IDU = Intravenous drug users
Figure 1. Diagnostic algorithm of pulmonary infiltrates in HIV infected patients
Multiple, bilateral, or diffuse pulmonary infiltrates*

- Tests specified in ‘Unilateral lobar infiltrate’.
- Induced sputum to detect *P. jiroveci*
- Fiberoptic bronchoscopy: stains for *P. jiroveci*, culture for aerobic and anaerobic bacteria, fungi, mycobacteria and viruses, viral antigen detection, cytologic study

No diagnosis and no improvement with empiric treatment

- Computed tomography-guided percutaneous needle biopsy (in case of peripheral infiltrates)
- Lung biopsy using either video-assisted thoracoscopic surgery or open thoracotomy
  - Pathologic studies
  - Microbiologic studies (cultures for aerobic and anaerobic bacteria, mycobacteria, fungi, and viruses, stains for *P. jiroveci*)

Etiologic diagnosis

Complete treatment

Specific treatment

Unilateral lobar infiltrate*

- Two sets of blood cultures
- Expectorated sputum (bronchoaspirate if MV): stain and culture for aerobic bacteria, fungi, and mycobacteria
- Induced sputum, if standard sputum specimen not available: stain and culture for mycobacteria
- Urinary antigen test for *L. pneumophila* serogroup 1 and *S. pneumoniae*
- Pleural effusion (if present): stain and culture for aerobic and anaerobic bacteria, fungi, and mycobacteria

Diagnosis and/or clinical or radiologic improvement with initial treatment

No diagnosis and no improvement after initial treatment

MV = mechanical ventilation

* In patients with a known or suspected CD4 cell count < 200/mm³, serum cryptoccal antigen, and blood and urine cultures for mycobacteria can be useful