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# AIDS and Opportunistic Infections

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## 1. Introduction

Pulmonary parenchymal complications remain the main cause of morbidity and mortality in human immunodeficiency virus (HIV) infected patients (McGuinness, 1997). Early diagnosis and treatment of these complications are important to improve survival.

HIV impairs the immune system, leading the infected person susceptible to a variety of infections, called opportunistic infections, a leading cause of mortality and morbidity in patients with HIV/AIDS. The effect of HIV on the immune system is monitored by measuring the CD4 (T-helper) lymphocyte count in the blood. Depletion of CD4 cell count is a hallmark of disease progression in AIDS. CD4 cell count is essential to decide about the timing of initiation of antiretroviral therapy and for prophylaxis of opportunistic infections.

It has been known that the lungs are principal targets of HIV-associated complications and persons with HIV infection are at an increased risk for opportunistic pneumonias, neoplasms, and other pulmonary conditions. The spectrum of pulmonary manifestations in patients infected with HIV is broad, including many infectious and noninfectious complications. Pneumonia is the leading HIV-associated infection. In a recent report in which 762 patients with HIV/AIDS were analyzed, pulmonary infections was found as the most prevalent infections (Huang et al., 2010). It is estimated that 65% of the patients infected with HIV will present pulmonary involvement as their first clinical manifestation of the syndrome and that approximately 80% of these patients will present some kind of pulmonary involvement in the course of the disease (Suffredini & Masur, 1988).

This section is related with the pulmonary infectious complications of HIV/AIDS.

## 2. Bacterial infections

Bacterial respiratory infections are one of the most common causes of respiratory complaints in HIV-positive patients.

Although HIV infection is most closely associated with altered cell-mediated immunity, a number of additional immune deficiencies may occur in association with HIV infection (Daley, 1993; Davis et al, 1993; Noskin & Glassroth, 1996). It usually includes a poor antibody response due to B cell dysfunction and defects in chemotaxis, phagocytosis and intracellular killing by monocytes, macrophages and neutrophils. Moreover, HIV-infected individuals may experience impairment of local defenses, manifested by a depression of specific IgA at the mucosal surfaces. These immune abnormalities all contribute to an increased risk of bacterial infection among HIV-infected persons.

Combination antiretroviral therapy (ART) is associated with a decreased risk for bacterial pneumonia and during the combination ART era the incidence of community-acquired bacterial pneumonia among HIV-infected patients has declined (Crothers et al., 2010). Antiretroviral regimens contain an HIV protease inhibitor (Sullivan et al., 2000) and the use of trimethoprim-sulfamethoxazole as prophylaxis for *Pneumocystis jiroveci* pneumonia may be associated with decreased risk for bacterial pneumonia (Kohli et al., 2006). However, community-acquired pneumonia represents a frequent cause of morbidity and is associated with an increased mortality in HIV-infected patients also in the ART era.

Bacterial pneumonia may be the first manifestation of underlying HIV infection and thus the presence of HIV infection should be considered in any person presenting with bacterial pneumonia, especially if the individual has no other risk factors for pneumonia or if the pneumonia is recurrent. Recurrent bacterial pneumonia (defined as two or more episodes within 12 months) is included as an AIDS-defining illness in the 1993 CDC Expanded Surveillance Case Definition for AIDS (Centers for Disease Control and Prevention, 1993).

The incidence of bacterial pneumonia among persons with HIV infection is greater than that among persons without HIV. It has been estimated that one third of all persons with AIDS will develop at least one episode of severe bacterial pneumonia over the course of their HIV infection (Noskin & Glassroth, 1996). Afessa et al. (Afessa et al., 1998) found bacterial pneumonia to be the most frequent pulmonary complication (42%) in an autopsy series of 233 HIV-infected individuals. In a recent autopsy study, in which 250 autopsies of HIV/AIDS patients who died of acute respiratory failure was analyzed, bacterial bronchopneumonia was present in 36% (91 cases) (Soeiro et al., 2008). According to another study, the incidence of pneumococcal pneumonia is five to 18 times greater than that in the general population, and the development of pneumococcal septicemia is 100 times greater (Janoff et al., 1992). In a multicenter, prospective, observational study, Hirschtick et al. monitored 1130 HIV-positive and 167 HIV-negative adults for up to 64 months for pulmonary disease and they found that, there were 237 episodes of bacterial pneumonia among the HIV-positive participants (rate, 5.5 per 100 person-years), as compared with 6 episodes among the HIV-negative participants (rate, 0.9 per 100 person years;  $p < 0.001$ ). They also showed that, the rate of bacterial pneumonia increased with decreasing CD4 lymphocyte counts (2.3, 6.8, and 10.8 episodes per 100 person-years in the strata with more than 500, 200 to 500, and fewer than 200 cells per cubic millimeter, respectively;  $p \leq 0.022$  for each comparison) (Hirschtick et al., 1995). Bacterial pneumonia is more common in smokers with HIV than in nonsmokers and injection drug use more than doubles the risk of bacterial lower respiratory infections compared with those who acquired HIV through sexual exposure (Fangman & Sax, 2008). Other risk factors are a low socioeconomic status, alcohol abuse, comorbidities (including cardiovascular, renal disease, malnutrition, and hepatic cirrhosis), low CD4 cell counts ( $< 200$  cells/ml), uncontrolled HIV replication and not receiving ART (Madeddu et al., 2010).

Similar to that in the general population, *Streptococcus pneumoniae* and *Haemophilus* species are the most frequently identified causes of community-acquired bacterial pneumonia (Hirschtick et al., 1995; Madeddu et al., 2008; Schneider, 1999). *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* account for most of the remainder of cases (Afessa & Green, 2000; Baron & Hollander, 1993; Madeddu et al., 2008). Risk factors for *S. aureus* include recent viral or influenza infection and use of injection drugs. Methicillin-resistant *S. aureus* which may be acquired in health care setting or in the community is increasingly common. *P. aeruginosa* has been increasingly recognized as an important source

of bacterial pneumonia in HIV-infected individuals, particularly in those with advanced HIV/AIDS (CD4 cell count less than 50 cells/ $\mu$ L), underlying structural lung disease (bronchiectasis), neutropenia, indwelling catheters, receipt of corticosteroid therapy, multiple antibiotic therapy, and severe malnutrition. Atypical pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia* species are less frequent causes of pneumonia (Sandkovsky et al., 2008). Other less causes of pneumonia include *Rhodococcus equi*, *Nocardia* species *Bartonella henselae* and *quintana*. *Rhodococcus equi*, an aerobic gram-positive, may cause focal consolidation, endobronchial disease and cavitation, and is usually associated with low CD4 cell count (100 cells/ $\mu$ L) in HIV/AIDS patients. *Nocardia asteroides* may cause nodules, consolidation, cavitation, pleural effusions, empyema and intrathoracic lymphadenopathy in HIV-infected persons.

In contrast with community-acquired pneumonia, the two most common bacterial causes of hospital-acquired pneumonia in patients with HIV are *P. Aeruginosa* and *S. Aureus*, while *S. pneumoniae* and *K. Pneumoniae* are other relatively frequent causes (Crothers et al., 2010).

The clinical features of bacterial pneumonia in HIV-infected persons is similar to those in immunocompetent persons and includes acute onset of fever, dyspnea, dry or productive cough, chills and chest pain. Physical findings consist of fever, tachypnea, tachycardia, rales or rhonchi, and other signs of consolidation and occasionally pleural effusion (Huang & Crothers, 2009). Bacterial pneumonia in HIV-infected patients can occur at all levels of CD4 cell count, and an inverse relationship between the incidence of pneumonia and the CD4 cell count has been observed (Hirschtick et al., 1995). However, patients with higher CD4 cell counts are more likely to present with a typical clinical picture, in contrast, patients with low CD4 cell count often present an atypical clinical picture (Madeddu et al., 2010).

The most common radiographic pattern in bacterial pneumonia is focal consolidation, which typically presents in either a segmental or lobar distribution (Boiselle et al., 1997; Gold et al., 2002; Kuhlman, 1999; Selwyn et al., 1998; Sider et al. 1993). In two studies of HIV-infected individuals with bacterial pneumonia, focal consolidation was observed in approximately 45–60% of patients (Boiselle et al., 1997; Magnenat et al., 1991). Most persons with *S. pneumoniae* or *Haemophilus* pneumonia present with unilateral, focal, segmental or lobar consolidation. Lobar pneumonia is seen most commonly in *S. pneumoniae* pneumonia. A variety of gram (+) and gram (-) bacteria, most commonly *Staphylococcus*, *Streptococcus*, *Pseudomonas*, *Klebsiella*, *Enterobacter*, and *Haemophilus*, may cause bronchopneumonia.

In almost half of the cases of bacterial pneumonia, a radiographic pattern other than focal consolidation is observed (Brecher et al., 2003). Solitary or multiple lung nodules, cavitary pulmonary lesions are other radiologic findings often associated with bacterial pneumonia in HIV-infected patients. *P. aeruginosa* or *S. aureus* are most common bacterial causes of cavitary nodules or cavitary consolidation, while less common bacterial causes include *N. asteroides* and *R. equi* infections. HIV-infected patients had an increased risk for complicated parapneumonic effusions, especially if due to *S. pneumoniae* or *S. aureus*.

Although conventional radiographs are the mainstay of imaging of bacterial respiratory infections in HIV-infected persons, CT provides more information about nodules, cavities, and pleural fluid collections. Hence, CT may be useful for further characterizing atypical radiographic findings, for diagnosing complications of infection such as abscess or empyema.

The diagnostic approach to bacterial pneumonia in HIV-infected patients is similar to that of HIV-negative patients. Current US guidelines recommend that persons hospitalized with suspected bacterial pneumonia should undergo diagnostic evaluation for specific pathogens (Centers for Disease Control and Prevention, 2009). The diagnostic tests include gram stain

and culture of sputum, blood cultures and thoracentesis should be performed in patients with pleural effusions. Bronchoscopy should be done to support or establish correct diagnosis via taking wash, brush or biopsy. In patients in whom the diagnosis is unclear, other supplemental testing such as a modified acid-fast stain (for *Nocardia* and *Rhodococcus*) or a urinary legionella antigen can be appropriate (Fangman & Sax, 2008). In pneumococcal pneumonia, pneumococcal urinary antigen testing offers the potential for early, specific diagnosis.

Although numerous guidelines (BTS guidelines, 2001; Mandell et al., 2007; Woodhead et al., 2005) for the management of community-acquired pneumonia (CAP) in HIV-negative patients have been developed by scientific societies, to date, no specific guidelines have been developed for HIV-infected patients. However, the principle of the treatment of bacterial pneumonia is similar in both HIV positive and negative patients (Fangman & Sax, 2008). The choice of antimicrobial agent should be based on the results of a sputum gram stain, the clinical and radiologic presentation, severity of the illness, presence of co-morbid disease and knowledge of local microbiology and resistance patterns. Duration of the therapy is generally similar or a bit longer than to that of HIV negative patients.

Although the emergence of antimicrobial resistant organisms is a global problem, in HIV-infected patients, there is limited data on the prevalence and the impact of drug resistant bacteria on the clinical course of the disease. The rate of penicillin-resistant *S. pneumoniae* in HIV-infected patients is reported to be higher than in HIV-noninfected patients (Madeddu et al., 2009). However, in a recent report, no obvious difference in pneumococci resistance patterns has been found between HIV-positive and negative patients (Stephan et al., 2009). Also, in a study in which the trend of *S. pneumoniae* antibiotic resistance has been evaluated, a near significant decrease in penicillin-resistant strains in the late-HAART compared with of pre and early-HAART era has been found (Grau et al., 2009). Patients on TMP-SMX prophylaxis for *Pneumocystis pneumonia* may be more likely to have penicillin and TMP-SMX resistant *S. pneumoniae*. With the widely use of TMP-SMX prophylaxis, an increase in resistance to TMP-SMX in other bacteria has also been reported (Marin et al., 1999).

Prevention strategies of bacterial pneumonia should address on several problems such as the role of cigarette smoking, alcohol abuse and ongoing injection drug use, hepatic and renal comorbidities, late presentation of HIV diagnosis, highly active antiretroviral therapy (HAART) lack of compliance, and virus effects and immunological failure. Combination antiviral therapy should be considered for all patients with recurrent bacterial lower respiratory tract infections. HIV patients not receiving HAART are clearly at an increased risk of bacterial pneumonia. Vaccination strategies are still controversial in HIV infected individuals. On the one hand, some studies showed a good response and a reduction in new cases among vaccinated patients, on the other, some reports found no evidence of efficacy. However, pneumococcal vaccine is recommended for all HIV patients who have a CD4 cell count greater than 200 cells/ $\mu$ l. The influenza vaccine should be given to all persons with HIV infection annually prior to influenza season. Trimethoprim-sulfamethoxazole, when administered daily for PCP prophylaxis, can reduce the frequency of bacterial respiratory infections (French et al., 2000; Loeliger et al., 1995; Rodriguez-Barradas et al., 1992).

### 3. Mycobacterial infections

Tuberculosis (TB) remains an important cause of morbidity and mortality among persons with HIV infection. Pulmonary TB is still the commonest form. In HIV infected persons, the

estimated annual risk of developing active TB ranges from 35 to 162 per 1,000 person-years, compared to 12.9 per 1,000 person-years for those without HIV infection (Centers for Disease Control and Prevention, 2009). The World Health Organization (WHO) estimated that, in 2007, of the 9.27 million new cases of TB worldwide, 1.37 million occurred in persons with HIV (World Health Organization, 2009). In 2008, nearly 1 of 3 TB-related deaths (29%) worldwide was considered to be related to HIV infection, and TB contributed to 26% of the estimated deaths due to HIV infection. HIV has increased the incidence of TB by up to sevenfold in African countries (Williams et al., 2010). Countries in southern Africa are particularly affected, with over 50% of TB patients diagnosed each year being co-infected with HIV (Corbett et al., 2003; World Health Organization, 2007). In 2007, countries in sub-Saharan Africa accounted for nearly 80% of the estimated global burden of HIV infection-associated TB. It has been reported that, TB is the commonest cause of death in hospitalized HIV-infected adults in sub-Saharan Africa (Sani et al., 2006; Lucas et al., 1993; Nelson et al., 1993) and in another report, among HIV-infected patients not on ART, it was the commonest cause of adult hospitalization, in Nigeria (Habib et al., 1998).

TB disease in persons with HIV infection can develop immediately after exposure (i.e. primary disease) or as a result of progression after establishment of latent TB infection. The risk of progression to active TB is highest in those with HIV coinfections (Lawn et al., 2011). While the lifetime risk of reactivation latent TB infection is 5% in HIV negative persons, the risk among HIV-infected persons has been estimated to be 10% per year. The interaction between HIV infection and tuberculosis is complex: HIV infection, by decreasing interferon-gamma production, increases the risk for the development of active TB disease. Following the initial exposure, the rate of progression of TB infection to active disease is higher than 40% in HIV positive patients compared to approximately 5% in HIV negative patients (Havlir & Barnes, 1999). On the other hand, *M. tuberculosis* enhances HIV replication and accelerates the natural progression of HIV infection by increasing cytokine production (in particular tumor necrosis factor-alpha).

TB disease occurs among HIV-infected persons at all CD4 T lymphocyte counts, but the incidence increases as the count decreases. Also, the clinical, radiographic, and histopathologic presentation of HIV-related TB disease is influenced by the degree of immunodeficiency. With CD4 T lymphocyte counts  $>350$  cells/ $\mu$ L, HIV positive TB appears like TB among HIV negative persons. The majority of patients have disease limited to the lungs. However, extrapulmonary disease is more common in HIV positive cases than in HIV negative ones and those with advanced immunosuppression (CD4 T lymphocyte count  $<200$  cells/ $\mu$ L) are more likely to have extrapulmonary or disseminated disease.

Although HIV positive persons with TB may have the classic symptoms of TB (eg, productive cough, chest pain, shortness of breath, hemoptysis, fever, night sweats, and/or weight loss), many such patients have few symptoms or have symptoms that are even less specific.

The radiographic findings of TB also depend on the degree of immunosuppression (Marchiori et al., 2005). In patients who have CD4 cell counts above 350-400 cells/ $\mu$ L, the findings tend to be similar to those without HIV infection. Most of these persons present with a classic reactivation TB radiographic pattern consisting of unilateral or bilateral upper lung zone reticulonodular infiltrates with or without cavitation. In more severely immunocompromised patients, the radiologic manifestations tend to resemble those of primary disease including areas of consolidation, miliary disease, pleural effusion, and lymph node enlargement (Laissy et al., 1998). Cavitation is less common but intrathoracic

adenopathy is more common in these individuals with advanced HIV/AIDS. Up to 20% of severely immunocompromised AIDS patients with pulmonary TB have radiographs that show normal findings (Boiselle et al., 2002). The small nodules and lymph node enlargement are the usual findings at high resolution CT.

The diagnostic approach to TB in HIV positive person is same with those HIV negative ones. The gold standard diagnostic test for TB remains the isolation and identification of *M. Tuberculosis* by culture (Crothers et al., 2010). It is more sensitive than sputum smear, allowing detection of TB in sputum smear negative cases such as HIV positive patients. In a setting in South Africa, 49% of sputum smear negative HIV patients were sputum culture positive. All cultures positive for *M. Tuberculosis* should be sent for susceptibility testing to identify drug resistance.

Typically, diagnostic evaluation of suspected TB includes 2 to 3 sputum specimens sent for acid fast bacillus (AFB) smear and, mycobacterial culture. The quality and number of collected specimens affect diagnostic results. A systemic review in 2007 concluded that, the average sensitivity of the first sputum slide (53,5%) increased following the addition of second slide (64.9%), but not further with a third slide (Mase et al., 2007). Sputum smear microscopy is the primary tool for TB diagnosis. However, a lower sensitivity in HIV-patients is often seen due to their lower sputum bacillary load. Sputum microscopy may also be false-negative if the sputum concentration of mycobacteria is below 10,000 organisms/mL. Alternative sample processing methods may increase sensitivity. A systemic review showed that centrifugation or overnight sedimentation with chemical processing increases sputum smear sensitivity (Steingart et al., 2006). Fluorescent microscopy (FM) is an alternative way to Ziehl-Neelsen (ZN) staining for the detection of AFB. The procedure is thought to be faster, more-cost effective, and more sensitive than ZN. In a study from Kenya, FM was twice as sensitive as ZN in HIV positive cases using the culture as a gold standard (Kivihya-Ndugga et al., 2003). An Indian study reported 26% more TB cases detected when FM was used compared to ZN in a population including 15% HIV positive patients (Prasanthi & Kumari, 2005). In many cases, especially those with advanced immunosuppression and low CD4 cell-counts, are unable to produce sputum spontaneously. In such patients, sputum induction by inhalation hypertonic solution should be performed. Mycobacterial blood cultures can be obtainable, especially in persons whose CD4 cell count is below 200 cells/ $\mu$ L and/or persons with evidence of disseminated disease. Nucleic-acid amplification (NAA) tests are useful in providing rapid identification of *M. tuberculosis* from sputum smear-positive specimens, but false-negative results can occur among patients with TB disease. The positive predictive value of NAA tests are decreased in persons who have sputum smear-negative results. Several reports indicate that in HIV patients, NAA tests may also be helpful for diagnosing TB when used on blood and urine (Kibiki et al., 2007; Rebollo et al., 2006; Torrea et al., 2005). Despite its possible advantages, NAA diagnostics remain expensive, technically demanding and prone to contamination, especially in high-volume settings (Rewata et al., 2009).

Current estimates are that one third of the world's population is infected with *M. Tuberculosis*. Yet, to date, there is no gold standard for diagnosis of latent TB infection (LTBI). Traditionally, the tuberculin skin test (TST) has been used to measure delayed hypersensitivity reaction following intradermal injection of purified protein derivative (PPD). However, its use in the diagnosis of LTBI lacks both specificity and sensitivity. More recently, IFN- $\gamma$  release assays (IGRA) such as QuantiFERON-TB Gold In-Tube and T-SPOT. TB has been developed (Lalvani et al., 2001). IGRA improve the specificity of LTBI diagnosis

by measuring cytokine production by immune cells to *M. tuberculosis*-specific proteins, transcribed from genes not found in Bacille Calmette-Guerin (BCG) and most other environmental mycobacteria. Early secreted antigenic target-6 and culture filtrate-10 are the two best studied to date and can improve the sensitivity of LTBI diagnosis to 96% compared with 69% achieved by TST.

In principle, the treatment of TB in individuals with HIV infection should be the same as that for patients with TB who do not have HIV disease. Currently, treatment guidelines recommend that the duration of TB therapy should be the same for both HIV positive and HIV negative cases (Blumberg et al., 2003; Hopewell et al., 2006; World Health Organization, 2003). Standard first-line therapy for TB with a 4-drug intensive treatment phase of 2 months, followed by 4 months of treatment with a 2-drug regimen, is highly effective in patients with HIV infection-related TB. Initial treatment of presumed drug-sensitive TB consists of isoniazid (INH), rifampin (RIF) or rifampicin (RFB), pyrazinamide (PZA), and ethambutol (EMB). Pyridoxine (B6 vitamin) should also be given to avoid peripheral neuropathy side effect of INH. Persons with cavitary lung disease whose 2-month repeat sputum culture remains positive should receive additional initial phase treatment for a month or an additional 3-4 months of treatment (total of 9-12 months). Consultation with a TB expert should be obtained in persons with known drug-resistant (multi drug-resistant, MDR, or extensively drug-resistant, XDR) TB and in persons who are failing standard 4-drug therapy, where drug-resistance is suspected. When results of species identification and susceptibility become available, drug selection can be tailored as needed. Because of the severity of TB disease among immunocompromised patients, directly observed therapy (DOT) is strongly recommended for patients with HIV-related TB.

It has been reported that trimethoprim-sulfamethoxazole, given a month after initiation of anti-TB therapy, reduced mortality by 46% among HIV1- and HIV2 coinfecting patients with TB (Wiktor et al., 1999). Use of trimethoprim-sulfamethoxazole appeared to reduce the risk of death by preventing gastrointestinal and respiratory infections. As a result, the WHO and the United Nations Joint Programme on HIV/AIDS (UNAIDS), recommend that patients with HIV infection-related TB be treated with trimethoprim-sulfamethoxazole during and after treatment for TB (Sterling et al., 2010).

HIV infection is associated with high rates of recurrent TB, particularly in developing countries. However, in such settings, recurrent disease is more likely to be attributable to exogenous reinfection than to relapse. A course of isoniazid after completion of standard anti-TB treatment has been associated with lower rates of TB recurrence, particularly among HIV-infected persons. Although this strategy has been proven to be effective in settings with a high incidence of TB and HIV infection, it is often not provided because of logistical constraints (Sterling et al., 2010).

Among HIV-infected persons who receive a diagnosis of TB and do not receive HAART, the mortality rate is high (as high as 91% among persons with AIDS). Initiation of HAART is associated with improved survival among all HIV infected persons, including those with TB. It is therefore recommended that HIV-infected patients with TB receive treatment for both diseases, regardless of their CD4 lymphocyte count. However, the optimal timing of HAART initiation in relation to the time of anti-TB therapy initiation is unclear, but it is generally recommended to wait at least 2 weeks or longer depending on the degree of immunocompromised status (Centers for Disease Control and Prevention, 2009).

In persons on ART, drug interactions can occur particularly between the rifamycins and both protease inhibitors and non-nucleoside reverse transcriptase inhibitors. As a result of

this interaction, decreased drug levels are associated with the development of resistance by both HIV and *M. tuberculosis*, whereas increased drug levels are associated with toxicity. In addition, persons receiving dual therapy for HIV infection and TB may develop the immune reconstitution syndrome. This shows a paradoxical reaction presenting as a temporary exacerbation of clinical and radiographic features which appears to be more common among those starting ART within 6 weeks of initiating anti-TB therapy and among those with disseminated TB.

TB prevention strategies with known efficacy include rapid identification and treatment of active TB cases (in source patients), infection-control measures to reduce nosocomial transmission of TB, isoniazid preventive therapy during latent TB infection, and ART to reduce the incidence of TB among HIV-infected patients (Chamie et al., 2010). Prevention of HIV infection is necessary to control TB. ART is one of the most potent tools in TB prevention, and increasing ART access in countries with a high TB burden is a necessary step in reducing TB incidence. Observational cohort studies have shown reductions in the risk of TB among persons receiving ART (Lawn et al., 2009). Treatment of latent TB, primarily studied using isoniazid preventive therapy in HIV-infected patients who have positive tuberculin skin test results, clearly reduces the incidence of active TB. In persons with HIV,  $\geq 5$  mm of induration at 48-72 hours is considered to represent a positive purified protein derivative (PPD) or TST. IFN- $\gamma$  release assays (IGRAs) can also be used to diagnose LTBI. Since HIV infection is associated with a high risk for progression to TB, current guidelines recommend that persons with either a positive TST or IGRA should be considered infected with *M. tuberculosis* (Centers for Disease Control and Prevention, 2009). Persons with HIV infection should receive INH either daily or twice weekly plus pyridoxine for 9 months.

### 3.2 Non-tuberculous mycobacteria

Since the beginning of the AIDS epidemic, nontuberculous mycobacterial (NTM) infections have been reported with increasing frequency in HIV-infected patients. The majority of these infections have been caused by members of the *Mycobacterium avium complex* (MAC). Occasionally, *M. kansasii*, *M. xenopi*, *M. fortuitum*, *M. chelonae* or *M. sherrisii* also causes pulmonary disease. MAC includes at least two species, *Mycobacterium avium* and *Mycobacterium intracellulare* and also *M. avium* is composed of several subspecies. In a report including a total of 2,269 cases with AIDS and disseminated nontuberculous mycobacterial infection; in 96% of cases, infection was caused by MAC (Horsburgh & Selik, 1989). However, Raszka et al. reported that, among the 92 patients infected with HIV and NTM organisms identified; MAC was recovered from 50 (77%) of the 65 NTM-positive cultures of blood or bone marrow, while MAC and other non-*avium* NTM accounted for 18% and 5% of the isolates, respectively and the authors concluded that those data demonstrate that HIV-positive patients develop disseminated disease with NTM other than *M. avium* more frequently than has been previously reported (Raszka et al., 1995).

The disease may manifest as disseminated infection, soft tissue infection, chronic pneumonia, or hypersensitivity pneumonitis, and isolated MAC pulmonary disease is very rare. Most patients have disseminated multiorgan infection. The risk of developing disseminated MAC increases as the CD4 lymphocyte count declines and more than 95% of cases occur when the lymphocyte count is 50 cells/ $\mu$ /L or less. Unlike TB, disseminated MAC is usually a primary infection and is often preceded by a period of respiratory or gastrointestinal colonization after ingestion or inhalation of contaminated food or water. The

clinical findings of disseminated MAC include fever, anorexia, night sweats, weight loss, abdominal pain, hepatosplenomegaly, lymphadenopathy, chronic diarrhea and anemia. The radiologic findings of pulmonary MAC include consolidation, cavities, nodules, bronchiectasis and adenopathy (Erasmus et al., 1999). While focal infiltration is extremely rare, a frequent finding is endobronchial lesion without pneumonia (Mehle et al., 1989; Salama et al., 2003). Pleural involvement in nontuberculous mycobacterium infection has also been reported rarely (Haider et al., 2009).

The diagnosis of pulmonary MAC is based on clinical, microbiological, and radiographic findings (Griffith et al., 2007). It is based on compatible clinical signs and symptoms coupled with the isolation of MAC from cultures of blood, bone marrow, or other normally sterile tissue or body fluids. The positive culture of sputum or BAL for MAC, may not be indicative for either pulmonary or disseminated disease. Culture of blood is the most useful diagnostic procedure to evaluate MAC infection. The sensitivity of blood cultures for disseminated MAC has ranged from 86% to 98%. Recently, Singh et al studied a rapid PCR method for the species-specific diagnosis of *M. tuberculosis* and its differentiation from other mycobacteria, and the authors concluded that, the combination of genus-specific PCR primers with the novel early-secreted antigen-6 primer set could provide accurate and rapid diagnosis of mycobacteriosis (Singh et al., 2007).

The therapy for pulmonary disease due to MAC includes three oral antimicrobials: a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin). Clarithromycin is the preferred first agent, but azithromycin can be substituted if needed, although its in vitro activity is less than clarithromycin. Ethambutol is the recommended second agent and should be combined with one of these macrolides. Rifabutin is also recommended as a third agent of combination therapy (Benson et al., 2003; Gordin et al., 1999). In a study in which clarithromycin (500 mg bid.) plus ethambutol (1,200 mg/d), with or without rifabutin (300 mg/d) was evaluated, rifabutin was found to no impact on bacteriologic response or survival but may protect against development of clarithromycin resistance in those who respond to therapy (Gordin et al., 1999). In another multicenter, randomized trial, Benson et al. reported that the addition of rifabutin to clarithromycin plus ethambutol, had improved the survival (Benson et al., 2003). A third or fourth drug among the fluoroquinolones (ciprofloxacin or levofloxacin) or parenteral amikacin may be given if rifabutin cannot be used or in patients with advanced immunosuppression and high mycobacterial burden (Centers for Disease Control and Prevention, 2009). Duration of treatment is for 12 months beyond the time that the patient's cultures convert to negative, which usually equates to 18 to 24 months of therapy (Kasperbauer & Daley, 2008).

## 4. Fungal infections

### 4.1 *Pneumocystis jiroveci*

PCP (shortened for *Pneumocystis pneumonia*) caused by *Pneumocystis jiroveci* (formerly classified as *P. carinii*), still remains the most common opportunistic infection in patients infected with HIV. Once thought to be a parasite, genomic analysis revealed that *P. jiroveci* is in fact a fungus that infects only humans. Before the widespread use of primary PCP prophylaxis and effective ART, PCP occurred in 70%–80% of patients with AIDS. The use of combination antiretroviral therapy and PCP prophylaxis has contributed to the dramatic declines. Nevertheless, despite a decrease of its overall incidence as a result of use of

combination ART and PCP prophylaxis, PCP remains the most frequent AIDS-defining diagnosis in the United States (Thomas, 2004). Pneumocystosis would cause life-threatening pneumonia in patients without chemoprophylaxis, without HAART or unaware of their HIV infection.

The risk factors for the development of PCP among HIV-infected persons include a CD4 lymphocyte count less than 200 cells/ $\mu$ L (approximately 90-95% of cases), a history of PCP and oropharyngeal candidiasis (Phair et al., 1990; Stansell et al., 1997). Clinical presentation of patients affected with *Pneumocystis* pneumonia differs among HIV and non-HIV immunosuppressed patients. HIV patients tend to present with subacute onset of progressive dyspnea, nonproductive or minimally productive cough, low-grade fever and malaise. However, up to 7% of these patients can be asymptomatic. In contrast, patients that are immunocompromised but HIV-negative usually present more acutely, with substantial dyspnea, fever, chills and some may initially present in urgent need of mechanical ventilation. The fulminant pneumonia observed among non-HIV-infected patients is less common. Approximately 90% of patients with PCP have an elevated serum LDH level, but this may occur with other pulmonary diseases, especially mycobacterial and fungal infections (Rosen, 2008). Other tests, including S-adenosylmethionine levels, KL-6 and beta-D-glucan, have been reported as the diagnostic tests for PCP (Skelly et al., 2008; Tasaka et al., 2007). Hypoxemia, the most characteristic laboratory abnormality, might range from mild-to-moderate (room air arterial oxygen [ $pO_2$ ] of  $>70$  mm/Hg or alveolar-arterial  $O_2$  difference,  $[A-a] DO_2 <35$  mm/Hg) to moderate-to-severe levels ( $pO_2 <70$  mm/Hg or  $[A-a] DO_2 >35$  mm/Hg). Recently, Sage et al. studied the prognostic value of C-reactive protein (CRP) in HIV-infected patients with PCP and reported that, higher CRP values were more suggestive of bacterial infection, but the finding lacked specificity and was not useful in distinguishing between PCP and other causes of respiratory infection. Moreover, in patients with PCP higher CRP values were associated with more severe disease and a poor outcome, suggesting CRP measurement might be used prognostically (Sage et al., 2010).

The chest X-ray (CXR) usually shows bilateral, symmetrical reticular or granular opacities. Less frequently, PCP may present with unilateral or asymmetrical opacities. Some patients with PCP have nodular densities, lobar consolidation or normal CXR findings. Cystic abnormalities and spontaneous pneumothorax in patients with known or suspected HIV infection are usually caused by PCP, but may also be caused by TB. Cavitation or pleural effusion is uncommon in the absence of other pulmonary pathogens or malignancy, and the presence of a pleural effusion might indicate an alternative diagnosis. At times clinical symptomatology, specifically in the absence of significant CXR findings, initiates more sensitive radiological approaches such as high-resolution chest CT. The most typical findings on chest CT are bilateral ground glass opacities. Less-common features can include reticular, granular, and cystic lesions.

Since *Pneumocystis* cannot be cultured, the gold standard for diagnosis is microscopic visualization of the organism of the characteristics cysts or trophic forms on stained respiratory specimens including expectorated or induced sputum, pulmonary secretions obtained by nasotracheal suction, percutaneous aspiration of the lung parenchyma; via flexible bronchoscopy including BAL, washing, brushing and transbronchial biopsy; or via thoracoscopic or open-lung biopsy (Carmona & Limper, 2011). Induced sputum can be the first diagnostic procedure. The reported diagnostic sensitivities of various methods are; induced sputum  $<50$  to  $>90\%$ , bronchoscopy with bronchoalveolar lavage  $90\%$ - $99\%$ , transbronchial biopsy  $95\%$ - $100\%$ , and open lung biopsy  $95\%$ - $100\%$ . PCR-based techniques

have also been employed and have been reported to be more sensitive and less specific leading to higher false-positive rates. Therefore, clinical correlation is always necessary. Since messenger RNA (mRNA) is less stable than DNA, if the patient is not actively infected with viable organisms, the mRNA should be largely degraded and no longer detected. Hence, new techniques that detect (mRNA) have been proposed as surrogate markers for organism viability. Recent data from HIV patients with suspected *Pneumocystis* pneumonia using reverse-transcriptase PCR targeting a heat shock protein of *Pneumocystis* mRNA (Phsb1) have yielded a diagnostic sensitivity and specificity of 100% and 86%, respectively, in BAL specimens (de Oliveira et al., 2007).

In patients without known contraindications, trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice regardless of the severity of disease. The standard dose is 15-20mg/kg/day of TMP and 75-100 mg/kg/day of SMX. However in a recent study, it has been reported that, treatment of PCP in adult HIV-infected patients with trimethoprim 10 mg/kg/day-sulfamethoxazole 50mg/kg/day appears to have comparable efficacy to treatment (Thomas et al., 2009).

For severe cases, the intravenous (IV) form is preferred over the oral formulation. However, IV regimen can be switched to oral route, once clinical improvement is achieved. Standard treatment for PCP is 21 days; some persons will have responded well before this time and therapy can often be stopped and others will remain symptomatic and require continued therapy. Dose reductions are necessary for patients with renal and liver failure. Alternatives to TMP-SMX include intravenous or aerosolized pentamidine, clindamycin plus primaquine, trimethoprim plus dapsone and atovaquone solution. Aerosolized pentamidine has been associated with the development of disseminated disease, likely due to poor systemic levels. The IV formulation of pentamidine has better coverage and greater efficacy than the aerosolized route. However, it is at times poorly tolerated due to side effects that include hypotension, hypoglycemia and pancreatitis (Carmona & Limper, 2011). Another important aspect of *Pneumocystis* treatment is the use of corticosteroids. The administration of corticosteroids at the beginning of the therapy reduces the likelihood of respiratory failure, the deterioration of oxygenation, and death in patients with moderate-to-severe pneumonia. Patients usually benefit from therapy especially with respiratory insufficiency (Rosen, 2008).

#### 4.2 Histoplasmosis

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum* and the infection causes significant morbidity and mortality in HIV-infected individuals. *Histoplasma capsulatum* is reported to exist throughout the world, although the Mississippi and Ohio River catchments of the United States represent areas of greatest endemicity (Kauffman, 2007). It is the most frequent opportunistic infection due to HIV in French Guiana, along with tuberculosis, and the first cause of AIDS-related death (Couppie et al., 2004; Lewden et al., 2004). Disseminated histoplasmosis usually occurs among persons with CD4 lymphocyte counts <150 cells/ $\mu$ L; while localized pulmonary histoplasmosis might occur when CD4 lymphocyte counts >300 cells/ $\mu$ L (Centers for Disease Control and Prevention, 2009).

In HIV-infected patients the most common clinical presentation is disseminated multiorgan disease. Common symptoms include fever, chills, anorexia, fatigue, weight loss, cough, chest pain, and dyspnea and specific symptoms and signs related to organ involvement. In a study of 200 cases of AIDS-related histoplasmosis, most patients had fever, lymphadenopathies, and pulmonary and digestive symptoms whereas neurological signs

and skin/mucosal locations were less common (Huber et al., 2008). The radiologic findings of patients with pulmonary involvement are diffuse interstitial or reticulonodular infiltrates. The patients with disseminated histoplasmosis may have normal CXR. Several laboratory abnormalities include increased lactate dehydrogenase, elevated liver enzymes, especially alkaline phosphatase, markedly increased ferritin, and pancytopenia.

Although the isolation and identification of fungus provides a definitive diagnosis, isolation can take 2–4 weeks and hence, the *Histoplasma* polysaccharide antigen (HPA) test is an initial test for the diagnosis of disseminated histoplasmosis (Centers for Disease Control and Prevention, 2009). Detection of circulating HPA in urine, serum, and other body fluids has an increasingly important role in the rapid diagnosis of disseminated histoplasmosis. Sensitivity is greater in urine than serum and the sensitivity of the urine assay for the diagnosis of disseminated histoplasmosis is approximately 90% (Wheat et al., 2002). In patients who have other fungal infections, including coccidioidomycosis, blastomycosis, paracoccidioidomycosis, and penicilliosis false positive reactions for HPA in urine may occur. The HPA test is often negative in isolated pulmonary disease. In such patients, direct examination and culture of sputum, BAL, or transbronchial biopsy can be performed. Bone marrow, lymph node, liver, or a skin or mucous membrane lesion provides other diagnostic sources.

Amphotericin B, either the deoxycholate formulation or liposomal amphotericin B is currently considered the drug of choice in HIV-positive patients with severe or disseminated histoplasmosis. Once clinical improvement was achieved, Amphotericin can be switched to itraconazole to complete at least a 12-month therapy course.

#### 4.3 Aspergillosis

Aspergillosis, an infrequent but commonly fatal infection among HIV-infected patients, is a mycotic disease caused by *Aspergillus* species, usually *Aspergillus fumigatus*. In a review including 342 cases of pulmonary aspergillosis among HIV-infected patients, *Aspergillus fumigatus* was the most common pathogen (95% of the cases), while strains of *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* were less common (Mylonakis et al., 1998).

The major risk factors for aspergillosis include, neutropenia and steroid treatment, whereas the other risk factors are low CD4 lymphocyte count, previous pneumonia, opportunistic infections, especially those involving the lungs, such as PCP and CMV infection and use of broad spectrum antibacterial therapy, alcohol and marijuana. Clinical manifestations of aspergillus infections include: allergic bronchopulmonary aspergillosis, intracavitary aspergilloma, chronic forms of pulmonary aspergillosis, tracheobronchitis and rhinosinusitis, and invasive pulmonary aspergillosis as the most severe clinical presentation. The two major syndromes that have been described are: respiratory tract disease, associated with fever, cough, dyspnea, stridor or wheezing caused by airway constriction and invasive parenchymal infection which is usually fatal.

Although the prevalence of invasive aspergillosis among patients infected with HIV is lower than in other immunocompromised patients (Mylonakis et al., 1998), invasive pulmonary aspergillosis is still a life-threatening opportunistic infection in the advanced stage of HIV infection. Most patients have a CD4 lymphocyte count lower than 50 cells/ $\mu$ L. Holding et al. reported that, among 35,252 HIV-infected patients, the incidence of aspergillosis was 350/100,000 (Holding, 2000).

The radiologic findings include cavities, nodules and localized or diffuse infiltrates. Since its presence in nasopharyngeal secretions, sputum and BAL fluid may represent contamination

or colonization, the definitive diagnosis of aspergillosis requires identification of the fungus on a biopsy specimen with the documentation of tissue invasion and the presence of appropriate clinical signs and symptoms. In a report, among 45 patients with AIDS and respiratory cultures positive for aspergillus, invasive pulmonary aspergillosis was documented in only four of these patients (Pursell et al., 1992). However, a presumptive diagnosis of respiratory tract disease can be made in the absence of a tissue biopsy if *Aspergillus spp.* are cultured from a respiratory sample, a compatible lesion or syndrome is present, and no alternative causative process is identified. Although serum galactomannan antigen testing and PCR-based techniques may be useful, they have not been studied in patients with HIV.

Voriconazole is the first-line recommended therapy for invasive aspergillosis. Conventional or lipid formulations of Amphotericin B, caspofungin and posaconazole are the other alternatives for antifungal therapy.

#### 4.4 Coccidioidomycosis

Coccidioidomycosis is a fungal disease caused by, *Coccidioides immitis* and *Coccidioides posadasii*. The disease is endemic in southwestern US and northern Mexico (Pappagianis, 1988). Although coccidioidomycosis is uncommon in HIV-infected patients, in endemic regions, it is a common opportunistic infection in HIV-infected individuals. In a study performed by Masannat et al, among 257 HIV-infected patients seen over a 64-month period, 29 cases (11.3%) of coccidioidomycosis were identified (Masannat & Ampel, 2010). The incidence of coccidioidomycosis has declined as a result of ART (Woods et al., 2000).

The risk factors for coccidioidomycosis include low CD4 cell counts (<250 cells/ $\mu$ L), black race, a history of oropharyngeal or esophageal candidiasis, whereas a reduced risk is associated with protease inhibitor therapy.

The most common clinical presentations of coccidioidomycosis in HIV-infected patients are disseminated disease, diffuse pneumonia and meningitis. Disseminated coccidioidomycosis, defined as disease that has spread beyond the thoracic cavity, is frequent among patients with HIV infection and associated with generalized lymphadenopathy, skin nodules or ulcers, peritonitis, liver abnormalities, and bone and joint involvement. The most common radiographic finding of coccidioidomycosis is reticulonodular infiltrates. Focal infiltrates are less common. The other findings include nodules, adenopathy, cavities and pleural effusion. The mainstays of diagnosis of coccidioidomycosis are serologic testing, histopathological identification, and culture (Ampel, 2005). In cases of pulmonary coccidioidomycosis, results of culture of respiratory specimens (sputum, BAL fluid, or transbronchial biopsy) are frequently positive. The diagnosis can be established by also, demonstration of the typical spherule on histopathological examination of involved tissue. Although, serologic tests are useful, it is less reliable for patients with HIV infection than for immunocompetent patients and the results may not always be positive.

Amphotericin B is the preferred initial therapy for patients with isolated pulmonary disease and disseminated disease without meningeal involvement (Centers for Disease Control and Prevention, 2009). Amphotericin B should be continued until clinical improvement, and then the therapy can be switched to fluconazole or itraconazole. In patients with mild disease such as focal pneumonia, fluconazole or itraconazole may be alternative agents. Fluconazole is the recommended drug for coccidioidal meningitis, since the reported success of this agent is approximately 80% (Galgiani et al., 1993).

#### 4.5 Candidiasis

Mucocutaneous candidiasis is frequently one of the first signs of HIV infection and 90% of patients with AIDS will develop oropharyngeal candidiasis at some time during their illness (Vazquez, 2000). However, pulmonary candidiasis is an uncommon manifestation among HIV-infected patients. In 1987, data from the Centers for Disease Control AIDS data base indicated a 50% prevalence of oropharyngeal *Candida* infection, a 10% rate of esophageal infection, and 5% rate of bronchopulmonary infection among AIDS patients (Selik et al., 1987). Due to the rare occurrence of pulmonary candidiasis, clinical features among HIV-infected patients are not well documented.

#### 4.6 Blastomycosis

Blastomycosis is a fungal infection acquired via inhalation of *Blastomyces dermatitidis*. The majority of cases occur in central, southeastern, and mid-Atlantic areas of the United States. Of the endemic fungi, blastomycosis is an uncommon disease among HIV-infected patients. The most common clinical manifestation of blastomycosis in immunocompetent hosts include skin and lung involvement which mimic those of bacterial infection. However, it is potentially much more severe and is characterized by disseminated multiple organ involvement including frequent involvement of the central nervous system, adult respiratory distress syndrome and/or miliary pulmonary involvement. In the largest case series reported to date, among 15 HIV-infected patients, the patterns of the disease was localized pulmonary involvement in seven patients, disseminated or extrapulmonary blastomycosis in eight patients and in 40% of patients central nervous system involvement was observed (Pappas et al., 1992).

In HIV-infected patients, blastomycosis tends to occur in persons CD4 counts less than 200 cells/mm<sup>3</sup>. In the largest case series mentioned above, among 15 patients, only one patient had a CD4 lymphocyte count greater than 200 cells/ $\mu$ L (Pappas et al., 1992).

The definitive diagnosis requires culture of respiratory specimens or tissue samples. The visualization of characteristic budding yeast form is also highly suggestive for diagnosis. Sputum analysis in most cases aids in the diagnosis, but bronchoscopy and/or tissue biopsy should be considered if the suspicion of blastomycosis is high and sputum analysis is inconclusive, negative or not possible (Patel et al., 1999). There is no serologic test for blastomycosis that has been validated in HIV-infected patients.

Intravenous amphotericin B is the drug of choice in patients with severe or disseminated blastomycosis. Amphotericin should be continued until a total of 1.5 to 2.5 g dose. Then, with the improvement of patient, the therapy can be switched to oral itraconazole.

#### 4.7 Cryptococcosis

Cryptococcosis is a disease caused by *Cryptococcus neoformans* a unique environmental fungus and an encapsulated budding yeast. In AIDS patients *Cryptococcus neoformans*, serotype D and in particular serotype A, is the major cause of cryptococcosis throughout the world (Sugar, 1991).

Although the lungs are the portal of entry of the infection, the most common clinical presentation of cryptococcosis among HIV-infected patients is meningitis. In a study performed by Chuck et al., 84% of patients with HIV infection and cryptococcosis had meningitis, whereas 4% of patients had isolated pneumonia (Chuck & Sande, 1989). The majority of cases of cryptococcal disease occur in persons with a CD4 cell count below 200

cells/ $\mu\text{L}$ , usually below 50 cells/ $\mu\text{L}$ . In a series of 15 HIV-infected patients with pulmonary cryptococcosis, the CD4 lymphocyte count was low in all cases (median, 24/ $\mu\text{L}$ ) (Ballou et al., 1997). With the use of combination ART, the incidence of cryptococcosis has dramatically declined.

The clinical manifestations of pulmonary cryptococcosis include fever, cough, dyspnea, expectoration, chest pain and hemoptysis. The most common radiographic finding is diffuse interstitial opacities, while others are focal interstitial abnormalities, alveolar opacities, adenopathies, cavitory lesions, and pleural effusions. Solitary pulmonary nodules, pulmonary masses, a milliary pattern and pneumothorax have also been reported.

The initial diagnostic test for cryptococcosis is cryptococcal antigen test, which is sensitive and specific. However, patients with isolated pulmonary disease may have a negative result. The test can be performed on serum, cerebrospinal fluid and respiratory samples. Blood fungal cultures are also specific and should be performed. The diagnosis of pulmonary cryptococcosis can be made by culture of sputum, BAL fluid, pleural fluid and transbronchial biopsy specimen. The measurement of cryptococcal antigen in the BAL can be a rapid, simple way to make the diagnosis (Baughman et al., 1992).

The treatment of meningitis and pneumonia is same and the recommended initial treatment for acute disease is amphotericin B, usually combined with flucytosine, for a 2-week duration followed by fluconazole (400 mg daily) alone for an additional 8 weeks (Centers for Disease Control and Prevention, 2009). Following this period, as a maintenance therapy, fluconazole (200 mg daily) for life or until the CD4 cell count rises above 200 cells/ $\mu\text{L}$  for at least 6 months should be continued.

#### 4.8 Penicilliosis

Penicilliosis is caused by *Penicillium marneffeii*, a dimorphic fungus which is endemic in Southeast Asia. Although it was a rare and sporadic disease before the HIV pandemic, penicilliosis is now the third most common AIDS-defining illness (after TB and cryptococcosis) in South East Asia (Fisher et al., 2004).

Although direct inoculation through skin can occur, inhalation is the main route of exposure. Most of the patients show absolute CD4 count less than 100 cells/ $\mu\text{L}$  (Maniar et al., 2005).

*Penicillium marneffeii* can cause focal or disseminated infection. The common presenting symptoms and signs of infection are: fever of unknown origin, anemia, weight loss, hepatosplenomegaly, lymphadenopathy and skin eruptions. The skin lesions commonly appear as papules (characteristically with central umbilication, resembling molluscum contagiosum), nodules, or necrotic lesions, and they are predominantly located over the face and upper trunk (Ustianowski et al., 2008). The most common radiographic finding is interstitial opacities, the other findings may include nodules, cavities and pleural effusion. In a study from Taiwan, in which etiology of cavitory lung lesions in patients with HIV infection was evaluated, fungi were the most common etiology (42.0%), followed by bacteria (29.6%) and mycobacteria (25.9%) and of the fungal pneumonias, 19 (55.9%) were caused by *Penicillium marneffeii* as the most common agent (Lin et al., 2009). Definitive diagnosis requires culture of the pathogenic fungus from clinical specimens. Among all the clinical specimens studied, the bone marrow gives the highest yield for culture, approaching 100%, followed by skin biopsy (90%) and blood culture (76%) (Supparatpinyo et al., 1994). Serologic testing including various types of antigen and antibody testing specific to *P. marneffeii* have been described but is of limited utility in penicilliosis (Wong & Wong, 2011).

PCR assay specific for *P. marneffei* has been developed in research setting but is not available for routine clinical use (Pornprasert et al., 2009).

The mainstay of therapy is amphotericin B (2 weeks) followed by itraconazole (10 weeks). Since relapse is common, secondary prophylaxis should be maintained until a CD4 count of greater than 200 cells/ $\mu$ L for at least 6 months.

## 5. Viral infections

Although a variety of viruses can cause pulmonary disease in HIV-infected patients, cytomegalovirus (CMV) is the most frequent agent of viral pneumonia. Pneumonia due to herpes simplex virus, varicella zoster virus, adenovirus, respiratory syncytial virus and parainfluenza virus is uncommon.

### 5.1 Cytomegalovirus

Cytomegalovirus (CMV) disease is a frequent opportunistic infection that usually occurs in the late stages of HIV infection as a result of reactivation of latent infection rather than new infection. It has been reported that, before ART, 21–44% of patients developed CMV-associated disease at some point during the course of HIV infection and with the use of ART, the incidence of CMV disease has declined by 75–80%, and it is now estimated to be 0.75–3.2 cases per 100 person-years (Jabs et al., 2007; Salmon-Ceron et al., 2000; Salzberger et al., 2005). The most common clinical manifestations of CMV are retinitis and gastrointestinal disease (colitis or esophagitis). CMV pneumonia is uncommon and has been observed in only 0.24–8% of HIV-infected patients (Ericc et al., 2003; Rodriguez-Barradas et al., 1996). Most of the patients have CD4 count less than 50 cells/ $\mu$ L. The chest radiograph findings include diffuse interstitial infiltrates, alveolar infiltrates or rarely pleural effusion. In HIV-infected patients, the presence of CMV in BAL fluid is not usually predictive of CMV pneumonia and a definitive diagnosis depends on the documentation of CMV infection in lung tissue specimens. Diagnosis of CMV pneumonitis should be made in the setting of pulmonary interstitial infiltrates and identification of multiple CMV inclusion bodies in lung tissue, and the absence of other pathogens. Neither BAL fluid nor transbronchial biopsy culture are sufficient to make the diagnosis of CMV pneumonitis (Huang & Crothers, 2009). Although there is limited data, the treatment options for CMV pneumonia include ganciclovir, foscarnet, cidofovir or valganciclovir. The duration of therapy is unknown, but a 2-3 weeks course is recommended.

## 6. Parasitic infections

Although, *Toxoplasma gondii*, *Strongyloides stercoralis*, microsporidia, cryptosporidium can cause pneumonia, among HIV-infected patients, parasitic pneumonia is an uncommon disease.

### 6.1 *Toxoplasma gondii*

*Toxoplasma gondii*, is the most common cause of parasitic pneumonia. Cerebral toxoplasmosis is the most common form of clinical manifestation, followed by ocular toxoplasmosis and pulmonary toxoplasmosis. As a result of widespread utilization of trimethoprim-sulphamethoxazole as primary PCP prophylaxis in AIDS patients, which is also effective against *Toxoplasma gondii*, there has been a fall in the prevalence of pulmonary

toxoplasmosis. Pulmonary toxoplasmosis (PT) is most commonly seen in patients with advanced disease (Renold et al., 1992). In an autopsy study of 78 cases of toxoplasmosis, the risk factors were founded as; intravenous drug addiction, homosexuality or bisexuality and multiple blood transfusions (Hofman et al., 1993). Bilateral interstitial infiltrates is the most frequent finding on chest radiography; however, other abnormalities including nodular densities and pleural effusion and/or pneumothorax may also occur. An elevated LDH is a common laboratory finding. In a large study of 64 HIV-infected patients with PT, the clinical features usually included fever, cough, and dyspnea and the radiological findings were mainly diffuse interstitial infiltrates (Rabaud et al., 1996). Since clinical and radiological abnormalities are not specific, the diagnosis of pulmonary toxoplasmosis is difficult. The diagnosis can be established by direct examination (by Giemsa staining or indirect immunofluorescence with a monoclonal antibody to membrane antigen P-30) and/or tissue or BAL fluid culture. Although, PCR for detecting *T. gondii* in BAL samples have been studied, the diagnostic utility of this test is unclear (Lavrard et al., 1995; Petersen et al., 2006). The treatment of PT is similar to that for central nervous system disease and the first-line treatment is pyrimethamine plus sulfadiazine. Leucovorin is recommended for the hematologic toxicities associated with pyrimethamine. Clindamycin plus pyrimethamine is the alternative regimen.

## 6.2 Other parasites

*Strongyloides stercoralis* is an intestinal nematode which usually induces a silent or limited intestinal infection in immunocompetent hosts. It can also cause hyperinfection syndrome or disseminated disease in immunocompromised patients (Kramer et al., 1990). However, disseminated infection of *Strongyloides stercoralis* to the lung is extremely rare (Armignacco et al., 1989; Glezerov & Masci, 1990; Gomples et al., 1991; Makris et al., 1993). The common symptoms and signs are dyspnea, cough, sputum, wheezing and hemoptysis. In patients with the hyperinfection syndrome and massive *Strongyloides* infection, adult respiratory distress syndrome with respiratory failure that requires mechanical ventilation may develop. Chest radiography findings include reticulonodular pattern, diffuse bilateral interstitial opacities and alveolar opacities. The diagnosis is established by the identification of *Strongyloides* larvae on BAL fluid. The recommended treatment is ivermectin plus albendazole.

Microsporidia and cryptosporidium are other parasites which can rarely cause respiratory tract disease. Cryptosporidiosis is a disease caused by a coccidial parasite of the genus *Cryptosporidium*. Pulmonary cryptosporidiosis is a rare complication of intestinal cryptosporidiosis in HIV-infected patients (Corti et al., 2008). The most frequent symptoms are cough, fever and dyspnea. Several respiratory infectious agents, mainly *P. carinii* and *Cytomegalovirus* may coexist (Brea Hernando et al., 1993). The major clinical manifestation of microsporidiosis is the involvement of gastrointestinal tract like cryptosporidiosis and it can rarely cause pulmonary symptoms (Remadi et al., 1995). The diagnosis of both diseases is made by the visualization of the organism on the respiratory specimen.

## 7. Conclusion

Human immunodeficiency virus (HIV), the cause of AIDS, has in the 30 years since its discovery spread rapidly to every region in the world. Since the beginning of epidemic, more than 65 million people have been infected with HIV and about 25 million people died from

AIDS. The lungs are principal target of HIV-associated complications and, accordingly, a major source of morbidity and mortality. The spectrum of pulmonary manifestations includes bacterial infections, viral infections, mycobacterial infections, protozoal infections, fungal infections, malignancies (eg, Kaposi sarcoma, lymphoma), and other disorders (eg, pulmonary hypertension, lymphocytic interstitial pneumonitis). Among HIV-associated pulmonary complications, opportunistic pneumonias are major cause of morbidity and mortality.

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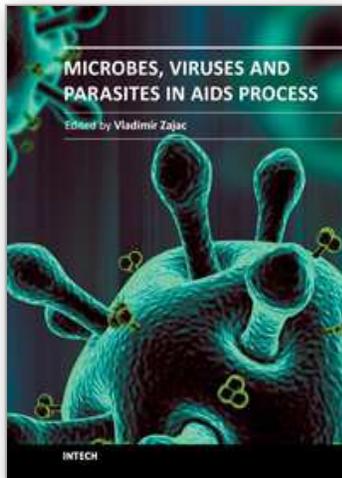
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## **Microbes, Viruses and Parasites in AIDS Process**

Edited by Prof. Vladimír Zajac

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The main goal in compiling this book was to highlight the situation in Africa in terms of AIDS and opportunistic diseases. Several chapters reveal great poverty, an apocalyptic situation in many parts of Africa. Global migration of people resulted in their exposure to pathogens from all over the world. This fact has to be acknowledged and accepted as African reality. New, unconventional hypotheses, not determined by established dogmas, have been incorporated into the book, although they have not yet been sufficiently validated experimentally. It still applies that any dogma in any area of science, and medicine in particular, has and always will hinder progress. According to some biologists, in the future, AIDS is very likely to occur in a number of variations, as a direct result of the ongoing processes in the global human society. Thus, we urgently need a comprehensive solution for AIDS, in order to be ready to fight other, much more dangerous intruders.

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