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Pulmonary Manifestations of HIV Disease

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1. Introduction

After the first cases of AIDS were described in 1981, the HIV pandemic rapidly expanded to become a major global public health problem with broad health, social, economic and developmental consequences that have not been seen with any other disease. In the 30 years that this disease has been known to mankind it has killed an estimated 25 million people and continues to affect not less than 33 million people many of whom could die if life saving therapies are not made available to them. The African continent has borne the largest impact of this disease. Of the 33.3 million people that UNAIDS estimated were living with HIV in 2009, nearly 67% were living in Africa.

Pulmonary disease is a major contributor to the morbidity and mortality suffered by persons infected with HIV. It was the appearance of previously rare Pneumocytis pneumonia often accompanied by Kaposis sarcoma in previously healthy young gay men, intravenous drugs addicts and their sexual contacts that alerted the world to the new syndrome of the Acquired Immune Deficiency Syndrome (AIDS) caused by HIV. Before combination anti retroviral treatment (cART) became available a high proportion of HIV infected individuals would experience respiratory symptoms, and serious life threatening lung disease. Lung disease was often the index diagnosis that would point to the presence of HIV infection. In general the incidence of serious pulmonary disease has declined following the wide availability of cART. For example in the USA rates of opportunistic infections decreased from 89.0 per 1000 person years in 1994-1997 to 25 per 1000 person years in 1998-2002, and 13 per 1000 person years in 2003-2007. However, the incidence of many infectious diseases remain relatively high even in the cART era and worryingly as HIV infected persons live longer, they appear to face an increased risk of non infectious lung diseases such as lung cancer, chronic obstructive lung disease and pulmonary arterial hypertension.

The range of pulmonary diseases that occur in HIV infected individuals is wide and includes infections, neoplasms, vascular lesions, interstitial pneumonias and obstructive airways disease. This chapter will summarize the current knowledge base on HIV associated lung disease including the burden and spectrum of the common diseases, diagnostic evaluation and approaches to treatment and prevention.

2. Burden of pulmonary disease in HIV

Prospective cohort studies carried out in the pre cART era out in North America and Western Europe documented a high incidence of both Pneumocytis and bacterial
Table 1. Common pulmonary complications of HIV/AIDS.

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Pneumocystis jirovecii, Aspergillus spp, Cryptococcus neoformans, Candida spp, Mycoses Endemic to specific geographic areas (Histoplasma spp, Coccidiodes spp, Paracoccidiodes, Pencillium marneffei)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Pseudomonas aeruginosa, Mycobacterium tuberculosis, Others</td>
</tr>
<tr>
<td>Fungal</td>
<td>Pneumocystis jirovecii, Aspergillus spp, Cryptococcus neoformans, Candida spp, Mycoses Endemic to specific geographic areas (Histoplasma spp, Coccidiodes spp, Paracoccidiodes, Pencillium marneffei)</td>
</tr>
<tr>
<td>Viral</td>
<td>Cytomegalovirus, Herpes Simplex, Influenza, Others</td>
</tr>
<tr>
<td>Parastic</td>
<td>Toxoplasma gondii, Strongyloides stercoralis</td>
</tr>
<tr>
<td>Malignancies</td>
<td>Kaposis sarcoma, Lymphoma, Lung cancer</td>
</tr>
<tr>
<td>Other non infectious diseases</td>
<td>Non specific Interstitial pneumonitis, Lymphoid Interstitial Pneumonitis, Pulmonary arterial hypertension, Chronic Obstructive Airway disease, Others</td>
</tr>
</tbody>
</table>

The advent of cART markedly reduced the burden of both Pneumocytis and bacterial pneumonia but more so for Pneumocystis pneumonia\textsuperscript{16,17,18,}. In contra distinction with situation in the developed world where Pneumocytis pneumonia was the hallmark of HIV lung disease, tuberculosis (TB) has been the predominant disease in HIV infected persons in Sub-Saharan Africa. Tuberculosis case notification rates rapidly escalated as the HIV epidemic spread\textsuperscript{19, 20, 21,}. In 2009 the World Health Organization estimated that HIV associated TB occurred in about 1.2 million people and was responsible for the deaths of about 200,000 people with nearly 85% of this burden occurring in Sub-Saharan Africa\textsuperscript{22,}.

3. Clinical evaluation of HIV infected persons with respiratory symptoms

3.1 History

Even though advances have been made in medical technologies for the diagnosis of lung disease, a good clinical history remains essential in the clinical evaluation of HIV infected persons with lung disease. A thorough understanding of the patient’s illness may assist to narrow down the specific diagnosis behind the patient symptoms. It is important to establish if the patient presenting with respiratory symptoms already knows his or her HIV status and...
if so how long that status has been known. It is also important to know if that person has suffered opportunistic infections in the past, and if the patient is taking cART and preventive therapy for opportunistic infections. If the patient has been taking cART current and previous regimens must be elucidated and enquiries on adherence to current and previous cART made. The appearance of a lung opportunistic infection in a patient who has been on cART may point to a failing regimen. Since certain infections occur only in specific geographic areas a travel history should be obtained. Other risk factors for disease occurrence or for poor outcomes must as far as feasible be sought. These risk factors include intravenous drug use, alcohol abuse and tobacco smoking. The pre-morbid health status must also be known.

3.2 Clinical examination
The clinical examination is intended to establish if serious lung disease is present and thus if urgent interventions are required. A common sense approach will help identify most patients with serious lung disease. Assessment of the patients' mental status together with measurement of the respiratory rate, pulse, temperature, blood pressure and transcutaneous arterial oxygen saturation should rapidly reveal the presence or absence of serious life threatening lung disease.

3.3 Laboratory tests
The choice of laboratory and other tests to be carried out will depend on the clinical condition of the patient, the setting in which the patient is seen and the laboratory infrastructure available. Ideally most patients should have a plain chest radiograph to confirm the presence of lung disease and the extent of pulmonary involvement which will influence the placement of patients into specific risk groups for various outcomes and guide further management. Further medical tests may be carried out to identify co-morbid states or other organ involvement to assist with prognostication while others may be carried to diagnose the specific disease and thus assist in provision of targeted treatment. Tests designed to identify specific diseases include examination of body fluids such as sputum, blood, urine, bronchoalveolar lavage fluid, pleural fluid and others for pathogens using various stains, cultures, antigen and nucleic acid detection tests. Fiberoptic bronchoscopy (FOB), where available, with lavage, brushing and biopsy has found a special place in the evaluation of HIV infected persons with
respiratory symptoms. However FOB should not be used routinely in all HIV infected persons. This procedure may not provide treatment changing results in some settings.

**Evaluation of the patient with HIV Lung Disease**

<table>
<thead>
<tr>
<th>Test/procedure</th>
<th>Purpose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray</td>
<td>Detection of lung disease/severity assessment</td>
<td>Universally done</td>
</tr>
<tr>
<td>CT scan</td>
<td>Detection of lung disease/severity assessment</td>
<td>Offers better detection and radiographic characterization of lung disease/May be abnormal in the presence of a normal chest x-ray</td>
</tr>
<tr>
<td>Pulse oximetry</td>
<td>Severity assessment/monitoring</td>
<td>Should be used in all patients with severe disease</td>
</tr>
<tr>
<td>Arterial blood gases</td>
<td>Severity assessment/monitoring</td>
<td>Should be used in all patients with severe disease</td>
</tr>
<tr>
<td>Blood count (WBC, HB, Platelets)/ coagulation tests</td>
<td>Severity assessment/monitoring</td>
<td>Should be used in all patients with severe disease</td>
</tr>
<tr>
<td>Renal and liver function tests</td>
<td>Severity assessment/monitoring</td>
<td>Should be used in all patients with severe disease</td>
</tr>
<tr>
<td>Induced Sputum gram stain and culture</td>
<td>Microbiological aetiology</td>
<td>Should be used in all patients with severe disease</td>
</tr>
<tr>
<td>Blood culture</td>
<td>Microbiological aetiology</td>
<td>Should be used in all patients with severe disease</td>
</tr>
<tr>
<td>Antigen detection (Blood/urine/sputum)</td>
<td>Microbiological aetiology</td>
<td>Especially for S. Pneumoniae and L. pneumophila sero group 1</td>
</tr>
<tr>
<td>Serological tests</td>
<td>Microbiological aetiology</td>
<td>Most for the detection of “atypical pathogens”. Provide retrospective diagnosis</td>
</tr>
<tr>
<td>Fiberoptic bronchoscopy with lavage, brushing and or biopsy</td>
<td>Microbiological aetiology/diagnosis of non infectious disease</td>
<td>Probably best reserved for patients with non diagnostic results with non invasive tests</td>
</tr>
<tr>
<td>Open Lung Biopsy</td>
<td>Histological diagnosis/Microbiological diagnosis</td>
<td>Used mostly if bronchoscopy with TBB fails to provide a diagnosis</td>
</tr>
<tr>
<td>Radio isotope studies</td>
<td>Diagnosis of infectious/non infectious disease</td>
<td>Gallium 67 citrate and 99m TCDTPA: expensive, time consuming and require complex infrastructure</td>
</tr>
<tr>
<td>Other tests (lung function tests)</td>
<td>Diagnosis of non infectious disease (COPD)</td>
<td>TLCO, KCO, FEV1, FVC: Sensitive but not specific for any lung disease</td>
</tr>
</tbody>
</table>

Table 2. Common tests and procedures for evaluating HIV associated lung disease.
4. Specific lung diseases

4.1 Fungal pneumonia in HIV infected persons

4.1.1 Pneumocystis pneumonia (PCP)

The causative organism of Pneumocystis pneumonia, *Pneumocystis jirovecii*, has had an interesting history in terms of its taxonomy. Initially the pathogen was thought to be protozoan in nature. Later it was placed on the fungal group based on its nucleic acid profile and the name of the human pathogen was changed from *Pneumocystis carinii* to *Pneumocystis jirovecii* based on the understanding that the species that affects humans is distinctly different from that which affects other animals including cats.

4.1.1.1 Epidemiology

Pneumocystis pneumonia was the dominant opportunistic infection in the pre cART era in North America and Europe. In contrast to the dominance of PCP in North America and Western Europe, other regions of the world and especially Sub-Saharan Africa, the current epicentre of the HIV/AIDS epidemic, did not experience this surge of PCP with rates of PCP ranging from 0-21% in the earlier case series and cohort studies. In fact for a while this infection was thought to be absent from Africa. As the HIV epidemic matured in Sub-Saharan Africa the prevalence of PCP in HIV infected patients appeared to have increased, but the rates of this infection did not reach the levels that were observed in Western Europe and North America during the early years of the HIV epidemic. Currently PCP remains relatively rare in Sub-Saharan Africa, with prevalence as low as 1% being reported. The reasons for the low prevalence of PCP in Sub-Saharan Africa are not fully known but racial factors influencing susceptibility to the development of disease following infection or colonization may partly play a role. It is also worth noting that African populations have been documented to have a high prevalence of exposure to this pathogen and therefore the low rates of PCP in Sub-Saharan Africa is not the result of the absence of the pathogen from the African environment.

4.1.1.2 Risk factors

Several studies have examined the risk factors for PCP in HIV infected individuals. These studies indicate that the risk of PCP is highest in those with declining CD4 T cell count especially when the count falls below 200, unexplained fever, history of AIDS defining illness, presence of oral thrush and not being on prophylaxis or when prophylaxis fails. HIV infected persons of the negroid race may have a lower risk of PCP compared to Caucasians.

4.1.1.3 Clinical manifestations

**Symptoms**

Pneumocystis pneumonia usually presents with a sub acute onset of cough and shortness of breath. The cough is usually non productive or may be productive of scanty mucoid sputum while shortness of breath is slowly progressive and gradually limits activity. Many patients do not experience chest pain and do not have other constitutional disturbances, the symptom complex being largely dominated by shortness of breath.

**Signs**

The majority of patients will appear anxious when they are first examined. The breathing frequency is usually rapid and shallow. The pulse is also rapid but most often at the first evaluation the blood pressure is normal. Patients with PCP may have no fever at
presentation. Lung signs including crackles may be absent and even when present are non specific. There may be evidence of other opportunistic infections such ano genital herpetic ulcers and oral thrush.

![Image of lung signs](image)

Fig. 2. Ano genital Herpetic Ulcers in a patient with PcP.

### 4.1.1.4 Pneumocystis pneumonia – Diagnostic tests

**Radiologic imaging**

Patients suspected to have PcP should have a chest radiograph which typically shows bilateral interstitial or alveolar shadows in the mid zones with basal and apical sparing. In some situations PcP may be present without any obvious changes on the chest radiograph. In these situations high resolution chest CT scan may reveal typical abnormalities that may render the performance of a fiberoptic bronchoscopy procedure unwarranted. Radiostopic studies using Gallium 67 scintigraphy, where available may help to distinguish lung infections from neoplastic and other diseases processes.

![Image of chest radiograph](image)

Fig. 3. Chest Radiograph showing shadows typical of PcP.

**Lung function testing**

Patients with PcP typically are hypoxemic and will desaturate further when exercised, an observation that has been used as a diagnostic test to predict the presence of this infection.
The measurement of diffusion capacity has also been found to be a useful diagnostic test\textsuperscript{43}.

**Microbiological tests**

The definitive diagnosis of PCP is based on the identification of the pathogen in lung samples most commonly obtained through induced sputum, fiberoptic bronchoscopy or open lung biopsy. While some controversy still exists, fiberoptic bronchoscopy with lavage is the standard procedure for the detection of Pneumocystis jirovecii\textsuperscript{44}. Both bronchial brushings and transbronchial biopsy during the bronchoscopy procedure may offer no added value in the evaluation of patients suspected to have PCP\textsuperscript{45}. In general lower respiratory tract specimens are subjected to either cytochemical staining using May-Grünwald-Giemsa (MGG), toluidine blue-O (TOL), Papanicolau (PAP) and Grocott methenamine silver (GRO); immunofluorescent staining with monoclonal antibodies or PCR. However PCR may not distinguish infection from colonization\textsuperscript{46}. Examination of expectorated sputum remains a useful procedure for the microbiological diagnosis of PCP especially in low resource settings. When toluidine blue O staining of expectorated sputum is carried out the sensitivity approaches 70\% and 35\% compared with immunofluorescent staining and PCR respectively while specificity is 100\% and thus in these settings examination of expectorated sputum may be a practical procedure for the diagnosis of PCP\textsuperscript{47}. The yield from sputum examination may be increased if sputum production is induced following inhalation of hypertonic saline. In a meta analysis of diagnostic procedures for PCP, it was found that, compared with bronchoalvelar lavage as the gold standard, examination of induced sputum had an overall sensitivity of 55.5\% and a specificity of 98.6\% with even better sensitivity at 67\% versus 43.1\% when comparing immunofluorescent staining with cytochemical staining. In settings where the prevalence of PCP is in the range of 25-60\%, the positive and negative predictive values ranged from 86-96.7\% and 66.2-89.8\%, respectively, with immunofluorescent staining, and 79-94.4\% and 53-83.5\% with cytochemical staining\textsuperscript{48}.

**Other tests**

The diagnosis of PCP may also be aided by the measurement of serum 1-3 beta D –Glucan, a cell wall component of most pathogenic fungi including Pneumocystis jirovecii which has been found to have a sensitivity of nearly 100\% and specificity of about 96.4\%. Therefore this test may be used as non invasive test for diagnosis of PCP\textsuperscript{49,50}. This test may however not correlate with disease severity and should not be used to monitor patients on treatment\textsuperscript{51}.

**Treatment of Pneumocystis Pneumonia**

The drug of first choice for the treatment of PCP remains cotrimoxazole. The recommended dose is 20mg per Kg body weight per day for the trimethoprim and 100 mg per Kg per day for the sulphamethoxazole, given in three or four divided doses. It has been reported, however that lower doses may be used without loss of efficacy and with the added advantage of a reduction in the rate of adverse events\textsuperscript{51}. Second line treatment options for patients unable to tolerate high dose cotrimoxazole include clindamycin /primaquine and pentamidine but pentamidine may be associated with a greater risk of death\textsuperscript{52}. Trimetrexate with folinic acid is generally well tolerated and has a clinical efficacy of about 70\%\textsuperscript{53}. Other second line therapies include atovaquone, dapsone, a combination product of trimethoprim and dapsone and efornithine hydrochloride. A metaanalysis of second line therapies, in patients who fail whatever initial treatment is given concluded that the combination of
clindamycin plus primaquine appears to be the most effective alternative treatment for patients with PcP who are unresponsive to conventional antipneumocystis agents.

**Outcomes**

Pneumocystis pneumonia is a serious life threatening illness in persons living with HIV. The overall in hospital mortality of this illness is in the region of 10-13%. Among the factors that have been associated with death in patients with PcP include older age, recent injection drug use, total bilirubin of greater than 0.6 mg/dl, serum albumin of less than 3 g/dl, alveolar-arterial oxygen gradient of equal or greater than 50 mm Hg, failure of cotrimoxazole treatment and the presence of co- morbidities such as bacterial pneumonia, Kaposi sarcoma and TB.

Patients who need to be admitted to the intensive care unit may suffer very high rates of deaths that could reach 80% within the ICU and up to 34 % three months post ICU admission. The high mortality of patients who need to be mechanically ventilated appears to be associated with high APACHE II scores, high levels of Positive End Expiratory Pressures (PEEP), the presence of co- infection with CMV and lower CD4 T cell counts.

In an attempt to lower the mortality of PcP adjunctive systemic steroids are recommended based on the results of clinical trials that documented a reduction in mortality in patients with moderate to severe disease. Use of adjunctive steroids for the treatment of moderate to severe PcP has not been associated with increased long term mortality after the PcP episode nor with an increase in the incidence of other opportunistic infections.

There have been concerns that patients infected with Pneumocystis jirovecii that has developed mutations in the dihydropteroate synthase reductase gene may not respond as well to cotrimoxazole as patients whose pathogen does not carry these mutations. The majority of studies however indicate that the development of mutations on the dihydropteroate synthase reductase gene does not have an impact on the efficacy of cotrimoxazole in the treatment of PcP. However it has been reported that DHPS mutations increase the risk of death in patients with PcP.

It has been suggested that measurement of C- Reactive Protein (CRP) may be a useful prognostic marker in patients with PcP. In one study the levels of CRP were negatively correlated with arterial oxygenation (PaO2).

**Prevention**

Pneumocystis pneumonia in HIV infected persons is a preventable disease. The most effective treatment for the prevention of PcP is cART which reconstitutes the immune system and dramatically reduces the incidence of opportunistic infections including PcP. Many HIV infected persons with risk factors for PcP will however require to be protected from this disease even if they have been placed on cART until CD4 T cell recovery has taken place. Although aerosolized pentamidine and cotrimoxazole may have equal efficacy, the preferred drug is cotrimoxazole but if this cannot be tolerated aerosolized pentamidine or atovaquone which have been found to have similar efficacy may be used.

Mutation in the dihydrofolate reductase gene may however, lead to prophylaxis failures. An alternative drug is dapsone which appears to have an efficacy equal to that of atovaquone but which may be less safe. In patients receiving cART it has been recommended that prophylaxis for PcP be discontinued when the CD 4 T cell count climbs to 200 and above but recent studies suggest that prophylaxis may be discontinued when viral suppression is achieved and before the CD 4 T cell count reaches 200 and above. These are reassuring observations because cotrimoxazole treatment may sometimes be associated serious life threatening complications including septic shock like syndrome.
Complications

Pneumocystis pneumonia may result in pneumothorax and pneumomediastinum both of which may be life threatening. These complications are thought to arise from newly formed cysts and bronchiectasis.

4.1.2 Other fungal pneumonias in HIV infected persons

Pneumonia caused by fungal pathogens, other than Pneumocystis jirovecii, though less common when compared with PcP and bacterial pneumonia is a frequent cause of morbidity and mortality in HIV infected persons. Fungal pathogens have been identified mostly in severely immunocompromised patients with CD 4 T cell count below 200 and the lung is often involved in a disease process that is often disseminated and or where multiple pathogens are causing disease. The mortality of fungal pneumonia in HIV infected persons is thus high.

Of the fungal pathogens that have been associated with lung disease in persons living with HIV Cryptococcus may not only be the commonest pathogen but also the best characterized. This fungus is ubiquitous and is more famous for causing meningitis in severely immunocompromised patients. Lung disease due to Cryptococcus neoformans has been reported in all parts of the world and tends to occur in patients who have CD 4 T cell counts below 200. The other ubiquitous fungus that has been associated with lung disease in HIV infected persons is Aspergillus spp. Invasive Aspergillosis occurs most commonly in patients who have a severely depressed immune system and often participates in disease in partnership with other pathogens, as a disseminated infection which confers a high mortality.

Other fungal pathogens are mostly confined to specific geographic areas where they have been reported to cause significant morbidity and mortality in HIV infected persons. These fungal pathogens include Histoplasma spp, Coccidioides spp, Paracoccidioides spp, Pencillium marneffei, Sporotrichosis spp and Blastomyces.

4.1.2.1 Clinical manifestations

Pneumonia due to fungal pathogens, other than PcP, may follow an acute or sub acute course. The disease may be indistinguishable from pneumonia due to bacterial pathogens and TB. There are no clinical features that distinguish fungal pneumonia from pneumonia due to other pathogens. As in other forms of pneumonia the clinical syndrome is characterized by the presence of a cough, shortness of breath and fever as the primary symptoms. In the presence of disseminated disease or meningitis, headache, malaise, vomiting, confusion and wasting may be present. Specific examination of the chest may reveal tachypnea, signs of consolidation or the presence of a pleural effusion while chest radiography may reveal segmental, lobar or multi lobar consolidation, pleural effusion and or widespread reticular, nodular, reticulo – nodular or mixed alveolar and interstitial shadowing.

4.1.2.2 Diagnosis

The diagnosis of fungal pneumonia is based on the identification of fungal pathogens in respiratory specimens mostly obtained at fiberoptic bronchoscopy with bronchoalveolar lavage, bronchial brushings or occasionally through biopsies. To confirm a fungal pathogen the lung specimens are cultured in Sabborauds media or subjected to PCR. For Cryptococcal disease measurement of serum Cryptococal antigen may be yield positive results, especially when the disease is disseminated. Cryptococcal antigen in serum may be negative in isolated pulmonary disease.
4.1.2.3 Treatment

The treatment of fungal pneumonia is dependent on the specific pathogen. Many classes of antifungal agents are now available for the treatment of serious fungal infections such as pneumonia. These include polyene antifungals such as amphotericin B, imidazole, triazole and thiazole antifungals such as ketoconazole, fluconazole and itraconazole and echinocandins such as caspofungin, micafungin and anidulafungin.

4.1.2.4 Prevention

The most important intervention for the prevention of fungal pneumonia is immune reconstitution using cART. While fluconazole has been used to prevent Cryptococcal infections in HIV infected persons it has not found widespread use and the efficacy may be suboptimal.

4.2 Community Acquired Bacterial Pneumonia (CABP) in HIV infected persons

4.2.1 Epidemiology

Persons living with HIV have a high incidence of community acquired bacterial pneumonia. Often CABP is the index diagnosis for HIV. With the advent of cART, the incidence of CABP fell but not as much as that of PCP in high income countries probably as a result of the presence of other risk factors that drive the susceptibility to bacterial pneumonia such as intravenous drugs use, smoking and alcohol abuse among HIV infected individuals. In one French study, CABP was the cause of admission to the intensive care unit in 74% of 147 HIV infected patients admitted to ICU and surpassed PCP as the predominant cause of acute respiratory failure in the era of cART. In African HIV infected patients CABP and in particular pneumococcal disease remains a major cause of morbidity and mortality. Autopsy studies have also documented high rates of bacterial pneumonia in HIV patients dying of lung disease. For example in one Brazilian autopsy study involving 240 HIV infected patients dying of respiratory failure, the cause of death was attributed to CABP in 36%. In a similar study from one USA centre, 47 patients with a pre mortem diagnosis of TB, CABP was deemed to have been the cause of death in 13 (26%).

The incidence of lower respiratory tract infection increases as the CD4 T cell count declines and in the absence of ART. Acute bronchitis, CABP and PCP will be experienced by more than 80% of patients with a CD 4 T cell count of less than 200 even when these patients are provided with chemoprophylaxis. Injecting drug users have an increased incidence of BP compared with other categories of HIV acquisition as are patients who smoke tobacco, have liver cirrhosis and have suffered a previous episodes of BP. Smoking cessation has been found to be beneficial in reducing the incidence of BP in HIV infected persons. Other factors that increase the risk of BP and in particular pneumococcal pneumonia include age, not being on HAART and neutropenia. On the other hand the major risk factor for nosocomial pneumonia is the duration of hospitalization. The pathogens commonly encountered in nosocomial pneumonia include Pseudomonas aeruginosa, Staphylococcus aureus, and Streptococcus pneumoniae.

4.2.2 Clinical manifestations

Community acquired bacterial pneumonia is largely an acute illness in which symptoms evolve rapidly over a few days. The classical symptoms include cough with or without sputum expectoration, chest pain which is often pleuritic in nature, difficulties in breathing
and rapid breathing primarily driven by the chest pain and fever. Clinical examination usually reveals a sickly patient who is febrile, tachypneic but usually not as tachypneic as the patient with PCP and who has a tachycardia. Specific examination of the chest may reveal dullness to percussion, with bronchial breath sounds and pulmonary rales over the affected lobe or lobes of the lungs.

4.2.3 Imaging
A plain chest radiograph should be obtained in all patients suspected to have bacterial pneumonia. The plain chest x-ray typically shows alveolar shadows with segmental, lobar or bronchopneumonic distribution and these changes are similar to those seen in HIV seronegative patients\textsuperscript{122}. Although diffuse interstitial shadowing is less common this radiographic picture should not be used to exclude BP. Other changes that may be visible on the chest radiograph include the presence of pleural effusions and cavitations. No radiographic appearance is pathognomonic of any specific pathogen. The chest x-ray in BP is largely uninfluenced by cART but patients with CD 4 T cell count less than 200 are likely to have a bronchopneumonic picture. It has also been documented that bacteremic patients were more likely to have a lobar lesion and a higher CD4 T cell count above 200\textsuperscript{113,114}. A chest CT scan may be very helpful. It may reveal lesions where the plain chest x-ray does not and have high specificity for certain infections such as PCP\textsuperscript{115}.

4.2.4 Laboratory tests
In hospitalized patients with CABP total white blood cell count, should be measured. A total white cell count of below 4x10\textsuperscript{9} /L has been associated with bacteremia and excess mortality in HIV negative patients with community acquired pneumonia\textsuperscript{116} and may carry the same risk in HIV infected persons\textsuperscript{117}. Similarly thrombocytopenia (count of less than 100,000 x10\textsuperscript{9}/l) appears to signify severe disease that necessitates aggressive treatment including admission to the intensive care unit\textsuperscript{118}. Measurement of the CRP has not been documented to be able to discriminate between PCP and BP\textsuperscript{119}, however, using the cut off value of 3ng/ml for procalcitonin and 246 mg/l for CRP one group of investigators reported an increased capability to distinguish BP from TB with a sensitivity of 81.8% and a specificity of 82.5% for the procalcitonin and 78.8% and 82.3% respectively for the CRP\textsuperscript{120}.

In hospitalized patients the measurement of blood urea, creatinine, sugar, albumin, bilirubin, AST and ALT helps to place patients in specific risk groups for poor outcomes using the CURB – 65\textsuperscript{121} and or Pneumonia Severity Index criteria\textsuperscript{122}. The microbiological diagnosis of CABP is dependent on the detection of the pathogen itself in culture, components of the pathogen (antigen) in body fluids or the antibody response to the pathogen. Relevant samples where the pathogen or its antigen may be identified include sputum, bronchoalveolar lavage fluid, bronchial brushings, lung biopsies or aspirates, blood, urine and pleural fluid. The interpretation of microbiological culture results from sputum and other respiratory secretions is hampered by the contamination of these samples by oropharyngeal bacterial colonizers and precautions must be taken to ensure that not only are good quality specimens obtained but also appropriate and proven methods for interpreting results of bacterial cultures from these specimens are followed. A good quality sputum sample is for example one that has low number of squamous cells and high number of polymorphonuclear cells\textsuperscript{123}.

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4.2.5 Sputum microbiologic testing
In hospitalized patients, as far as feasible, sputum samples should be collected for gram staining and bacterial culture. If a sputum gram stain reveals a predominance of a pathogen with specific staining and morphological features (e.g. gram positive diplococci) this is highly predictive of the pathogen that is responsible for that episode of pneumonia. The sensitivity of sputum gram stain may reach 58%. Sputum bacterial culture may be diagnostic in up to 34% of pneumonia episodes and be correlated with the organism isolated from a sterile site. Compared with BAL and TBB the sensitivity and specificity of induced sputum is about 60% and 40% respectively. Using quantitative bacterial culture the cut off for significant bacterial growth is usually considered to be 10^5 colony forming units per ml of sputum. In settings where PCP incidence may be low the fiberoptic bronchoscopy procedure may add little value to the examination of sputum for other pathogens.

4.2.6 Urinary antigen testing
Urinary antigen tests are available for two bacterial pathogens: Streptococcus pneumoniae and Legionella pneumophila serogroup 1. The urinary pneumococcal antigen test is a rapid test with good test performance parameters including a sensitivity in the region of 81%, specificity 98%, positive (PPV) and negative predictive values (NPV) 98%, and 82%, respectively. The urine pneumococcal antigen test may be positive many weeks after the pneumonia has resolved. The urinary antigen test for Legionella pneumophila serogroup 1 has a sensitivity of 70-90% and a specificity of nearly 100% for the detection of this pathogen.

4.2.7 Serological tests
These tests are used primarily for the detection of atypical pathogens such as Mycoplasma pneumoniae, Chlamydophila Spp and Legionella Spp other than Pneumophila Sero group 1. The major draw back is that interpretation often requires comparison of results of acute and convalescent sera and thus may not be useful for clinical decision making.

4.2.8 Fiberoptic bronchoscopy
Fiberoptic bronchoscopy is a commonly used procedure for the evaluation of respiratory symptoms in HIV infected persons. Although the diagnostic yield may reach 74% only about 25% of bronchoscopies yield useful results that lead to a change in diagnosis and therapy. In situations where there are low rates of PCP and Kaposi sarcoma the fiberoptic bronchoscopy procedure may not yield additional results from that obtained through examination of expectorated sputum and other easily obtained body fluids, and therefore in such settings this procedure should be used judiciously.

4.2.9 Fine needle transthoracic biopsy/aspiration
This may be an underutilized procedure for the evaluation of respiratory symptoms in patients infected with HIV. The suitable patient for this procedure has a peripheral lesion close to the pleural membrane. The common complication with this procedure is pneumothorax which rarely requires pleural drainage.

4.2.10 The range of pathogens
The range of pathogens involved in CABP in HIV infected persons is wide but the most common pathogens include Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella
Streptococcus pneumoniae is the most common pathogen isolated in 40-60% of bacteriologically confirmed cases\textsuperscript{136,137,138}. In TB endemic areas TB is a common cause of acute community acquired pneumonia and should always be screened for in all patients presenting with this condition. Persons living with HIV are at increased risk of pneumococcal bacteraemia associated with community acquired pneumonia\textsuperscript{139,140,141}. However the impact of the bacteraemia on survival appears to be uncertain with some studies suggesting there is no increase in the risk of mortality while others have found an association between pneumococcal bacteraemia and mortality from community acquired pneumonia\textsuperscript{142,154,155}. Compared with sero negative patients HIV infected patients may be predisposed to harbouring penicillin resistant pneumococci\textsuperscript{155,143}.

Other pathogens that have been identified in HIV infected patients with community acquired pneumonia include:

- **Rhodococcus equi**, a gram-positive, coryneform bacterium that causes zoonotic infection mainly in horses and foals. Most cases have been reported in case reports and or case series\textsuperscript{144,145,146}.

- **Enterococcus** that may be vancomycin resistant and associated with lung abscess and empyema\textsuperscript{147}

- **Nocardia asteroides** a gram positive filamentous rod which may cause chronic lung infection and may sometimes disseminate with associated high mortality\textsuperscript{148,149}. This infection may be difficult to diagnose.

- **Legionella pneumophila**, although it remains unclear if HIV infected persons are at increased risk of infection or severe disease\textsuperscript{150,151}

- **Mycoplasma pneumoniae** which has been found in up to 17% of patients with community acquired pneumonia in both HIV negative and positive persons\textsuperscript{152,153}.

- **Moraxella catarrhalis** though this pathogen appears to be an uncommon cause of community acquired pneumonia. In one large study only 4 cases among 2123 patients hospitalized over a nine year period were found to have this pathogen\textsuperscript{154}.

- **Community acquired Pseudomonas aeruginosa** which has been described as a cause of severe and often fulminant community acquired pneumonia in patients who are severely immune suppressed and who may not have the traditional risk factors for this infection such as central lines and neutropenia\textsuperscript{155,156,157}.

- **Salmonella** which has been described mainly in patients with Salmonella bacteraemia\textsuperscript{158}.

Often the HIV infected person has multiple pathogens causing the respiratory illness\textsuperscript{159,160,161,162} such as fungi, bacterial and viral pathogens.

### 4.2.11 Treatment of community acquired bacterial pneumonia in HIV infected persons

A holistic approach should be adopted to the care of HIV infected patients with community acquired pneumonia. The benefit of targeted antimicrobial therapy are likely to accrue if attention is paid to hydration, oxygenation and nutritional needs among other needs of the patient. Control of symptoms such as pain, fever, vomiting and diarrhoea which often are part of the pneumonia syndrome in HIV infected persons will ensure patient comfort as specific antimicrobial treatment takes effect. The initial antimicrobial treatment will usually be chosen on an empiric basis and this choice should be based on the range of common pathogens isolated in the specific setting, the anti
microbial susceptibility patterns of common pathogens, the cost of treatment, co morbid states and to some extent the experience of the treating practitioner. No studies have specifically examined the efficacy of various antibiotics for the management of CABP in HIV infected persons. Thus current practice is based largely on guidelines derived from studies involving HIV sero negative individuals and clinical experience. In TB endemic settings the combination of a beta lactam and a macrolides is preferred over the use of fluoroquinolones to avoid masking TB. The combination of a beta lactam and a macrolide has been associated with better outcomes in HIV sero negative patients, but not in all studies\textsuperscript{163}, and is recommended by the Infectious Disease Society of America and the American Thoracic Society\textsuperscript{164}. Pneumococcal penicillin resistance may be more common in HIV infected persons\textsuperscript{165} but outcomes of treatment appear not to be influenced by the presence of intermediate levels of penicillin resistance\textsuperscript{166, 167}. In patients with Rhodococcus infection at least two antimicrobial agents should be given simultaneously to treat this infection for a period of up to several months. The combinations of erythromycin and rifampin or teicoplanin have been found to be the most effective treatments in Rhodococcus infections\textsuperscript{168}. The anti microbial treatment of Nocardia asteroides involves the use of combinations with proven synergy, such as imipenem and amikacin, as the recommended initial therapy.

4.2.12 Outcomes of community acquired bacterial pneumonia

Several risk factors may work together to increase the risk of death in HIV infected patients receiving treatment for CABP. These risk factors include not being on ART, presence of pneumococcal antigen in urine for patients with pneumococcal pneumonia\textsuperscript{169} and comorbid states such as liver cirrhosis (mostly from alcohol abuse)\textsuperscript{170}. Compared with HIV sero negative patients and in situations where health care delivery may be described as optimal HIV infection appears not to increase the mortality risk in hospitalized patients with Community Acquired Pneumonia and neither does it lead to prolongation of hospital stay\textsuperscript{171,172}. In patients with acute respiratory failure admitted to the ICU, the risk of death is related to extent of organ failure such as need for mechanical ventilation and use of vasopressor agents rather than HIV parameters such as CD4 T cell count, HIV plasma viral load or use of ART\textsuperscript{173}.

Bacteremic pneumococcal disease may confer a higher mortality risk but this has not been a consistent finding \textsuperscript{155-159}. Certain pathogens confer a greater risk of death. Compared with Streptococcus pneumoniae for example patients with Legionella, were found to have a higher risk of death probably from a greater prevalence of co morbid conditions\textsuperscript{174}. Advancing age and low CD4 T cell count are also risk factors for severe disease and death in HIV infected patients including patients on ART\textsuperscript{175,176}. It has been proposed that HIV infected patients be placed in a low risk immunosuppressed group for death and that in this group the Pneumonia Severity Index (PSI) can be used to define patients at risk of death similar with the use of this tool to define groups of patients at risk of death in HIV negative patients\textsuperscript{177, 178, 179}.

4.2.13 Prevention

Vaccination is available for Streptococcus pneumoniae. The 23 valent polysaccharide vaccine appears to be effective in HIV infected persons in North America for reducing all cause pneumonia but those with plasma viral load of greater than 100,000 may not
benefit\textsuperscript{180,181,182}, but the results of clinical trials have not always been consistent\textsuperscript{183}. On the other hand African patients have not been documented to benefit from the 23 valent pneumococcal vaccine, \textsuperscript{184,185}. To avoid the sub optimal efficacy of the 23 valent pneumococcal vaccine in African HIV infected persons a conjugate vaccine has been developed. A clinical trial of the 7 valent conjugate vaccine among Malawian patients found a protective efficacy of about 74\% for the prevention of recurrent pneumococcal pneumonia\textsuperscript{186}. The other intervention available for preventing BP in HIV infected persons is cotrimoxazole preventive therapy which is most effective in those with CD 4 T cell count below 200,\textsuperscript{187,188}.  

4.2.14 Other issues
Recent data suggests that recurrent BP may be associated with an increased risk of lung cancer in HIV infected persons probably related to the persistent or recurrent inflammation in the lung\textsuperscript{189}. Parapneumonic effusions may be more common in HIV infected patients with community acquired pneumonia and patients with parapneumonic effusions may have more severe disease with higher rates of bacteraemia\textsuperscript{189}.

4.3 Mycobacterial pneumonia in HIV infected persons
4.3.1 Mycobacterium tuberculosis
4.3.1.1 Epidemiology
Tuberculosis is the most common opportunistic infection and the most common cause of death in HIV infected persons. The dramatic increase in the burden of TB in Sub – Saharan Africa has been largely blamed on the HIV epidemic\textsuperscript{191}. However, other than for differences in magnitude, TB is the most common opportunistic infection that is observed in the first three months of initiation of cART in both Sub–Saharan Africa and the industrialized world of North America and Europe\textsuperscript{192,193}. The TB and HIV epidemics are so intricately intertwined in Sub–Saharan Africa that care and control of one must be linked with the prevention and care of the other\textsuperscript{194}. HIV influences TB by increasing the risk of reactivation of latent TB infection, rapid progression of new TB infection to disease and recurrent disease from both re-infection and relapse\textsuperscript{195}.

4.3.1.2 Clinical manifestations
Pulmonary tuberculosis is characterized by the sub acute onset of cough with or without the production of sputum associated with systemic symptoms of fever, night sweating and loss of weight. The sputum may be stained with blood. These symptoms are not specific for TB. The only symptoms that are significantly more common in TB than in other patients are night sweats and loss of weight\textsuperscript{196}. There may also be pleuritic chest pain but shortness of breath is uncommon until the late stages of the disease. The symptoms of TB are largely similar between HIV negative and positive patients, however, depending on the stage of HIV disease, HIV infected persons may have stigmata of the HIV infection such as oropharyngeal candidiasis, oral hairy leukoplakia, a non specific skin rash, cutaneous Kaposi sarcoma and peripheral lymph node enlargement. There may be no significant signs unearthed on specific examination of the chest and even when present these signs are non specific. The chest radiograph is a sensitive but non specific test for detection of TB in both HIV infected and un infected individuals\textsuperscript{197}. It may show a variety of lesions which to a large extent depend on the severity of the HIV related immunosuppression. When immune function is still relatively well preserved the classical
upper lobe fibrocavitary shadows may be seen. With advancing immune dysfunction the radiologic shadows become atypical and include mid and lower zone shadows, intrathoracic lymph node enlargement, pleural effusions, miliary shadowing among others lesions\textsuperscript{198, 199}.

4.3.1.3 Diagnosis of pulmonary TB

Most TB occurs in middle and low income countries where conventional light microscopic examination of sputum using the Ziehl Nielsen stain is the primary diagnostic test. The test is rapid, relatively simple, inexpensive and highly specific in these settings, however, this test has provided inconsistent sensitivity results ranging from as low as 20\%\textsuperscript{200} to as high as 80\%\textsuperscript{201} in comparison to culture confirmed TB and is more commonly negative in HIV infected individuals compared to HIV negative individuals\textsuperscript{202}. Currently WHO recommends that two sputum specimens are obtained immediately the patient makes contact with the health care system. The examination of a third sputum specimen has not been found to add much value with the incremental yield of the third specimen not exceeding 4\%\textsuperscript{203}. Similarly a morning specimen only marginally increases the diagnostic yield of smear microscopy\textsuperscript{204} and therefore may not be necessary in the evaluation of patients suspected to have TB. To increase the sensitivity of smear microscopy sputum may treated with bleach or sodium hydroxide and concentrated by centrifugation, or overnight sedimentation preceded by treatment with ammonium sulphate or bleach\textsuperscript{205}. However the value of these sputum processes in HIV infected persons is not clear. The yield of sputum microscopy is consistently increased by up to 10\% using fluorescence microscopy with auramine O or auramine – rhodamine stains\textsuperscript{206} and recently fluorescence microscopy has been simplified by the development of Light Emitting Diode (LED) Fluorescence microscopy\textsuperscript{207}. The Gold standard for TB diagnosis remains culture on solid or liquid media. Conventional culture on solid or liquid media for the diagnosis of TB is however a slow process that may take too long to reliably influence clinical decisions. The development of rapid liquid culture systems such as the Mycobacterial Growth Inhibitor Tube (MGIT) has improved the turn around time and thus the clinical utility of culture for the diagnosis of TB\textsuperscript{208}. The WHO recently recommended rapid liquid TB culture systems for the diagnosis of TB especially in HIV infected persons\textsuperscript{209}. Although recommended by WHO as a bridge to fully automated liquid culture systems for TB diagnosis, non commercial culture systems such Mycobacteria Observation Drug Susceptibility (MODS), Nitrate Reductase Assays (NRAs), Thin layer Agar (TLA) and Colorimetric Redox Indicators (CRIs) systems do not decrease the time to TB diagnosis and drugs susceptibility results\textsuperscript{210}. Even though the PCR technique has been used for a long time for the detection of TB, it is the automated cartridge based nucleic acid detection test called the Xpert MTB/Rif test that has the potential to revolutionize the diagnosis of TB especially in HIV infected persons\textsuperscript{211}. The WHO recently recommended rapid liquid culture systems for the diagnosis of TB especially in HIV infected persons\textsuperscript{212}. Although recommended by WHO as a bridge to fully automated liquid culture systems for TB diagnosis, non commercial culture systems such Mycobacteria Observation Drug Susceptibility (MODS), Nitrate Reductase Assays (NRAs), Thin layer Agar (TLA) and Colorimetric Redox Indicators (CRIs) systems do not decrease the time to TB diagnosis and drugs susceptibility results\textsuperscript{213}. Even though the PCR technique has been used for a long time for the detection of TB, it is the automated cartridge based nucleic acid detection test called the Xpert MTB/Rif test that has the potential to revolutionize the diagnosis of TB especially in HIV infected persons. This test not only provides the diagnosis of TB in under two hours but also is able to indicate if there is likelihood of multi drug resistant TB based on the detection of mutations that confer rifampicin resistance. Diagnostic studies on this test suggest that it has an overall sensitivity of about 92.2\% and a specificity of 99\% using a single Xpert test. The sensitivity increases to 97.6\% using three Xpert tests. Among HIV positive individuals the overall sensitivity of a single Xpert test has been reported to be about 94\% compared to 98\% in HIV negative individuals. For the detection of rifampicin resistance the sensitivity of this test is about 98\%\textsuperscript{210,212}. This test is now recommended as the initial test for the detection of pulmonary TB in HIV infected persons\textsuperscript{213}. Although several serological tests are commercially available for the detection of TB, none has been found to have a consistently high sensitivity and specificity to replace smear microscopy and their use has recently been discouraged by WHO\textsuperscript{214}.
4.3.1.4 Treatment of TB in HIV infected persons
Current treatment of pulmonary TB involves the use of combinations of 5 primary drugs: Isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z), and streptomycin (S). The WHO and the International Standards of TB Care (ISTC) recommends a rifampicin based regimen made of RHZE given daily for two months followed by RH given daily, or two to three times weekly for six months for previously untreated patients. With this regimen most HIV infected patients get cured with a lower risk of failure, relapse and acquired drug resistance. Patients who have been treated previously must be assessed for risk of drug resistance, investigated for drug resistance using the Xpert MTB/Rif test, rapid molecular based line probe assays and culture, and treated with either primary, first line drugs if no drug resistance exists or with second line drugs if drug resistance, especially multi drug resistant TB, is present.

4.3.1.5 Drug resistant TB and HIV
The WHO estimated that there were 400,000 cases of multi drug resistant TB, defined as TB bacilli that are resistant to both R and H, in 2009. Although HIV per se appears not to be a risk factor for MDR TB, a link between MDR TB and HIV has been suggested by epidemiologic data from parts of Eastern Europe. Outbreaks of MDR TB in HIV infected persons have been linked to nosocomial transmission of TB and have in general been characterized by high mortality among affected patients. The more recent reports were from Southern Africa where a large majority of the patients were HIV infected, had extensive drug resistance (MDR TB with additional resistance to a fluoroquinolone and an injectable such as kanamycin, amikacin or capreomycin) and died within a few weeks after the diagnosis of XDRTB, emphasizing the critical role of implementing robust measures to prevent TB transmission in situations where HIV infected persons receive care.

4.3.1.6 Outcomes
HIV infected PTB patients are at increased risk of death during treatment for TB. Up to 30% of such patients may die during treatment if no life prolonging ART is provided. The risk of death is higher in patients with smear negative disease and those with a lower CD4 T cell count. Life prolonging ART is able to dramatically reduce the deaths rates in HIV infected TB patients and the earlier it is given the better. Cotrimoxazole preventive therapy is also able to reduce the mortality of HIV associated TB.

4.3.1.7 Prevention
HIV associated TB is a preventable disease. Several randomized clinical trials have demonstrated that TB can be effectively prevented using isoniazid given for 6-12 months in HIV infected persons. With the advent of combined ART it was observed that TB incidence fell in persons on ART in North America and Europe. The fall in TB incidence has been observed to be greater in persons with a higher baseline CD4 T cell count, a lower base line viral load and robust immunological and virological responses. Similar observations have been made in South Africa. The combination of ART and Isoniazid Preventive Therapy (IPT) has been observed to confer greater protection against TB and provides further impetus to provide IPT in all HIV infected persons irrespective of whether they are or are not on ART. Currently there is no evidence that appropriately applied IPT leads to the expansion of isoniazid resistance.
4.3.2 Other Mycobacteria

4.3.2.1 Mycobacterium Avium Complex and other Non Tuberculous Mycobacteria

Mycobacterium avium complex (MAC) is isolated with increasing frequency from respiratory specimens in HIV infected persons, however, the significance of isolating MAC from respiratory specimens is unclear. Criteria have been developed for defining clinical disease in patients who have non Tuberculous Mycobacteria isolated from respiratory samples. HIV infected persons with pulmonary MAC are more likely to have fever, diffuse pulmonary abnormalities, lymphadenopathy and concurrent disease including disseminated MAC, Pcp and BP compared with HIV negative individuals. These infections generally occur late in the course of HIV disease and confer a poor long term prognosis.

4.4 Viral pneumonia

Viral pathogens have also been implicated in HIV associated lung disease. These viruses have included Cytomegalovirus (CMV), Herpes Simplex Virus (HSV) and Influenza including H1N1. For CMV the difficult has been distinguishing infection from colonization. The most important risk factor for viral pneumonia is a CD4 T cell count below 200. These pneumonias may be difficult to diagnose and carry a high mortality.

4.4.1 CMV

This is the most common virus that has been implicated in HIV associated pneumonia. The clinical presentation is similar to pneumonia due to other pathogens and is largely non specific. The symptoms include fever, shortness of breath, and cough. Pneumonia due to CMV may be the initial presentation of HIV disease and in the pre ART era, survival post CMV pneumonia, when successfully treated was short. Often CMV pneumonia is not recognized or diagnosed prior to death. Patients with a high plasma viral load may also be at risk of CMV pneumonia.

The diagnosis of CMV may be problematic. When isolated in respiratory specimens such as bronchoalveolar lavage this virus may be a colonizer and not necessarily the cause of the lung disease. To diagnose respiratory disease the current consensus is that CMV should be isolated in lung secretions (BAL or brushes), and demonstrated to be available in histological specimens through immunohistochemistry or in situ hybridization in the presence of pulmonary infiltrates on the chest radiograph. The treatment of CMV involves the use of ganciclovir or foscarnet.

As with fungal pneumonia the most important intervention for the prevention of CMV pneumonia is immune reconstitution using anti retroviral treatment. No chemo preventive intervention has been identified. Acyclovir has been tried but was not found to be efficacious.

4.4.2 Herpes simplex

Herpes simplex virus type 1 and type 2 have both been associated with HIV pneumonia. The pneumonia may occur in association with cutaneous herpes and thus represent disseminated disease. Varicella pneumonia has been described and may present as a recurrent pneumonia.

4.5 Parasitic lung disease in HIV

Lung disease caused by parasites may less common. The most common parasites that have been associated with HIV lung disease are Toxoplasma gondii and Strongyloides stercoralis.
Epidemiological studies to obtain good estimates of the incidence of these parasites in HIV infected persons have not been carried out.

4.6 Non infectious HIV associated lung disease
Several non infectious lung diseases have been observed in HIV infected persons. These diseases include pulmonary arterial hypertension, bronchiolitis obliterans organizing pneumonia, sarcoidosis and chronic obstructive pulmonary disease. The incidence of these diseases may be increasing as HIV infected individuals survive longer with cART.

4.6.1 Interstitial pneumonitis
The HIV syndrome is associated with an increased incidence of non specific interstitial pneumonitis and lymphoid interstitial pneumonitis, both of which may result from the chronic inflammatory state induced by HIV. Lymphocytic Interstitial pneumonia in HIV infected persons may be associated with respiratory symptoms of cough and dyspnoea and cause lung function abnormalities. The radiological picture is diffuse interstitial shadowing and a lung biopsy procedure is required for the diagnosis. The disease has been thought to be related to the host immune response and directly linked to HIV. There is usually a predominance of CD8 positive T lymphocytes. This entity may also occur as part of the immune reconstitution inflammatory syndrome. It responds to systemic steroids and also resolves with ART.

The incidence has declined with the widespread use of anti-retroviral treatment.

4.6.2 Non specific pneumonitis
A non specific pneumonitis associated with cough and dyspnoea and diffuse interstitial shadowing on the chest x-ray often occurs in HIV infected persons. This disease entity may mimic PJP and even appear to respond to PJP treatment. However a search for Pneumocystis jirovecii is usually negative.

4.6.3 Immune reconstitution inflammatory syndrome
The immune reconstitution inflammatory syndrome represents an exaggerated immune response to infectious and non infectious agents as immune recovery occurs. The syndrome is characterized by the appearance of worsening symptoms and signs of specific infections as immune recovery takes place. While most episodes are mild, severe life threatening disease may occur. The syndrome has been described to occur with many infections including Pneumocystis jirovecii CMV, TB and Cryptococcus.

4.6.4 Pulmonary Arterial Hypertension (PAH)
Pulmonary arterial hypertension associated with HIV is a rare clinical entity but when it occurs it leads to significant morbidity and mortality. The available literature is mostly based on case reports. This clinical entity appears to occur at relatively high CD4 T cell count of about 300. The clinical, radiographic and echocardiographic findings are similar to idiopathic PAH in HIV sero negative persons. Highly active antiretroviral therapy, bosentan, and prostaglandin therapy have all been reported to be beneficial in improving hemodynamic and functional status in HIV-related PAH. In a French study the median survival of patients with HIV associated PAH receiving ART and PAH specific therapy was 88% and 72% at 1 and 3 years respectively. There was better survival in patients with CD4 T cell count of greater than 200 and a higher cardiac index. Anti-retroviral therapy did not appear to influence hemodynamic parameters.
4.6.5 Pulmonary malignancies in HIV infected persons

Both Kaposi sarcoma (KS) and non Hodgkins Lymphoma (NHL), the two AIDS defining malignancies (ADMs) have been associated with lung disease. Of the two malignancies KS has been the more common one. In HIV associated KS, the tumour most often afflicts the lung as part of a disseminated disease process but may also occur as a primary lung disease. Non Hodgkins lymphoma occurring as primary lung disease has been described in several case reports and series. Persons living with HIV appear to be at increased risk of primary lung cancer, a non ADM.

Endobronchial Kaposis Sarcoma is seen in about 15% of patients with advanced HIV disease. The clinical presentation is indistinguishable from that of other pulmonary complications of HIV. Thus patients may present with cough, haemoptysis and dyspnoea. Both alveolar and interstitial shadows may be seen on the chest radiograph. Chest CT scans usually reveal the shadows better. The diagnosis requires visual detection of typical cherry red lesions at fiberoptic bronchoscopy. The lesions are usually not biopsied because of the risk of bleeding. Pulmonary KS usually occurs in the setting of disseminated KS and the prognosis is typically poor.

Non Hodgkins lymphoma involving the lung has been reported in case series and cohorts. The clinical presentation is usually non specific and includes fever, weight loss, dyspnea, generalized lymphadenopathy, chest pain and cough. The chest radiograph reveals nodular lesions or interstitial shadows. The diagnosis of lymphoma is more reliably made on open lung biopsy. In the pre – ART era the diagnosis of NHL carried with it a poor prognosis even with specific lymphoma treatment.

The risk of lung cancer in HIV infected persons appears to be increased and this increase may not be fully explained by smoking. Although the data is scanty, recurrent pneumonia, through the promotion of chronic infection has been found to be associated with the increased risk of lung cancer in HIV infected persons. The incidence of lung cancer, may have increased in post HAART era. However the incidence of lung cancer in HIV infected women appears not to be higher that in HIV un infected women and the driver of the lung cancer risk is tobacco smoking and not the HIV infection. HIV infected patients with primary lung cancer are younger, tend to present with aggressive and advanced disease and have poorer outcomes.

4.6.6 Chronic obstructive pulmonary disease

Respiratory symptoms and functional abnormalities are common in patients infected with HIV including those on combined anti –retroviral therapy. A recent observational study documented respiratory symptoms and functional abnormalities in 47.3% and 64.1% of study participants respectively. Irreversible airways obstruction compatible with COPD, independently associated with pack years smoked, intravenous drug use and the use of anti –retroviral therapy was found in 21% of study participants. In patients with obstructive airways disease, HIV infection appears to confer a higher risk of moderate but not severe dyspnoea.

4.6.7 Bronchiolitis obliterans organizing pneumonia

Bronchiolitis obliterans organizing pneumonia (BOOP) is a disease of the small airways characterized by intraluminal polyps of myxoid connective tissue. The concomitant occurrence of BOOP with HIV has been described in a few case reports. In the cases reported, the clinical manifestations have included sub acute onset of dyspnoea which...
progressed to respiratory failure, non productive cough and fever. The most common chest radiographic findings included bilateral mixed interstitial and alveolar shadows. When these patients are investigated for infection, no pathogens are found and empiric antibiotic therapy is not effective. The diagnosis of BOOP is made at open lung biopsy. Patients respond very well to corticosteroids at a dose of about 1 mg/Kg for up to three months.

4.6.8 Hypersensitivity pneumonitis
Case reports of hypersensitivity pneumonitis associated with drugs used in the management of HIV infection including dapsone\(^\text{270}\), efavirenz\(^\text{271}\), and other anti retrovirals\(^\text{272}\) have been published. The burden of illness and or death caused hypersensitivity pneumonitis in HIV infected persons is currently unclear.

4.6.9 Sarcoidosis
Sarcoidosis is a multi system disease in which tissues are infiltrated with non caseating granulomas. The lung is a common target of sarcoid lesions. Pulmonary sarcoidosis associated with HIV has been reported in case reports and series\(^\text{273,274}\). Many of the sarcoidosis case reports have appeared in the post HAART era and it is unclear if this entity, in the ART context is related to immune recovery. In patients who use adulterated drugs talc granulomatosis must be considered in the differential diagnosis of interstitial lung disease. This clinical entity is indistinguishable from opportunistic infections and requires examination of lung biopsy specimens which show granulomas with intracellular talc crystals\(^\text{275}\).

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HIV Infection in the Era of Highly Active Antiretroviral Treatment and Some of Its Associated Complications


Human immunodeficiency virus (HIV) infection is a complex illness affecting the immune system. Acquired immunodeficiency syndrome (AIDS) is an advanced form of HIV infection in which the patient has developed opportunistic infections or certain types of cancer and/or the CD4+ T cell count has dropped below 200/µL. More than 40 million persons around the world are infected with HIV, with approximately 14,000 new infections every day. The disease causes 3 million deaths worldwide each year, 95% of them in developing countries. Optimal management of human immunodeficiency virus requires strict adherence to highly active antiretroviral treatment (HAART) regimens, but the complexity of these regimens (e.g., pill burden, food requirements, drug interactions, and severe adverse effects) limits effective treatment. However, more patients with HIV are surviving longer today because of these drugs. This allows further study of commonly associated adverse effects. These may affect all body systems and range from serious toxicities to uncomfortable but manageable events. This book reviews some of HAART-related metabolic and neurological complications.

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