

## HIV-associated *Pneumocystis* pneumonia

Robert F. Miller, MBBS, FRCP

Research Department of Infection and Population Health, University College London,  
London, UK

London, WC1E 6JB, UK

E-mail address: [robert.miller@ucl.ac.uk](mailto:robert.miller@ucl.ac.uk)

Telephone: +44 203 108 2094

Peter D. Walzer, MD, MSc

University of Cincinnati College of Medicine Cincinnati, OH 45267-0560

E-mail address: [peter.walzer@uc.edu](mailto:peter.walzer@uc.edu)

Telephone: 513-558-4704

Corresponding author: R. F. Miller

Key words: *Pneumocystis jirovecii*, *Pneumocystis* pneumonia, acquired  
immunodeficiency syndrome, HIV, lung, diagnosis

Word count: manuscript = 5582

: synopsis = 104

The authors have nothing to disclose

## Synopsis

*Pneumocystis pneumonia* (PCP) is caused by the yeast-like fungus *Pneumocystis*. Despite the widespread availability of specific anti-*Pneumocystis* prophylaxis and of combination antiretroviral therapy (cART) PCP remains a common AIDS-defining presentation in the United States and in Europe. PCP is increasingly recognized among persons living in Africa. *Pneumocystis* cannot be cultured and bronchoscopic alveolar lavage is the “gold standard” diagnostic test to diagnose PCP. Use of adjunctive biomarkers for diagnosis requires further evaluation. Trimethoprim-sulfamethoxazole remains the preferred first-line treatment regimen. In the era of cART mortality from PCP is approximately 10-12%. The optimal time to start cART in a patient with PCP remains uncertain.

## Introduction

Different species of the *Ascomycetous* yeast-like fungus *Pneumocystis* asymptotically infect/colonize numerous healthy mammalian hosts and in immune compromised mammals (including humans) can cause a potentially life-threatening pneumonia (PCP). The organism is host-obligate and species specific: it cannot be grown outside the host and organisms from one host cannot infect other mammalian hosts [1].

*Pneumocystis* was identified in 1909 by Chagas, who mistakenly described it as part of the life cycle of the protozoan parasite *Trypanosoma cruzii*. It was first recognized as a human pathogen when it was described as the cause of “interstitial plasma cell pneumonia” among premature/malnourished infants in European orphanages immediately after WW2. In the 1960s and 1970s descriptions of PCP were mainly in children with congenital immunodeficiency and also among

adults/children with acquired immunological deficits resulting from malignancy (specifically, glioma, and acute leukemia) or its treatment (with glucocorticoids and purine analogues). The advent of organ transplantation and iatrogenic immunosuppression in the 1960s was associated with reports of PCP among this patient population.

In 1981 description of PCP in 15 previously healthy men who had sex with other men and/or who were injection drug users heralded the advent of the global HIV/AIDS pandemic [2][3]. Despite the availability of prophylaxis and of combination antiretroviral therapy (cART) PCP remains an important clinical presentation among HIV-infected persons [4].

### **Epidemiology of HIV-associated PCP**

Before the onset of the AIDS epidemic PCP was uncommon in the United States; between November 1967 and December 1970 194 patients were reported to Centers for Disease Control [5], and in the 1970s fewer than 100 cases per year were seen in the United States. During the early years of the AIDS epidemic, PCP accounted for two thirds of AIDS-defining illness in patients in the United States, and an estimated 75% of HIV-infected patients developed PCP during their lifetime [6][7]; rates of PCP were as high as 20 per 100 person-years among those with CD4 cell counts <200 cells/ $\mu$ L [7][8].

The first substantial decline in the incidence of PCP occurred after the introduction of anti-*Pneumocystis* prophylaxis in 1989 [9]. In the United States because of an increasing incidence of AIDS from 1989 to 1992, absolute numbers of reported cases of PCP as an AIDS-defining illness remained stable, but the percentage with PCP declined, from 53% in 1989 to 42% in 1992, respectively [7].

The advent of cART resulted in further declines in rates of PCP and other opportunistic infections [7][10][11]. Several large, multicenter studies have tracked the incidence and epidemiologic features of PCP in the era of cART. Data from the Adult and Adolescent Spectrum of HIV Disease (ASD) study showed a marked reduction in incidence of all opportunistic infections in 1996 and 1997, when cART first became widely available; from 1992 to 1995 cases of PCP declined by 3.4% per year, and from 1996 to 1998 declined by 21.5% per year [7][11]. Multicenter AIDS Cohort Study also showed a marked reduction in opportunistic infections after introduction of cART [12]

In Europe, the EuroSIDA study has examined changes in incidence of AIDS-defining disease before and after cART was introduced (1994–1998) and found results similar to those in the United States. The incidence of PCP fell from 4.9 cases per 100 person-years before March 1995 to 0.3 cases per 100 person-years after March 1998 [13][14].

Despite these improvements, data from the Hospital Outpatient study (HOPS) shows that PCP remains the second most common AIDS-defining opportunistic infection in the United States; in 1994-1997 the incidence was 29.9 per 1000 person-years, and fell to 7.7 and 3.9 per 1000 person-years, in 1998-2002 and 2003-2007, respectively [14]. In the United Kingdom PCP was the commonest AIDS-defining illness in the decade 2001-2010 [16].

In the United States, Western Europe and Australasia PCP still occurs among HIV-infected persons despite the availability of cART and anti-*Pneumocystis* prophylaxis. The ASD study examined use of PCP prophylaxis among HIV-infected adults who developed PCP during 1999-2001 [12]. More than 43% of PCP cases occurred in persons not receiving medical care, the majority of who were likely not

known to be HIV-infected, and a further 41% were prescribed prophylaxis but were either non-adherent with treatment, or PCP developed despite treatment adherence. Possible explanations for PCP in this group include decreased efficacy of prophylaxis among those with low CD4 counts and development of drug-resistant *Pneumocystis*. An additional 9.6% were under medical care but did not receive prophylaxis, based on current recommendations (i.e. CD4 count >200 cell/ul, or >14% of total lymphocyte count) [17].

In the pre-cART era the greatest risk factor for PCP in an HIV-infected person was a CD4 cell count <200 cells/ $\mu$ L; this remains an important risk factor in the cART era. The lower the CD4 count falls below 200 cells/ $\mu$ L the risk for PCP increases exponentially [18]. Those who develop PCP despite receipt of cART usually have a low CD4 count. In the ASD study the CD4 count among persons developing PCP while receiving cART was low (median=29 cells/ $\mu$ L), and was lower among those not taking cART (median=13 cells/ $\mu$ L) [11]. The prospective pan-European EuroSIDA study reported that the median CD4 count was 30 cells/ $\mu$ L among persons developing PCP while receiving cART, and was similar among those not receiving cART who got PCP [8]. Patients without improvement in their CD4 count after starting cART remain at risk for PCP. One recent study showed that approximately 5% of HIV-infected persons have a CD4 count >200 cells/ $\mu$ L at presentation with PCP [19].

Other clinical risk factors for development of PCP include gender, race or ethnicity, and risk factor for HIV acquisition. Men are more likely than women to develop PCP [17]; one study demonstrated that African Americans have a lower risk for PCP than white persons [17] but this finding has not been replicated [10] MSM appear to be at equal risk, when compared with other risk exposure groups [10].

PCP still occurs frequently among HIV-infected patients in many parts of the developing world [20]. Studies from Thailand show the prevalence of PCP is up to 40% [21]. Central and South America also report large numbers of PCP cases. One Brazilian study found that 55% of HIV-infected persons with respiratory symptoms had PCP [22], another study from Mexico reported a 24% PCP prevalence [23].

By contrast, PCP has until recently been thought to be rare in African adults. However, high rates of anti-*Pneumocystis* antibodies among African children suggest that exposure to the organism is common, and PCP is a common cause of pneumonia among children in Sub-saharan Africa [24]. PCP might have been under-reported in Africa for several reasons. Limited local diagnostic resources, including lack of trained clinical and laboratory personnel and expensive equipment mean that invasive investigations such as induced sputum and bronchoscopic alveolar lavage are less commonly performed, and reliance on empiric therapy of HIV-infected persons with presumed PCP potentially results in under-estimation of the true incidence of PCP. Many HIV-infected African adults may not reach a stage at which they would be susceptible to PCP as these populations have high rates of tuberculosis and bacterial pneumonia that may result in death at higher CD4 counts. Environmental factors, such as temperature and seasonality, might also contribute to a low rate of PCP in Africa. The population may be more resistant to development of PCP; HIV-infected African Americans have been shown to have lower rates of PCP than white Americans [18]; or *P. jirovecii* strains isolated in Africa may be less virulent, a possibility that can only be answered by large-scale molecular epidemiologic studies.

As the AIDS epidemic progresses in Africa most, but not all studies suggest that the incidence of PCP is increasing [20][24][25][26][27]; it is unclear whether this

increase results from changes in incidence of PCP or from improvements in detection techniques.

## **Pathogenesis**

Studies in animal models have demonstrated that *Pneumocystis* is communicable via the airborne route. Young animals acquire *Pneumocystis* infection soon after birth and have an important role in spreading infection. Molecular epidemiologic studies in humans support the findings from these experimental models [28][29]. The human incubation period from inhalation to presentation with PCP is thought to be approximately 4 to 8 weeks.

The majority of healthy adults do not have detectable *Pneumocystis* in respiratory specimens [30][31], but several groups of individuals, both HIV-infected and uninfected infected, including those with chronic obstructive pulmonary disease (COPD), and pregnant women may become colonized with *Pneumocystis*, thus increasing the potential number of persons affected [32][33][34]. *Pneumocystis* colonization may increase the risk for progression to PCP among HIV-infected and uninfected persons. Persons colonized with *Pneumocystis* may also transmit infection to others who have minor or significant immune suppression, and as such act as an “infectious reservoir”. Long-term colonization of asymptomatic HIV-infected and uninfected (eg COPD) hosts may result in pulmonary inflammation and progressive impairment of lung function [33][35][36].

After inhalation, *Pneumocystis* eludes the upper airway defenses and deposits in alveoli: where it adheres tightly to alveolar type I cells, and provokes a host inflammatory response [36]. In the majority of hosts with an intact immune system the organism is rapidly coughed out. If the host has any underlying “minor” immune suppression/HIV-associated immunodeficiency, colonization with *Pneumocystis*

ensues [34][35]. If the host then becomes more immune compromised, by progression of HIV, or by additional therapeutic immune suppression then *Pneumocystis* propagates within the alveoli, and slowly “floods them out.” At the same time disruption of the alveolar-capillary membrane, with ventilation-perfusion abnormalities similar to changes seen in acute respiratory distress syndrome, also occur and manifest as impaired gas exchange. These events culminate in presentation with PCP; in humans PCP is caused by *Pneumocystis jirovecii*; *Pneumocystis carinii* is the cause of PCP in rats.

### **Clinical manifestations**

The clinical presentation of PCP among HIV-infected patients is non-specific and can be mimicked by a wide variety of infectious and non-infectious etiologies. Patients typically present with a triad of progressive exertional dyspnea, nonproductive cough, and fever of several days or weeks duration, which is often associated with an inability to take in a maximum inspiration (not due to pain) [37][38]. Although a productive cough and chest tightness may occur, purulent sputum should raise suspicion of bacterial infection. Hemoptysis is not a feature. Among HIV-infected persons, symptoms are usually of longer duration than among medically-immunosuppressed patients [39]. HIV-infected patients frequently have prolonged prodromal periods with subtle clinical manifestations developing over 3-8 weeks, however some individuals present with a fulminant deterioration of symptoms over 7-10 days, or less. On physical examination varying degrees of respiratory distress (tachycardia, central cyanosis) may be evident as well as stigmata of immune suppression, including oral hairy leukoplakia, molluscum contagiosum, seborrhoeic dermatitis and cutaneous Kaposi sarcoma; auscultation of the chest is



usually normal; rarely, fine end-inspiratory crackles may be heard.

## **Diagnosis**

### **Non-invasive investigations**

#### **Chest radiology**

In early PCP, the chest radiograph may be normal; with later presentations, and with more severe disease, diffuse perihilar interstitial infiltrates are seen ([Figure 1](#)). These appearances may progress to diffuse bilateral air space (alveolar) consolidation resembling pulmonary edema. With delayed presentation or untreated severe disease, there may be confluent alveolar shadowing (“white out”) throughout both lungs, with sparing of the costophrenic angles and apices ([Figure 2](#)). The chest radiographic appearances in PCP may change rapidly from normal at presentation to markedly abnormal over a period of only 2–3 days ([Figure 3a](#), [Figure 3b](#)). Atypical radiographic features include cystic air space and pneumatocele formation, unilateral consolidation, lobar infiltrates, nodules, mediastinal lymphadenopathy, pleural effusions and upper zone infiltrates resembling tuberculosis ([Figure 4](#)).

Although the chest radiograph is a sensitive way of detecting PCP, it is non-specific; these typical and atypical radiographic appearances are also seen in other fungal, mycobacterial and bacterial infections, and in non-infectious conditions, such as interstitial pneumonitis and pulmonary Kaposi sarcoma. With treatment of PCP, improvements in the chest radiographic appearances are not usually apparent for 7–10 days. After clinical recovery, some radiographs show residual fibrosis or post-infectious bronchiectasis.

#### **High-resolution computed tomography**

This may be useful in the symptomatic patient with suspected PCP who has a

normal or equivocal chest radiograph. Patches of “ground glass” shadowing are typical for PCP, but also occur in viral (eg cytomegalovirus, influenza A) or fungal pneumonia and in occult alveolar hemorrhage (Figure 5).

### **Arterial blood gases**

In patients presenting early with PCP, even though the arterial oxygen tension ( $\text{PaO}_2$ ) may be normal or near normal, respiratory alkalosis with hypocarbia (indicating hyperventilation) is often detected; hypoxia may occur with progression of the PCP. The alveolar-arterial oxygen gradient ( $A-a\text{O}_2$ ) is widened in >90% of patients with PCP, but this finding, although suggestive, is non-specific as both hypoxemia and a widened  $A-a\text{O}_2$  gradient also occur in bacterial and mycobacterial infection, non-specific interstitial pneumonitis and pulmonary Kaposi sarcoma.

### **Exercise oximetry**

Among HIV-infected patients, not in receipt of cART, and who have respiratory symptoms, a normal or near-normal chest radiograph and normal resting  $\text{PaO}_2$  values, exercise-induced arterial desaturation is a sensitive and specific method of detecting PCP. A normal exercise test (without desaturation) virtually excludes the diagnosis.

### **Pulmonary function testing**

Data from the North American Pulmonary Complications of HIV infection Study suggest that HIV-individuals who are not in receipt of cART and who have rapid rates of decline in DLCO are at an increased risk for development of PCP [18]. A normal DLCO in an individual who has respiratory symptoms but a normal or

unchanged chest radiograph makes the diagnosis of PCP extremely unlikely.

### **Serum lactate dehydrogenase**

An elevated serum lactate dehydrogenase (LDH) level is highly suggestive of PCP in an HIV-infected patient with sub-acute respiratory symptoms [40]. However an elevated serum LDH is non-specific as it is also found in other pulmonary diseases, including pulmonary embolism, non-specific interstitial pneumonitis, fungal, bacterial and mycobacterial pneumonia, as well in extra-pulmonary disease, such as multicentric Castleman disease and lymphoma.

### **Serum (1-3) $\beta$ -D-glucan**

Measurement of the fungal cell wall component (1-3)  $\beta$ -D-glucan (BG) in serum has been used as an adjunctive diagnostic tool for diagnosis of PCP [41][42]. BG levels are higher among both HIV-infected and uninfected patients with PCP, when compared with symptomatic patients with confirmed alternative diagnoses, including aspergillosis and histoplasmosis. False positive results occur in bacterial pneumonia, patients undergoing hemodialysis, and those who recently received intravenous immunoglobulin. Currently, the serum BG assay appears to be a promising adjunctive non-invasive test for diagnosis of PCP, but further validation is needed before it can be used to monitor treatment response in PCP, as despite clinical recovery, reductions in BG titer are both delayed and unpredictable [43].

### **Plasma/serum S-adenosylmethionine**

*Pneumocystis* lacks S-adenosylmethionine synthetase, is unable to metabolize S-adenosylmethionine (SAM, or Adomet), and so 'scavenges' this from

the human host. It was hypothesized that HIV-infected persons with PCP would have low serum/plasma SAM levels. Whereas measurement of plasma SAM levels enabled discrimination between PCP and “other” causes of pneumonia in some studies [44], one study showed overlapping serum SAM levels [45]. Currently, this assay lacks clinical diagnostic utility.

## **Invasive investigations**

### **Sputum induction**

*Pneumocystis* is rarely identified in spontaneously expectorated sputum. Induced sputum, obtained by inhalation of an aerosol of hypertonic saline is a useful screening technique. The diagnostic yield from this technique varies considerably between centers. Supervision of the procedure by an experienced nurse or respiratory therapist increases the yield; a negative result for *Pneumocystis* from sputum induction should prompt referral for bronchoscopy.

### **Fibreoptic bronchoscopy**

Fibreoptic bronchoscopy with bronchoscopic alveolar lavage (BAL) has a high diagnostic yield, >90% for detection of PCP. Transbronchial biopsy adds little to diagnosis, and is associated with complications, including pneumothorax and hemorrhage. Treatment should never be deferred in an HIV-infected person with suspected PCP pending results of bronchoscopy, as significant clinical deterioration may occur. The yield for diagnosis of PCP from BAL fluid is not reduced for up to 14 days after starting treatment.

### **Video-Assisted thoracoscopic biopsy**

This is occasionally performed in HIV-infected patients with suspected PCP and who have negative results from  $\geq 2$  bronchoscopies, and among patients whose clinical course is at variance with laboratory-confirmed PCP.

### **Histologic diagnosis**

*Pneumocystis* cannot reliably be cultured *ex vivo*, and so diagnosis of PCP is by microscopic visualization of the organism in BAL fluid, induced sputum, or lung tissue. Histopathologically, PCP is characterized by the presence of a foamy, vacuolated exudate filling alveoli. With late presenting or severe disease, there may be interstitial fibrosis, edema, and development of hyaline membranes. Hypertrophy of type II alveolar cells, inferring tissue repair, is frequently seen.

Several histologic stains have been used to identify *Pneumocystis*. Stains that identify the wall of the cystic form (methenamine silver, toluidine blue O and cresyl violet), are widely used as they require minimal laboratory expertise and are easily interpreted, and stains that demonstrate the nuclei of all *Pneumocystis* developmental stages (Diff-Quik or Wright-Geimsa) can provide a rapid diagnosis (within minutes) but require laboratory expertise. Other reagents, including Papanicolaou and calcofluor white, a chemiluminescent agent, are used by some laboratories.

Use of *Pneumocystis*-specific monoclonal antibodies and immunofluorescence has greater diagnostic sensitivity than histologic stains, but is more expensive and requires specific laboratory expertise.

### **Molecular detection tests**

Detection of *Pneumocystis*-specific DNA using the polymerase chain reaction

in BAL fluid and induced sputum is superior to histologic staining for diagnosis of PCP. *Pneumocystis* DNA may also be detected in oropharyngeal wash (OPW) samples in HIV-infected persons presenting with PCP. The specificity and clinical significance of molecular detection assays is impaired by the finding of *Pneumocystis* DNA in respiratory samples (BAL fluid, induced sputum, or OPW) from HIV-infected patients without respiratory symptoms, and in symptomatic persons without PCP with confirmed alternative diagnosis who are colonized with *Pneumocystis*. Currently, the clinical significance of detectable *P. jirovecii* DNA (representing colonization) in a respiratory sample from an HIV-infected person in the absence of respiratory symptoms or other confirmatory tests is unclear.

Although PCR is not licensed for diagnosis, several clinical laboratories in the United States and Europe use this method applied to invasive (BAL and Induced Sputum) and noninvasive sampling techniques (OPW) for diagnosis of PCP [46][47][48].

### **Empirical therapy**

Empirical therapy for HIV-infected patients presenting with symptoms, chest radiographic and arterial blood gas abnormalities typical of PCP is used in healthcare settings that lack diagnostic facilities. This strategy is possible if a patient with a CD4 <200 cells/uL (or stigmata of immune suppression) has typical radiological abnormalities, is not receiving *Pneumocystis* prophylaxis or cART, and has a low probability of other (opportunistic) infections, such as tuberculosis [38].

### **Treatment**

An assessment of the severity of the pneumonia, using the results of arterial

blood gas estimations, will enable decisions to be made about choice of therapy; some drugs are unproven or ineffective in severe disease. When breathing room air, PaO<sub>2</sub> >70mmHg (>9.3 kPa) indicates mild PCP, and <70 mmHg (<9.3 kPa) indicates moderate to severe PCP. Alternatively, A-aO<sub>2</sub> an gradient <35 mmHg, 35-45 mmHg, and, >45 mmHg (>6 kPa) indicates mild, moderate and severe PCP, respectively. Severity stratification also identifies patients who will benefit from adjunctive glucocorticoids (see below).

Patients with glucose 6-phosphate dehydrogenase deficiency should not receive TMP-SMX, dapson, or primaquine as they increase the risk of hemolysis.

### **Trimethoprim-sulfamethoxazole**

Trimethoprim-sulfamethoxazole (TMP-SMX), [Bactrim, Bactrimel, Co-trimoxazole, Cotrim, Septra, Septrin, Sulfatrim, Trisul] (20 mg/kg daily of TMP and 100 mg/kg daily of SMX ) given in two to four divided doses orally or intravenously is first choice therapy for PCP of all grades of severity; this drug combination acts by inhibiting folic acid metabolism. In HIV-infected patients treatment is given for 21 days because shorter courses are associated with treatment failure. In patients with moderate or severe disease, TMP-SMX is given intravenously for the first 7–10 days, then orally; in patients with mild disease oral TMP-SMX may be given throughout. This treatment regimen is effective in 70-80% of patients. Adverse reactions to TMP-SMX, which are usually first evident at 6–14 days of treatment, are common and include neutropenia and anemia in ≤40% of patients, rash in 25%, fever in >30% and abnormal liver function tests in approximately 10% [49][50].

Co-administration of folic or folinic acid does not reduce or prevent hematologic toxicity and may be associated with increased therapeutic failure. Dose

reduction of TMP-SMX, to 75% of the dose given above, is associated with a reduced toxicity profile but may be associated with reduced efficacy. It is not clear why there is such a high frequency of adverse reactions to TMP-SMX among HIV-infected patients compared to patients immunosuppressed by other causes, but it may be due to HIV-induced changes in acetylator status, accumulation of toxic metabolites such as hydroxylamines, or to glutathione deficiency.

### **Alternative therapy**

Several other treatments are available if TMP-SMX is not tolerated by the patient or if treatment fails [17].

### **Clindamycin and primaquine**

This combination was originally only used to “salvage” patients with mild and moderately severe PCP failing TMP-SMX or pentamidine. It is now used as alternative therapy in patients with PCP of all severity. Clindamycin (Cleocin, Daclin) 450–600 mg four times daily is combined with primaquine 15 mg daily (orally). Clindamycin is usually given intravenously for the first 7–10 days, then orally in moderate and severe disease; the treatment may be given orally throughout in patients with mild disease. The mechanism of action of this combination is not known. Clindamycin-primaquine is as effective as TMP-SMX or dapsone-trimethoprim (see below) when given as initial treatment for patients with PCP of mild and moderate severity and is superior to intravenous pentamidine when used in patients intolerant of, or who are failing treatment with TMP-SMX [51]. Almost two-thirds of patients develop a rash and approximately quarter develop diarrhea (both caused by clindamycin). Analysis of stool for detection of *Clostridium difficile* is



indicated if diarrhea occurs. Methemoglobinemia (due to primaquine) occurs in  $\leq 40\%$  of patients, but this is less likely if 15mg rather than 30mg of primaquine is used.

### **Dapsone with trimethoprim**

Among patients with mild or moderate severity PCP a combination of oral dapsone (Axzone) (100 mg per day) and TMX (20 mg/kg daily) is as effective as TMP-SMX (doses as above) and is better tolerated. Rash, nausea and vomiting, mild hyperkalemia (caused by trimethoprim, in  $\leq 50\%$ ) and asymptomatic methemoglobinemia (caused by dapsone) are common side-effects. This combination has not demonstrated efficacy in severe PCP.

### **Atovaquone**

Oral atovaquone (Mepron) is a hydroxynaphthoquinolone that acts against Plasmodia by inhibiting electron transport. At a dose of 750 mg twice daily it is ineffective in patients with severe PCP and less effective than either oral TMP-SMX or intravenous pentamidine for treatment of mild and moderate severity PCP, but is better tolerated than either drug. Adverse reactions include fever, rash, nausea and vomiting, constipation and abnormal liver function tests.

### **Parenteral pentamidine**

Intravenous pentamidine (Pentacarinat, Pentam 300, pentamidine isethionate for injection) is now rarely used in mild and moderately severe PCP. Its mode of action against *Pneumocystis* is unknown. It continues to be used in patients with severe PCP. It is given at a dose of 4 mg/kg daily, by intravenous infusion over at

least one hour. Compared with TMP-SMX, intravenous pentamidine has almost equivalent efficacy but greater toxicity; ≤60% of patients develop increases in the serum creatinine level; approximately half develop leucopenia. Hypotension and nausea/vomiting both occur in up to a quarter of patients; hypoglycemia occurs in approximately 20%; cardiac dysrhythmias (torsade de points) pancreatitis, hypocalcemia, and hypomagnesemia are also described. Autopsy data suggests that it takes at least five days for pentamidine to reach therapeutic concentrations in the lung. Using a dose of 3mg/kg daily is associated with fewer ADR, but data showing equivalent efficacy with the 4mg/kg dose are lacking. There are no therapeutic advantages to combining TMP-SMX and intravenous pentamidine and this combination has a much higher toxicity profile.

### **Caspofungin**

Caspofungin (Cancidas) is an echinocandin that inhibits (1-3)-β-D-glucan synthase and is effective against *Aspergillus* and *Candida* spp. Several case reports and small case series show that caspofungin as monotherapy or combined with other therapy, may be effective in patients with PCP who are not responding or tolerating first-line therapy. Caspofungin has not been prospectively evaluated against TMP-SMX or other regimens as first-line therapy.

### **Nebulized pentamidine**

This has no role in treatment of PCP.

### **Adjunctive Corticosteroids**

In HIV-infected patients with moderate and severe PCP adjunctive therapy

with corticosteroids has been shown to reduce the likelihood of respiratory failure (by half) and death (by one-third). Corticosteroids probably act by reducing the body's intrapulmonary inflammatory response to *Pneumocystis*. It is recommended that glucocorticoids are given to HIV-infected patients with proven or suspected PCP who have a PaO<sub>2</sub> <70mmHg (< 9.3 kPa) or A aO<sub>2</sub> >35 mmHg (>4.7 kPa) [17]

Corticosteroid treatment should begin at the start of specific anti *Pneumocystis* therapy. In some patients treatment will begin on an empiric basis and the diagnosis should be confirmed as soon as practicable. Regimens include oral prednisolone 40 mg twice daily for 5 days, thereafter 40 mg once daily for days 6–10 and then 10 further days of 20 mg daily and intravenous methylprednisolone at 75% of these doses [17]. There is no evidence that adjunctive corticosteroids are of benefit in patients with mild PCP. Patients receiving adjunctive corticosteroids should be monitored for hyperglycemia. In the long term patients receiving this intervention are at greater risk of developing avascular necrosis of the hip.

### **General management**

In the first few days of treatment HIV-infected patients with PCP may experience a deterioration in their clinical condition, with worsening of the chest radiograph and oxygenation. This is thought to arise either from the host inflammatory response to dying *Pneumocystis*, or to *Pneumocystis*-induced changes in surfactant leading to worsening of lung injury.

Patients with mild PCP may be treated as outpatients with oral TMP-SMX under close supervision of a physician. Patients with moderate and severe PCP should be treated with intravenous TMP-SMX, or with clindamycin with primaquine,

and adjunctive corticosteroids. Patients not responding by 5–7 days should be switched to alternative therapy. Before ascribing deterioration to treatment failure and considering a change in therapy, evaluation for alternative causes should be done (Table). Additionally, it is important to perform bronchoscopy if the diagnosis is empiric, and to treat any co-pathology already detected in BAL fluid.

All hypoxemic patients with PCP should receive supplemental oxygen therapy via a tight-fitting facemask in order to maintain the  $\text{PaO}_2 \geq 60\text{mmHg}$  ( $\geq 8.0\text{ kPa}$ ). If an inspired oxygen concentration of 60% fails to maintain the  $\text{PaO}_2 \geq 60\text{mmHg}$  ( $\geq 8.0\text{ kPa}$ ), referral to the ICU for mechanical ventilation should be considered. The prognosis of patients with severe PCP with respiratory failure has improved in recent years, as a consequence of general improvements in ICU management of respiratory failure [52] [53]. Most centers would mechanically ventilate patients with a first or second episode of PCP and those who rapidly deteriorate following bronchoscopy.

## **Prognosis**

Over the last 20 years the outcome for HIV-infected persons with PCP has improved. This is likely due to a combination of earlier detection of disease, timely institution of treatment and more effective management of complications. In the cART era mortality from PCP is 9.7-11.6% [19][54][55]. Several clinical and laboratory features have been shown predict a poor outcome among HIV-infected patient with PCP. Prognostic factors include at presentation, increasing patient age, lack of knowledge of HIV status, presentation with a second or subsequent episode of PCP, evidence of poor oxygenation ( $\text{PaO}_2 \leq 53\text{ mmHg}$  ( $<7.0\text{ kPa}$ ) or an  $\text{A-aO}_2$  gradient  $>30\text{ mmHg}$  ( $>4.0\text{ kPa}$ ), marked chest radiographic abnormalities, peripheral blood leukocytosis (white blood cell count  $\geq 10.8 \times 10^9/\text{L}$ ), a low hemoglobin ( $<12\text{ g/dL}$ ), a

low serum albumin ( $\leq 35$  g/L), and raised serum lactate dehydrogenase (LDH) enzyme levels ( $\geq 300$  IU/L). After admission and investigation, identification in BAL fluid of a (viral, eg CMV, or bacterial) co-pathogen,  $\geq 5\%$  neutrophilia or elevated IL-8 levels, evidence of fibrosis and edema on transbronchial biopsy, and elevated serum LDH enzyme levels (that do not fall despite treatment), identification of co-morbidity eg non-Hodgkin lymphoma, presence of pulmonary Kaposi sarcoma, or admission to the intensive care unit (ICU), a high APACHE II (Acute Physiology and Chronic Health Evaluation) score, need for mechanical ventilation, and/or development of a pneumothorax are also predictive of a poor outcome.

Several prognostic scores have been derived from factors present at/soon after an HIV-infected person's presentation with PCP; scores based on wasting, A-aO<sub>2</sub> gradient, and serum albumin, [56]; age, injection drug use, A-aO<sub>2</sub> gradient, serum albumin and serum bilirubin [57]; age, hemoglobin, PaO<sub>2</sub>, pulmonary Kaposi sarcoma, and co-morbidity [58] all associate with mortality. The potential value of such prognostic scores lies in their ability to identify those at greatest risk of death and to inform clinicians about which patients can safely be managed in an outpatient setting. While these prognostic scores have been derived from large cohorts of HIV-infected patients with PCP in the United States or United Kingdom, none has been validated in other US/UK cohorts nor in developing-world settings[56][57][58].

### **Starting antiretroviral therapy in a patient with PCP**

The optimal time to initiate cART in a person with PCP remains to be determined; some clinicians start cART immediately while others prefer to see a clinical response to PCP treatment. One randomized trial of patients with opportunistic infection (OI), approximately two-thirds of whom had PCP,

demonstrated that cART when initiated early (within 2 weeks) and compared to therapy deferred until  $\geq 4$  weeks after initiation of treatment for the OI was associated with a significant reduction in mortality, but no increased risk of IRIS [59] [60]. While this study supports early cART, it does not show whether immediate treatment at time of PCP diagnosis or waiting for a response to PCP treatment (usually within 4–7 days) is a better strategy. Of note, the study excluded those with severe laboratory abnormalities and required patients to be able to take oral medication - mechanically ventilated patients were not studied - inferring possible selection bias in favor of less sick patients. By contrast, marked respiratory deterioration from cART, if initiated early, has been reported [61].

## **Prophylaxis**

With progressive immunosuppression and falls in CD4 counts, HIV-infected individuals are at increased risk of developing PCP. Primary prophylaxis, to prevent a first episode of PCP, is given when the CD4 lymphocyte count falls  $< 200$  cells/ $\mu$ L or the CD4:total lymphocyte ratio is less than 1:5 (or  $< 14\%$ ), to patients with HIV-related constitutional symptoms such as unexplained fever ( $> 100^{\circ}\text{F}$ ) of 2 weeks or more in duration, or oral candida regardless of CD4 count, and to patients with other AIDS-defining diagnoses, such as Kaposi sarcoma. Secondary prophylaxis is given in order to prevent a recurrence.

One double strength (DS) TMP-SMX tablet (containing 160 mg of TMP and 800mg of SMX) once daily is the first-choice regimen for both primary and secondary prophylaxis. Lower doses, one DS TMP-SMX three times weekly or one single strength TMP-SMX tablet (containing 80mg of TMP and 400mg of SMX) once daily, may be equally effective and have fewer adverse drug reactions. Rash, with or

without fever, occurs in  $\leq 20\%$  of patients. Desensitization should be attempted in those unable to tolerate TMP-SMX. Alternative, other less effective agents are available for prophylaxis, including nebulized pentamidine (Nebupent), 300 mg (delivered via a Respigard II nebulizer) once per month, (once per fortnight in HIV-infected patients with CD4 counts  $\leq 50$  cells/ $\mu$ L), dapsone 100 mg OD (or 50mg BID), dapsone 50mg OD with pyrimethamine 75 mg once weekly and leucovorin 25mg once weekly, or dapsone 200mg with 75 mg pyrimethamine and 25 mg leucovorin (all once weekly), and oral atovaquone 750 mg twice daily, with or without pyrimethamine 75 mg OD and leucovorin 25mg OD [17].

### **Stopping prophylaxis**

The widespread availability and uptake of cART in North America, Europe and Australasia has been associated with marked reductions in incidence of many opportunistic infections, including PCP, hospital admissions and mortality from HIV infection. In most patients, within a few weeks of starting cART, there are rapid decreases in plasma HIV RNA and, in parallel, increases in CD4 counts. The US Public Health Service/Infectious Disease Society of America recommend that primary prophylaxis against PCP may be discontinued in HIV-infected persons who respond to cART with an increase in CD4 counts to  $>200$  cells/ $\mu$ L, sustained for at least 6 months [17]. Many of these patients will also have reduction in HIV RNA to below the limit of detection. Withdrawal of secondary prophylaxis may be carried out, using these criteria. If, despite cART, the CD4 lymphocyte count falls to  $<200$  cells/ $\mu$ L and/or the plasma HIV RNA “load” rises, then prophylaxis should be re-instituted using the criteria for primary prophylaxis. Clearly, close patient monitoring is needed to detect any such changes rapidly.

Recent data accrued from a cohort study, a retrospective review and a case series show a low incidence of PCP among patients who discontinue or never start PCP prophylaxis, who received ART and had CD4 counts between 100-200 cells/ $\mu$ L and plasma HIV viral loads <50-400 copies/mL [62][63][64]. Although these data support discontinuation of primary PCP prophylaxis in certain patients with CD4 counts between 100-200 cells/ $\mu$ L, with some experts recommending this approach for their patients, this intervention has not yet been widely adopted [17].

## **Summary**

The yeast-like fungus *Pneumocystis* causes *Pneumocystis* pneumonia (PCP) which, despite the widespread availability of specific anti-*Pneumocystis* prophylaxis and of combination antiretroviral therapy (cART) remains a common AIDS-defining presentation in the United States and in Europe, and is increasingly recognized among persons living in Africa. *Pneumocystis* cannot be cultured and the “gold standard” diagnostic test to diagnose PCP is bronchoscopic alveolar lavage. Use of adjunctive biomarkers such as Serum (1-3)  $\beta$ -D-glucan for diagnosis requires further evaluation. Recommended first-line treatment is with TMP-SMX. Mortality from PCP in the era of cART is approximately 10-12%. The optimal time to start cART in a patient with PCP remains uncertain.



## References

- 1] Cushion MT. Are members of the fungal genus *Pneumocystis* (a) commensals; (b) opportunists; (c) pathogens; or (d) all of the above? PLoS Pathogens 2010 6: e1001009.
- 2] Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med 1981;305:1425-31.
- 3] Masur H, Michelis M, Greene J, et al. An outbreak of community-acquired *Pneumocystis carinii* pneumonia - initial manifestation of cellular immune dysfunction. N Engl J Med 1981;305:1431-38.
- 4] Huang L, Cattamanchi A, Davies JL, et al, on behalf of the International HIV-associated opportunistic pneumonias (IHOP) study; the lung HIV study. Proc Am Thorac Soc 2011;8:294-300.
- 5] Walzer PD, Perl DP, Krogstad DJ, Rawson PG, Schultz MG. *Pneumocystis carinii* pneumonia in the United States. Epidemiologic, diagnostic, and clinical features. Ann Intern Med 1974;80:83-93.
- 6] Hay JW, Osmond DH, Jacobson MA. Projecting the medical costs of AIDS and ARC in the United States. J Acquir Immune Defic Syndr 1988;1:466-85.
- 7] Morris A, Lundgren JD, Masur H, et al. Current epidemiology of *Pneumocystis* pneumonia. Emerg Infect Dis 2004; 10: 1713-1720.
- 8] Phair J, Muñoz A, Detels R, Kaslow R, Rinaldo C, Saah A. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study. N Engl J Med 1990;322:161-5.
- 9] Jones JL, Hanson DL, Dworkin MS, et al. Surveillance for AIDS-defining

opportunistic illnesses, 1992-1997. MMWR CDC Surveill Summ 1999;48:1-22.

10] Kaplan JE, Hanson DL, Navin TR, Jones JL. Risk factors for primary *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected adolescents and adults in the United States: reassessment of indications for chemoprophylaxis. J Infect Dis 1998;178:1126-32.

11] Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. Clin Infect Dis 2000 Apr;30 Suppl 1:S5-14.

12] Detels R, Tarwater P, Phair JP, Margolick J, Riddler SA, Muñoz A; Multicenter AIDS Cohort Study. Effectiveness of potent antiretroviral therapies on the incidence of opportunistic infections before and after AIDS diagnosis. AIDS 2001;15:347-55.

13] Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994-98: the EuroSIDA study. Lancet 2000;356:291-6.

14] Weverling GJ, Mocroft A, Ledergerber B, et al. Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. EuroSIDA Study Group. Lancet 1999;353:1293-8.

15] Buchacz K, Baker RK, Palella FJ, et al; HOPS Investigators. AIDS-defining opportunistic illnesses in US patients, 1994-2007: a cohort study. AIDS 2010; 19;24:1549-59.

16] HIV in the United Kingdom: 2011 report.

[http://www.hpa.org.uk/webc/HPAwebFile/HPAweb\\_C/1317131685847](http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317131685847) [accessed 22 August 2012].

17] Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention

and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2012 (in press).

18] Stansell JD, Osmond DH, Charlebois E, et al. Predictors of *Pneumocystis carinii* pneumonia in HIV-infected persons. Pulmonary Complications of HIV Infection Study Group. Am J Respir Crit Care Med 1997;155:60-6.

19] Walzer PD, Evans HE, Copas AJ, Edwards SG, Grant AD, Miller RF. Early predictors of mortality from *Pneumocystis jirovecii* pneumonia in HIV-infected patients: 1985-2006. Clin Infect Dis 2008;46:625-33.

20] Fisk DT, Meshnick S, Kazanjian PH. *Pneumocystis carinii* pneumonia in patients in the developing world who have acquired immunodeficiency syndrome. Clin Infect Dis 2003;36:70-8.

21] Wannamethee SG, Sirivichayakul S, Phillips AN, et al. Clinical and immunological features of human immunodeficiency virus infection in patients from Bangkok, Thailand. Int J Epidemiol 1998;27:289-95.

22] Weinberg A, Duarte MI. Respiratory complications in Brazilian patients infected with human immunodeficiency virus. Rev Inst Med Trop Sao Paulo 1993;35:129-39.

23] Mohar A, Romo J, Salido F, et al. The spectrum of clinical and pathological manifestations of AIDS in a consecutive series of autopsied patients in Mexico. AIDS 1992;6:467-73.

24] Morrow BM, Hsaio NY, Zampoli M, Whitelaw A, Zar HJ. *Pneumocystis* pneumonia in South African children with and without human immunodeficiency virus infection in the era of highly active antiretroviral therapy. Pediatr Infect Dis J 2010;29:535-9.

- 25] Worodria W, Okot-Nwang M, Yoo SD, Aisu T. Causes of lower respiratory infection in HIV-infected Ugandan adults who are sputum AFB smear-negative. *Int J Tuberc Lung Dis* 2003;7:117-23.
- 26] Hartung TK, Chimbayo D, van Oosterhout JJ, et al. Etiology of suspected pneumonia in adults admitted to a high-dependency unit in Blantyre, Malawi. *Am J Trop Med Hyg* 2011;85:105-12.
- 27] Aderaye G, Bruchfeld J, Olsson M, Lindquist L. Occurrence of *Pneumocystis carinii* in HIV-positive patients with suspected pulmonary tuberculosis in Ethiopia. *AIDS* 2003;17:435-40.7
- 28] Choukri F, Menotti J, Sarfati C, et al. Quantification and spread of *Pneumocystis jirovecii* in the surrounding air of patients with *Pneumocystis* pneumonia. *Clin Infect Dis* 2010;51:259-65.
- 29] Le Gal S, Damiani C, Rouillé A, et al. A cluster of *Pneumocystis* infections among renal transplant recipients: molecular evidence of colonized patients as potential infectious sources of *Pneumocystis jirovecii*. *Clin Infect Dis* 2012;54:e62-71.
- 30] Nevez G, Raccurt C, Jounieaux V, et al. Pneumocystosis versus pulmonary *Pneumocystis carinii* colonization in HIV-negative and HIV-positive patients. *AIDS* 1999;13: 535-6.
- 31] Medrano FJ, Montes-Cano M, Conde M, et al. *Pneumocystis jirovecii* in general population. *Emerg Infect Dis* 2005;11:245-50.
- 32] Vargas SL, Ponce CA, Sanchez CA, Ulloa AV, Bustamante R, Juarez G. Pregnancy and asymptomatic carriage of *Pneumocystis jirovecii*. *Emerg Infect Dis* 2003;9:605-6.
- 33] Gutiérrez S, Respaldiza N, Campano E, Martínez-Risquez MT, Calderón EJ, De La Horra C. *Pneumocystis jirovecii* colonization in chronic pulmonary disease.

Parasite 2011;18:121-6.

34] Morris A, Wei K, Afshar K, Huang L. Epidemiology and clinical significance of *Pneumocystis* colonization. J Infect Dis 2008;197:10-7.

35] Morris A, Norris KA. Colonization by *Pneumocystis jirovecii* and its role in disease. Clin Microbiol Rev 2012;25:297-317.

36] Calderón EJ, Rivero L, Respaldiza N, et al. Systemic inflammation in patients with chronic obstructive pulmonary disease who are colonized with *Pneumocystis jirovecii*. Clin Infect Dis 2007;45:e17-9.

37] Malin A, Miller R. *Pneumocystis carinii* pneumonia: presentation and diagnosis. Reviews in Medical Microbiology 1992; 3: 80-87.

38] RF Miller, AB Millar, IVD Weller and SJG Semple. Empirical treatment without bronchoscopy for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. Thorax 1989; 44: 559-564.

39] Kovacs JA, Hiemenz JW, Macher AM, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. Ann Intern Med 1984;100;5:663-71.

40] Zaman MK, White DA. Serum lactate dehydrogenase levels and *Pneumocystis* pneumonia. Diagnostic and prognostic significance. Am Rev Respir Dis 1988;137:796-800.

41] Watanabe T, Yasuoka A, Tanuma J, et al. Serum (1->3) beta-D-glucan as a noninvasive adjunct marker for the diagnosis of *Pneumocystis* pneumonia in patients with AIDS. Clin Infect Dis 2009;49:1128-31.

42] Sax PE, Komarow L, Finkelman, et al; AIDS Clinical Trials Group Study A5164 Team. Blood (1->3)-beta-D-glucan as a diagnostic test for HIV-related *Pneumocystis jirovecii* pneumonia. Clin Infect Dis 2011;53:197-202.

- 43] Morris AM, Masur H. A serologic test to diagnose *Pneumocystis* pneumonia. Are we there yet? Clin Infect Dis 2011; 53: 2043-4.
- 44] Skelly MJ, Holzman RS, Merali S. S-adenosylmethionine levels in the diagnosis of *Pneumocystis carinii* pneumonia in patients with HIV infection. Clin Infect Dis 2008;46:467-71.
- 45] Wang P, Huang L, Davis JL, et al. A hydrophilic-interaction chromatography tandem mass spectroscopy method for quantitation of serum s-adenosylmethionine in patients infected with human immunodeficiency virus. Clin Chim Acta 2008;396:86-8.
- 46] Larsen HH, Huang L, Kovacs J, et al. A prospective, blinded study of quantitative touch-down polymerase chain reaction using oral-wash samples for diagnosis of *Pneumocystis* pneumonia in HIV-infected patients. J Infect Dis 2004; 189:1679-83.
- 47] Alvarez-Martinez MJ, Miro JM, Valls ME, et al. Sensitivity and specificity of nested and real-time PCR for detection of *Pneumocystis jirovecii* in clinical specimens. Diagn Microbiol Infect Dis 2006;56:153–60.
- 48] Huggett JF, Taylor MS, Kocjan G, et al. Development and evaluation of a real-time PCR assay for detection of *Pneumocystis jirovecii* DNA in bronchoalveolar lavage fluid of HIV-infected patients. Thorax 2008;63:154-9.
- 49] Fisk M, Sage EK, Edwards SG, Cartledge JD, Miller RF. Outcome from treatment of *Pneumocystis jirovecii* pneumonia with co-trimoxazole. Int J STD & AIDS 2009;20: 652-3.
- 50] Helweg-Larsen J, Benfield T, Atzori C and Miller RF. Clinical efficacy of first- and second-line treatments for HIV-associated *Pneumocystis jirovecii* pneumonia: a tri-centre cohort study. J Antimicrob Chemother 2009;64:1282-90.

- 51] Benfield T, Atzori C, Miller RF and Helweg-Larsen J. Second-line salvage treatment of AIDS-associated *Pneumocystis jirovecii* pneumonia: a case series and systematic review. J Acquir Immune Defic Syndr 2008;48:63-7.
- 52] Miller RF, Allen E, Copas A, Singer M, Edwards SG. Improved survival for HIV infected patients with severe *Pneumocystis jirovecii* pneumonia is independent of highly active antiretroviral therapy. Thorax 2006;61:716-21.
- 53] Davis JL, Morris A, Kallet RH, et al. Low tidal volume ventilation is associated with reduced mortality in HIV-infected patients with acute lung injury. Thorax 2008;63:988-93.
- 54] Radhi S, Alexander T, Ukwu M, Saleh S, Morris A. Outcome of HIV-associated *Pneumocystis pneumonia* in hospitalized patients from 2000 through 2003. BMC Infect Dis 2008;8:118.
- 55] Fei MW, Sant CA, Kim EJ, et al. Severity and outcomes of *Pneumocystis pneumonia* in patients newly diagnosed with HIV infection: an observational cohort study. Scand J Infect Dis 2009;41:672-8.
- 56] Arozullah AM, Yarnold PR, Weinstein RA, et al. A new pre-admission staging system for predicting inpatient mortality from HIV-associated *Pneumocystis carinii* pneumonia in the early highly active antiretroviral therapy (HAART) era. Am J Respir Crit Care Med 2000;161:1081-6.
- 57] Fei MW, Kim EJ, Sant CA, et al. Predicting mortality from HIV-associated *Pneumocystis pneumonia* at illness presentation: an observational cohort study. Thorax 2009;64:1070-6.
- 58] Armstrong-James D, Copas AJ, Walzer PD, Edwards SG, Miller RF. A prognostic scoring tool for identification of patients at high and low risk of death from HIV-associated *Pneumocystis jirovecii* pneumonia. Int J STD AIDS. 2011;22:628-34.

- 59] Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS One 2009;4:e5575
- 60] Grant PM, Komarow L, Andersen J, et al. Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of early vs. deferred ART during an opportunistic infection. PLoS One 2010;5:e11416.
- 61] Jagannathan P, Davis E, Jacobson M and Huang L. Life-threatening immune reconstitution inflammatory syndrome after *Pneumocystis* pneumonia: a cautionary case series. Aids 2009;23:1794-6.
- 62] D'Egidio GE, Kravcik S, Cooper CL, Cameron DW, Fergusson DA and Angel JB. *Pneumocystis jiroveci* pneumonia prophylaxis is not required with a CD4+ T-cell count < 200 cells/microl when viral replication is suppressed. AIDS 2007;21:1711-5
- 63] Cheng CY, Chen MY, Hsieh SM, et al. Risk of pneumocystosis after early discontinuation of prophylaxis among HIV-infected patients receiving highly active antiretroviral therapy. BMC Infect Dis 2010;10:126.
- 64] Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE), Mocroft A, Reiss P, Kirk O, et al. Is it safe to discontinue primary *Pneumocystis jiroveci* pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? Clin Infect Dis 2010;51:611-9



**Table.** Causes of deterioration in an HIV-infected person receiving treatment for PCP

Cause	Explanation
Severe progressive PCP	
Iatrogenic	Pulmonary edema due to intravenous fluid overload when giving TMP-SMX IRIS following early initiation of cART
Side effects of therapy	Anemia eg TMP-SMX, Methemoglobinemia eg dapsone, primaquine
Inadequate therapy	Incorrect dosage or route of administration Adjuvant glucocorticoids not given for moderate or severe PCP
Post-bronchoscopy	Sedation Pneumothorax
Pneumothorax	Spontaneous Associated with mechanical ventilation
Co-pathology in lung	Bacterial infection Pulmonary Kaposi sarcoma Intercurrent pulmonary embolism
Wrong diagnosis	Empiric diagnosis of PCP and correct diagnosis is another pathology eg bacterial pneumonia

### Figure legends

Figure 1. CXR showing bilateral diffuse interstitial infiltrates

Figure 2. CXR showing severe PCP. The patient is intubated and mechanically ventilated; there is a left-sided pneumothorax.

Figure 3a. CXR on admission with PCP

Figure 3b. CXR (same patient as Figure 3a), after an interval of 3 days, showing marked deterioration in radiographic abnormalities.

Figure 4. CXR showing atypical radiologic appearances; asymmetric infiltrates

Figure 5. CT showing widespread changes of “ground glass” shadowing.