

## High Mortality Among Clinically Pneumocystis Pneumonia Infection in Low CD4 HIV Patients: Case Series

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### ABSTRACT

**Objective:** The number of HIV cases in Indonesia reached a peak in 2019 with 50,282 cases dispersed over 407 of 507 districts and cities (or 80%) of the country's provinces. Central Java is the province after DKI Jakarta and East Java which has a mortality of 12.41 and an HIV/AIDS prevalence of 22% of all cases. High mortality in HIV patients influenced by very low CD4 count  $\leq 50$  cells/mm<sup>3</sup>. Identification of clinical characteristics, risk factors and causes of death is very important to carry out optimal management of HIV/AIDS for delaying the progression of infection and saving lives.

**Design and method:** We identified three patients with newly diagnosed HIV between January to April, 2023. We provide demographic data, clinical characteristics, laboratory examination, chest x-ray imaging and final outcome. **Results:** We presented 3 newly diagnosed HIV patients. They are still young < 40 years old, the majority have BMI < 18.5. Major opportunistic infections are oral candidiasis (100%), Pruritic Popular Eruption (PPE), pulmonary infection due to Tuberculosis, Pneumocystis pneumonia (PCP) and bacterial pneumonia. Hematological alteration dominated by anemia. Increased of transaminase enzyme and hyponatremia are also common. All patients had CD4 count < 20 cells/mm<sup>3</sup>, only one patient survived. Causes of death were pulmonary infection mainly due to clinical PCP. **Conclusion:** PCP is one of the fatal opportunistic infections in HIV. It is necessary to be diagnosed as early as possible so that patients can start Anti-Retro Viral (ARV) at an early stage to improve prognosis.



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### KEYWORDS:

HIV/AIDS, Low CD4, Opportunistic infection, PCP infection, Cause of Death

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## INTRODUCTION

There were 48,000 new cases of Human Immunodeficiency Virus (HIV) infection in 2016. Indonesia is one of the Asian countries experiencing an increase in the number of cases of this virus. Indonesia is a country in the Asia Pasific that ranks third for HIV infection rates after China and India. The Data and Information Center of the Ministry of Health of the Republic of Indonesia reported that the number of HIV cases in Indonesia reached its peak in 2019 with 50,282 cases spread across 407 of the 507 districts and cities (or 80%) of the provinces in Indonesia. After the provinces of DKI Jakarta and East Java, Central Java has a death rate of 12.41 and

an HIV/AIDS prevalence of 22% of all cases (RI Ministry of Health, 2020).

Factors that cause high mortality rates in HIV patients are very low CD4 counts  $\leq 50$  cells/mm<sup>3</sup>, moderate-severe anemia and Body Mass Index (BMI) <18.5, late diagnosis of HIV and the stage of HIV-AIDS at diagnosis (Sumantri et al., 2012).

CD4 levels are an important prognostic marker of residual immunological function. Because the CD4 levels can decrease before the clinical condition occurs, CD4 cells are an early sign of disease progression. The progression of HIV infection, the likelihood of contracting an opportunistic infection, and sudden death are all highly predictable based on

CD4 levels. The increased risk of morbidity and mortality in HIV/AIDS patients is correlated with low CD4 levels. In general, the CD4 levels to be the lower threshold for serious opportunistic infections is 200 cells/mm<sup>3</sup> (Orsini *et al.*, 2013) .

However, the rate of HIV disease progression among patients with CD4 <50 cells/mm<sup>3</sup> is wide. Identification of clinical characteristics, risk factors and causes of death in these patients is very important, especially in health facilities that provide CD4 levels checks. This effort aims to carry out optimal management of HIV/AIDS in order to reduce the development of infection and save lives.

## **METHOD**

We identified three patients who were newly diagnosed with HIV between January and April 2023. This study was approved by the Institutional Review Board of Muhammadiyah University of Surakarta with number 4882/B.2/KEPK-FKUMS/V/2023. These patients suffer from severe opportunistic infections that cause high mortality rates. We provided demographic data, clinical characteristics, laboratory tests, chest x-ray, and outcomes.

## **RESULTS AND DISCUSSION**

### **Case 1**

On January 26<sup>th</sup> 2023, a 28 years old man, a man who likes men (MSM), came to the Emergency Room (ER) with complaints of shortness of breath for three months, fluctuating fever, dry cough, and significant weight loss. A month ago, the patient was

hospitalized with similar symptoms and has not fully recovered. The patient worked as a salesman, had no other previous medical history. On examination, a fever was found with a temperature of 37.8°C and tachycardia, his BMI was 17.6, oral candidiasis, no enlarged lymph nodes in the neck, and bronchovesicular sounds in both lungs. His oxygen saturation was 94% on room air, increasing to 98% with nasal oxygen supply. His laboratory results showed mild anemia with hemoglobin levels was 9.7 g/dL, elevated liver function tests (LFTs), with aspartate aminotransferase (AST) was 51 U/L (reference range 8–37 U/L) and alanine aminotransferase (ALT) was 87 U/L (reference range 8–35 U/L). Nasopharyngeal samples for SARS CoV-2 were negative, chest x-ray showed bilateral infiltrates with a differential diagnosis of bacterial or viral infection.

On the day of admission, the patient received a positive result for anti-HIV examination. His CD4 levels was 11 cells/mm<sup>3</sup> (reference range 515–1642 cells/mm<sup>3</sup>). A second chest x-ray showed suspicious PCP infection. The patient was diagnosed with stage IV HIV infection with oral candidiasis and clinical PCP infection. He was treated with oxygen supplementation starting with nasal cannula 3 L/min to 10 L/min with Non-Re-Breathing Mask (NRM) due to a decrease in oxygen saturation up to 90% during hospitalization, oral Nystatin drops, intravenous Fluconazole, Co-trimoxazole 15 mg/Kg body weight

divided dose, and steroid dose titration. The patient recovered clinically and was discharged on the 9<sup>th</sup> day after admission. The patient was planned to start the ARV regimen after day 21. One week after being discharged from the hospital, the patient suffered from fever again, multiple erythematoses all over his body, oral mucosal lesions, and diarrhea. The patient admitted to suffering from Steven Johnson Syndrome again due to Cotrimoxazole. The patient was given high doses of corticosteroids,



Figure 1a. First X-ray

topical emollients, and cetirizine so that his condition began to recover. Because of this major allergic reaction, co-trimoxazole should be discontinued and replaced with clindamycin. We decided to start ARVs with DTG 50mg/3TC 300mg/TDF 300mg (TLD) as soon as his condition stabilized. Tuberculosis chemoprophylaxis should be maintained due to the increase in transaminase enzymes. The patient recovered completely after 10 days, and was clinically stable at the 4<sup>th</sup> month of ART.

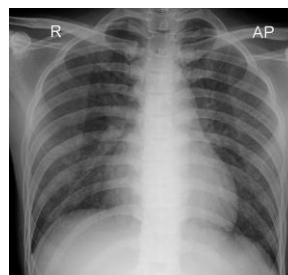


Figure 1b. Second X-ray

**Picture 1.** Case 1 X-ray

**Case 2**

A 31 years old man, MSM, was admitted to our hospital on January 13<sup>rd</sup> 2023. Previously the patient was hospitalized for five days due to typhoid fever and dry cough in December 2022. On January 3<sup>rd</sup> the patient registered again with fever and admitted lost almost 12 kg of weight (BMI was 20) and was diagnosed with HIV. On the third visit, the patient suffered from fever, cough, mouth ulcers and shortness of breath. Vital sign examination showed the blood pressure was 105/62 mmHg, heart rate was 120x/minute, temperature was 36.4°C, respiratory rate was 24x/minute, oxygen saturation

was 96% in room air, oral candidiasis, bronchovesicular breath sounds, PPE on both arms, legs, back. The patient did not suffer from anemia with hemoglobin levels was 14.4 g/dL, leukocyte levels was  $9.32 \times 10^3$  U/L, AST was 58 U/L, ALT was 123 U/L, sodium was 126.3 mmol/L, CD4 levels was 7 cells/mm<sup>3</sup>. Chest x-ray examination with bilateral diffuse infiltration suggestive of PCP. SARS CoV-2 antigen was negative, Mycobacterial TB was also negative. The patient was initiated with oxygen supplementation 3 L/minute, co-trimoxazole 15 mg/KgBW in divided doses, steroids, oral Nystatin drops and Fluconazole.

On the fifth day, his condition did not improve, his oxygen saturation started to reach 91% even with an NRM of 15 L/minute. The results of blood gas analysis (AGD) showed pH was 7.58, PCO<sub>2</sub> was 35 mmHg, HCO<sub>3</sub> was 29.3 mmol/L, PO<sub>2</sub> was 58 mmHg, SpO<sub>2</sub> was 91%, lactate was 1.1 mmol/L. The patient was transferred to the ICU. The second x-ray examination showed worsening bilateral pneumonia, then Meropenem was added as a broad spectrum

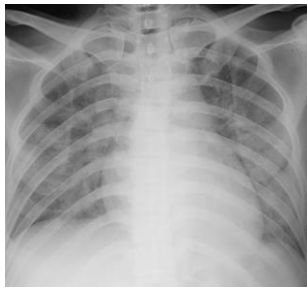


Figure 2a. First X-ray

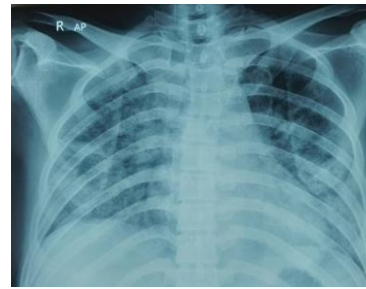


Figure 2b. Second X-ray

**Picture2.** X-ray Case 2

**Case 3**

A 26 years old man, MSM, in the second week of January 2023, came to the emergency room because of shortness of breath for a month, dry cough, fever and weight loss. The patient lives in another city, admitted that he had known about his HIV status for a year but had not sought treatment. In the last three months, his health condition has deteriorated, his weight has decreased drastically (BMI was 14.6), he often has fever and diarrhea. His condition was not good on arrival, blood pressure was 118/80 mmHg, heart rate was 118x/minute, respiratory rate was 30x/minute, oxygen saturation was 75% increasing to 95% with NRM 10 L/minute, mouth

antibiotic for nosocomial infections. On the seventh day, his oxygen saturation continued to decrease to 83%. The patient was referred to another tertiary hospital for ventilator support, because our hospital's ventilators were all occupied at that time. The patient received ventilator support for almost seven days, unfortunately the patient died after 15 days of hospitalization.

ulcers and PPE. Laboratory examination showed hemoglobin levels was 13.3 g/dL, leukocytes was 7950 U/L, normal electrolytes, AST was 62 U/L, ALT was 46 U/L, CD4 levels was 12 cells/mm<sup>3</sup>. Chest x-ray examination showed infiltration in the right upper and lower middle lung fields of the right and left lungs, which could be a specific process (tuberculosis) with secondary infection.

The patient was initiated with HIV stage 4, suspected tuberculosis and clinical PCP infection. The patient was given co-trimoxazole 15 mg/KgBW in divided doses, Nystatin oral drops, Fluconazole, steroids, and intravenous azithromycin. The patient continued to improve until the seventh day. Then the

patient began to become increasingly restless, heart rate above 130x/min, pH was 7.49, PO<sub>2</sub> was 70 mmHg, PCO<sub>2</sub> was 43 mmHg, HCO<sub>3</sub> was 25.3 mmol/L SO<sub>2</sub> was 94%, lactate was 3.6 mmol/L. The patient was transferred to the intensive care unit and received ventilator support. Antigen for SARCOV-2

was negative, rapid molecular test for TB was also negative. The second x-ray showed more complex and severe consolidation, especially in the right lung. Antibiotics were increased by administering Meropenem. The patient died on the tenth day.

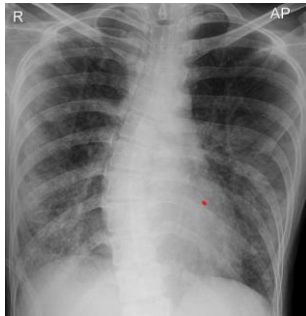


Figure 3a. First X-ray



Figure 3b. Second X-ray

**Picture3.** Case 3 X-ray

There were three MSM patients. All of them were <40 years old and were of productive age. Nutritional status was normal in one patient and below normal (BMI <18.5) in the other two patients.

Mucocutaneous manifestations include oral candidiasis and Pruritic Popular Eruption (PPE). Pulmonary manifestations were dominated by clinical and radiological suspicion of PCP infection where two people died during hospitalization.

Hematological changes due to anemia, elevated transaminase enzymes, and hyponatremia were common in our patients. Meanwhile, the CD4 levels that <15 cells/mm<sup>3</sup> was 11.7 cells/mm<sup>3</sup> and 12 cells/mm<sup>3</sup> respectively. This suggests that all these patients presented very late for diagnosis and treatment.

The mortality rate in this case series is quite high. The causes of death were all lung infections, clinically Pneumocystis pneumonia (PCP), and secondary bacterial pneumonia. One patient remains on the Anti-Retro Viral (ARV) DTG 50mg/3TC 300mg/TDF 300mg (TLD) regimen.

**Discussion**

HIV infection can be fatal if not treated, with the average survival time from seroconversion being 8 to 10 years. However, the widespread introduction of combination antiretroviral therapy (cART) in many countries in the mid-1990s resulted in rapid and dramatic reductions in mortality rates in those living with HIV. However, the case fatality rate is still high in patients who late to be diagnosed (Sabin, 2013). Many studies have tried to find out what the main

risk factors are that cause death in severe HIV/AIDS patients.

Sumantri R, et al in their research reported on important risk factors causing death in HIV/AIDS patients at the Bandung Regional General Hospital, Indonesia, including CD4 levels  $\leq 50$  cells/mm<sup>3</sup>, moderate-severe anemia and a Body Mass Index (BMI)  $< 18.5$  (Sumantri et al., 2012).

Three factors—hemoglobin, body mass index, and CD4 levels at diagnosis—were used in a study involving large numbers of HIV patients to learn more about direct classification of mortality risk. Using the following criteria, this categorization divides HIV patients into three groups: Patients under 40 years old or male and suffering from mild anemia are at high risk, as are patients with severe anemia or who have a low body mass index (BMI; measured as weight in kilograms divided by the square of height in meters)  $\leq 18$  is at very high risk (Srasuebkuil *et al.*, 2019).

In the CD4 levels model, patients with CD4 levels  $< 50$  cells/L, severe anemia, or BMI)  $\leq 18$  had very high risk, while patients with CD4 levels 51–200 cells/L, were included in the high risk group. Age  $< 40$  years, and have a BMI  $> 18$  are at high risk. According to the model of CD4 cell levels and HIV RNA levels, patients with CD4 cell levels  $< 50$  cells/L, detectable viral load, severe anemia, or BMI)  $\leq 18$  are at very high risk, whereas patients with CD4 cell levels 51–200 cells/L and mild anemia are at high

risk. In the clinical model, the incidence of new AIDS cases or deaths was 1.3, respectively; 4.9 and 15.6 events per 100 person-years in the low risk, high risk, and very high risk categories (Srasuebkuil *et al.*, 2019). According to this classification, our patient fits into the very high risk group.

Researchers in the study calculated that preventing the late of diagnosed would have reduced the AIDS death rate from 2003 to 2006 by 39.5%, a reduction equivalent to the reduction caused by cART. In Brazil, an estimated 95.5% of deaths occurring in the first year after diagnosed due to late of diagnosed. Early diagnosis will reduce short-term mortality in the UK by 84% in MSM and 56% in heterosexually infected individuals (first year after diagnosed) (Sabin, 2013).

Men are a risk factor for death in HIV/AIDS sufferers with a risk of death 1,966 times greater than women ( $p=0.030$ , OR 1,966). This finding is consistent with the research by Gunda W. et al. (2017) who found that male gender is a risk factor for death in HIV/AIDS patients. The course of HIV infection is significantly influenced by biological differences between genders, such as the impact of sex hormones on immunity (Kusumaadhi, Farhanah and Udji Sofro, 2021). However, several studies have linked this problem to men's hesitation to undergo HIV testing early, resulting in delays to start Highly Active Antiretroviral Therapy (HAART) which



is associated with poor prognostic outcomes (Rubaihayo et al., 2015).

Age <45 years is the most frequent infected with HIV because it is associated with active sex which is the main factor in HIV transmission. With a risk 2,119 times higher than those aged over 45 years, age <45 years is a significant risk factor for death in HIV/AIDS patients ( $p = 0.035$ , OR 2,119). This is in accordance with research conducted by Rubaihayo et al. in 2015, which found that HIV/AIDS patients were more likely to die if they were under 45 years old (Rubaihayo et al., 2015).

Clinical stages III and IV of HIV according to WHO are risk factors for death in HIV/AIDS patients. This is consistent with research conducted in 2017 and 2015 respectively by Gunda W. et al. and Utami, et al., who found that Clinical stages III and IV of HIV according to WHO were risk factors for death in HIV/AIDS patients. Compared with clinical stages I and II, clinical stages III and IV have a clinical picture that is 7.19 times more serious (Crabtree-Ramírez *et al.*, 2012).

The CD4 levels is known to have a significant impact on a person's clinical stage of HIV/AIDS. Opportunistic infections are more likely to occur when the CD4 levels is below 200 cells/mm<sup>3</sup>. The clinical stage of HIV/AIDS will worsen as the levels of CD4 cells decreases because more opportunistic infections will develop (Engsig *et al.*, 2010). All our study cases were at stage 4 of the disease.

Coinfection with pulmonary tuberculosis increases the chance of death in HIV/AIDS patients. For HIV/AIDS sufferers, pulmonary tuberculosis is the main cause of death. HIV-infected people with pulmonary tuberculosis co-infection have twice the risk of death than people without co-infection (Kusumaadhi, Farhanah and Udji Sofro, 2021). However, it is not easy to get a sputum sample to check for Mycobacterium tuberculosis, in this case report we did not get a positive result for tuberculosis.

The most common hematological problem in HIV/AIDS patients in Indonesia is anemia, which is associated with HIV disease progression and unfavorable clinical outcomes. In this study, hemoglobin levels <10 g/dL were associated with a 2.308-fold increased risk of death in HIV/AIDS patients compared to hemoglobin levels of 10 g/dL ( $p = 0.008$ , OR 2.308). Hemoglobin levels can be used to predict the prognosis of a disease and measure how quickly a condition progresses. Hemoglobin levels and CD4 levels were closely correlated in this study because a decrease in hemoglobin levels was associated with a decrease in CD4 levels (Rubaihayo *et al.*, 2015).

### **Cause of Death**

Pneumocystis pneumonia (PCP) has long been known due to its high prevalence in Human Immunodeficiency Virus (HIV) positive patients. Today, most patients with HIV-associated PCP have

very low CD4 levels and have never undergone treatment; some of these patients do not know they are HIV positive until they visit the hospital (Schmidt et al., 2018).

PCP was all observed in HIV individuals who did not receive TMP-SMX chemoprophylaxis. Overall, 25% of PCP patients do not recover from their condition. About 40% of patients require critical care, and the in-hospital mortality rate increases to 58% among of them (Wininger et al., 2020).

Diagnosis of PCP is very difficult because symptoms, physical examination, and chest radiology examination are not specific for PCP. Routine PCP culture can not be performed so definitive diagnosis requires histopathological or cytological examination. However, detection of PCP cases must be done as early as possible, especially in patients with oral candidiasis, advanced stage and low CD4 so that PCP prophylaxis and treatment is not delayed and can reduce mortality rates (Charisma, Dewi and Marfiani, 2021).

PCP symptoms are various and 7% are asymptomatic. Common symptoms include fever, unproductive cough, and shortness of breath, which are discovered several months before the appearance of clinical symptoms of PCP. Patients may experience respiratory failure, such as tachypnea, tachycardia, and cyanosis, requiring mechanical ventilation and vasopressors. Coarse wet crackles or crepitus on inspiration may be found on

lung auscultation. In mild cases, lung abnormalities are rarely found. In severe cases, the disease is characterized by a decrease in partial arterial pressure of oxygen (PaO<sub>2</sub>) and the risk of respiratory failure. Blood gas analysis shows an increased gradient between the alveoli and arteries (aADO<sub>2</sub>). The classic triad of PCP in HIV/AIDS patients is shortness of breath when doing heavy activities, unproductive cough, and subfebrile or fever (Cillóniz et al., 2018).

Two of the three cases we reported ended in death. All had clinical PCP despite overlapping clinical and radiological findings with bacterial pneumonia as well as tuberculosis. Clinical PCP was based on all patients having comorbid fungal infections in the oral cavity, low CD4, dry cough, fever and radiological suspicion of PCP. Only one patient survived and was started on an ARV regimen. Two other patients have not even been able to start an ARV regimen. These two patients were very unstable, and died.

According to WHO guidelines, opportunistic infections should be treated first before starting ARVs. This strategy is to avoid Immune Reconstitution Inflammatory Syndrome (IRIS), a drug and allergy interaction that can be dangerous and fatal. Therefore, knowledge of the presence of latent infections in antiretroviral-naïve patients is essential before starting HAART (WHO, 2020).



## CONCLUSIONS AND SUGGESTIONS

The clinical characteristics of HIV sufferers are very broad, ranging from typical symptoms to atypical. In HIV patients with low CD4, life expectancy is still low. The large number of opportunistic infections that must be treated, polypharmacy and drug interactions make the therapy difficult to carry out effectively and efficiently. Infections that threaten life and cause the death in HIV patients including lung infections, such as PCP, tuberculosis and also pneumonia.

Diagnosis as early as possible needs to be done so that patients can start ARVs early to increase the life expectancy of HIV sufferers. Every patient should be screened for lung infections (tuberculosis, pneumonia and PCP), for patients with CD4 <200 they should be advised to have prophylaxis with TMX-SMX and chemoprophylaxis for tuberculosis. Socialization and education to the community continues to be encouraged to prevent transmission, find and provide ARV therapy to people living with HIV/AIDS (PLWHA).

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