# CD4 LEVELS AND THEIR RELATIONSHIP WITH PENICILLIOSIS INCIDENCE IN HIV PATIENTS: A STUDY AT HAJI ADAM MALIK MEDAN HOSPITAL

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## Abstract

**Introduction:** Penicilliosis is an one of opportunistic infection with high mortality if left untreated, caused by infection of *Penicillium marneffei*. Penicilliosis in AIDS patients was first reported by Piehl in 1988, described as having symptoms of persistent fever, anorexia, and papular rash on the skin. Culture of blood, bone marrow, sputum and skin specimens all showed P. marneffei. Factors affecting penicilliosis infection in HIV patients are environmental predictors and levels of Cluster Differentiation (CD4). Therefore we were interested in examining the relationship between CD4 levels, which reflecting the immune state of an individual, with the incidence of penicilliosis in HIV patients.
**Method:** This study was an observational analytic study with a cross sectional design to determine the relationship between CD4 levels and the incidence of penicilliosis in HIV patients. The population in this study were HIV patients in Haji Adam Malik Medan Hospital admitted since 2014 to 2018 aged ≥ 18 years. All patients had the CD4+ level tested, as well as the biopsy of skin lesion for *P. marneffei.*
**Result:** Of 2859 research subjects, it was found that patients with positive touch biopsy who had CD4 levels <100 cells / µL is 32 patients which is 2.5% of all patients with CD levels <100 cells / µL. There were no patients with positive biopsy results who had CD4 cells ≥100 cells / µL (0.0%).
**Conclusion:** There was a statistically significant correlation between CD4 levels and the incidence of penicilliosis (p = 0.001).

## Introduction

Human Immunodeficiency Virus (HIV) infection is an infection that attacks white blood cells and causes a decrease in human immunity, while AIDS or Acquired Immune Deficiency Syndrome is a collection of symptoms of a disease that arises due to immune deficiency caused by HIV infection.[1,2,3]

In 2012, an estimated 35.3 million people were infected with HIV. In 2010, HIV was a major cause of disability in people aged 30-44 years, and the fifth highest cause of disability for all ages worldwide.[2] HIV / AIDS has spread in 386 cities in all provinces in Indonesia. The cumulative number of HIV sufferers from 1987 to September 2014 reached 150,926 people, and the cumulative number of AIDS cases reached 55,799 people.[4]

*Penicillium marneffei* infection in AIDS sufferers was first reported by Piehl in 1988, in which a patient was described with symptoms of persistent fever, anorexia, and papular rash on the skin. All culture of blood, bone marrow, sputum and skin specimens showed P. marneffei. Prevalensi infeksi ini meningkat seiring dengan meningkatnya infeksi HIV. Factors affecting penicilliosis infection in HIV patients are environmental predictors and levels of Cluster Differentiation (CD4).[4] Several studies on CD4 levels with penicilliosis in HIV patients have been done. Low CD4 levels tend to be associated with a higher risk of penicilliosis.[4]
Moreover, penicilliosis is an opportunistic infection with high mortality if left treated. Therefore we were interested in examining the relationship between CD4 levels, which reflecting the immune state of an individual, with the incidence of penicilliosis in HIV patients.[4]

## Method

### Study Sample

The population in this study were all patients with a diagnosis of HIV infection in Haji Adam Malik Medan Hospital admitted since 2014 to 2018 aged ≥ 18 years.

### Study Design

This study was an observational analytic study with a cross sectional design to determine the relationship between CD4 levels and the incidence of penicilliosis in HIV patients. This research was conducted at General Hospital of Haji Adam Malik Medan from October 2018 to December 2018 which included literature study, data collection, data processing and research report writing. The sampling technique type used is consecutive sampling, where all subjects registered in the medical record fulfilling the selection criteria were included in the study sequentially.

**Statistical Analysis**

To analyze the relationship between CD4 levels and the incidence of penicilliosis in HIV patients, a chi-square test will be conducted only if no more than 20% of the number of cells that have an expected value of less than five. If the data does not meet the requirements, the Fisher exact test will be conducted. The results were significant if $p < 0.05$.

## Result

**Characteristic Distribution of the Patients**

This study was participated by 2859 subjects who had met the inclusion and exclusion criteria. The majority of the subjects were male (68.9%) with the highest age group of 25-34 years old (43.9%). The majority of the subjects were semi-trained workers of 1049 people (36.7%). (Table 1)

***Table 1. Characteristic Distribution of Study Subjects***

| Characteristic | n (%) |
|---|---|
| Sex | |
| Male | 1969 (68,9) |
| Female | 890 (31,1) |
| Age Group | |
| 18 – 24 Years | 164 (5,7) |
| 25 – 34 Years | 1256 (43,9) |
| 35 – 44 Years | 969 (33,9) |
| 45 – 54 Years | 337 (11,8) |
| ≥ 55 Years | 133 (4,7) |
| Occupation | |
| Trained | 432 (15,1) |
| Semi-trained | 1049 (36,7) |
| Blue-collar workers | 664 (23,2) |
| Unemployment | 520 (18,2) |
| Housewives | 163 (5,7) |
| Students | 31 (1,1) |
| CD4 Level (Median) | 152 sel/uL |
| CD4 Levl | |
| <100 sel/µL | 1260 (44,1) |
| ≥100 sel/µL | 1599 (55,9) |
| *Touch Biopsy* | |
| Negative | 19 (37,2) |
| Positive | 32 (62,8) |

Of all subjects, the median CD4 T-lymphocyte level was 152 cells / ml with the highest CD4 cell count of ≥100 cells / µL in 1599 people (55.9%) while CD4 levels <100 cells / µL were found in 1260 patients (44, 1%). Based on the results of the touch biopsy of inflammed skin lesions, a typical appearance of yeast-like cells from T. marneffei was found in 32 patients (62.8%) while as many as 19 subjects has negative yeast-like cells result (37.2%). (Table 1)

Based on occupation, this study followed by several types include trained, semi-trained, blue collar workers, unemployment, housewives, and students. (Table 2)

***Tabel 2. Occupational Characteristic of Study Subjects and touch biopsy***

| | | *Touch Biopsy* | | | | Total |
|---|---|---|---|---|---|---|
| | | Positive | | Negative | | |
| | | n | % | N | % | |
| Occupation | Trained | 12 | 37,5 | 7 | 36,8 | 19 |
| | Semi-trained | 20 | 62,5 | 12 | 63,2 | 32 |
| | Blue Collar Workers | 0 | 0,0 | 0 | 0,0 | 0 |
| | Unemployment | 0 | 0,0 | 0 | 0,0 | 0 |
| | Housewives | 0 | 0,0 | 0 | 0,0 | 0 |
| | Students | 0 | 0,0 | 0 | 0,0 | 0 |
| | Total | 32 | 100,0 | 2827 | 100,0 | 51 |

**Correlation between CD4+ level with Penicilliosis Incidence**

The relationship of CD4 levels with the incidence of penicilliosis was analyzed by the Fisher Exact test. Patients with positive touch biopsy with CD4 levels <100 cells / µL were found in 32 patients, which is 2.5% of all patients with CD levels <100 cells / µL. There were no patients with positive biopsy results who had CD4 cells

≥100 cells / µL (0.0%). There was a statistically significant correlation between CD4 levels with the incidence of penicilliosis (p = 0.001). (Table 3)

***Table 3. Correlation Between CD4 Level and Penicilliosis Incidence***

| | | CD4 Level | | | | Total | % | *p* |
|---|---|---|---|---|---|---|---|---|
| | | <100 sel/µL | | ≥100 sel/µL | | | | |
| | | n | % | N | % | | | |
| *Touch Biopsy* | Positive | 32 | 2,5 | 0 | 0,0 | 32 | 1,1 | 0,001[a] |
| | Negative | 1228 | 97,5 | 1599 | 100 | 2827 | 98,8 | |
| | Total | 1260 | 44 | 1599 | 56 | 2859 | 100 | |

[a] Fisher's Exact Test

## Discussion

**Characteristics of the Subjects Based on Sex and Age Group**

Male has more incidence of HIV / AIDS because they are more involved in active transmission of the virus through sexual intercourse with multiple partners, more exposed to syringe drug use, and same-sex sexual activity. In previous studies it was known that this was related to the route of HIV transmission, reported 67.8% in heterosexuals; 10.5% in injecting drug users; 4.1% in homosexuals, and 3% in perinatal transmission.[5]

Most are in productive adult age which is very influencing the economy and social function of the community. Therefore, HIV / AIDS cases are things that should be taken seriously because of their broad impact on the economy and quality of life.

This study found that based on the patients occupations, semi-trained and unskilled workers, the two types of occupations suffered HIV / AIDS the most, followed by trained workers, housewives, and students. This is different from Molpariya et al's study which reported that housewives are occupation with the most cases of HIV. Housewives has the high incidence due to main transmission route in women is sexual contact with their partners who are not well protected. In untrained workers and unskilled workers, the incidence is high because most patients reside in remote areas with low educational background this is related to the patient's understanding of transmission of HIV / AIDS transmission.[6]

In this study, subjects with penicilliosis came from trained and semi-trained group of workers. In accordance with the research of Chitasombat M et al., trained and semi-trained workers generally have a tendency to close contact with soil, low immunity, poor hygiene and geographical conditions of Southeast Asian countries has high humidity which is the habitat of bamboo mice that known as T. Marneffei's reservoir. It can be concluded that transmission of penicilliosis infection in HIV / AIDS patients starts from economic status, level of knowledge regarding transmission of penicilliosis infections, and behavior of the work environment.[7]

**Correlation between Characteristics of Research Subjects and the Penicilliosis *touch biopsy* of Patients**

In the study, of 2859 patients infected with HIV / AIDS, a typical picture of yeast-like cells from T. marneffei was found in 1.1%, while the rest of the patients did not have biopsied (98.9%). The Kawila R et al study found skin lesions in 85.1% of patients, but penicilliosis test was only based on blood cultures. Of the 116 HIV patients, only 47 were screened for skin culture and 42 of the HIV patients (89.4%) were Penicilliosis positive with a median of 14 cells / $mm^3$ CD4 levels.[7]

The majority of positive touch biopsy are semi-trained workers (Table 2). T. marneffei infection increased in other groups of patients who had a decreased immune condition (immunocompromise). There are several factors that can reduce immunity, such as hygiene, nutrition, and cytotoxic drugs. Severe protein energy malnutrition can cause leukopenia, decrease in the number of Th cells (CD4 +) and cytotoxic T cells (CD8 + ¬), and a decrease in the CD4 + / CD8 + — ratio which is considered to be significantly correlated with susceptibility to infection. Micronutrient malnutrition often occurs along with protein energy malnutrition, although it can also occur alone.[8,9,10]

In this study the results showed that there was a statistically significant relationship between CD4 levels and the incidence of penicilliosis with p <0.05 (p = 0.001). In this study the results showed that there was a statistically significant relationship between CD4 levels and the incidence of penicilliosis (p = 0.001). It was concluded that lower CD4 levels would increase opportunistic infections both systemic and skin manifestations, this was also

reported by Molapariya A et al. Opportunistic infections in the form of herpes zoster, dermatophytosis, and scabies were found to increase in CD4 levels of 200-499 cells / mm3.[6] Penicilliosis are more commonly found in CD4 levels ranging from <200 cells / mm3 even though the cases encountered were few but this could prove penicilliosis to occur in patients with very low immunity.

## Conclusion

The conclusion of this study is that there is a correlation between CD4 levels and the incidence of penicilliosis in HIV patients which is statistically significant at $p < 0.05$ ($p = 0.001$). Of the total sample, there were more male HIV patients than women, with the majority of aged group of 25-34 years of age, having semi-trained jobs, and CD4 levels of <100 cells / µL.

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