



**THE RELATIONSHIP BETWEEN CD4 OF T LIMFOSITS TOWARDS THE OPPORTUNISTIC INFECTION OF ESOPHAGEAL CANDIDIASIS IN HUMAN IMMUNODEFICIENCY VIRUS INFECTION/ACQUIRED IMMUNODEFICIENCY SYNDROME IN H. ADAM MALIK GENERAL HOSPITAL**

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### ABSTRACT

**Introduction.** The course of infection of the Human Immunodeficiency Virus (HIV) can lead to opportunistic infections (OIs). Esophageal Candida Infection (KE) is an opportunistic infection in people with HIV and is classified as an invasive candida infection. Cluster of Differentiation 4 (CD4) as a measure of the immunity of HIV sufferers.

**Aim.** These researchers looked for an association of CD4 cell counts in HIV patients with Esophageal Candidiasis in HIV sufferers, mean CD4 cell count and antifungal resistance.

**Methods.** Sampling was carried out at H. Adam Malik General Hospital using the Case Control method. Data were analyzed using Chi-Square test.

**Results.** Ages 20-40 years are the age of the most frequent occurrence of HIV / AIDS infection, men have a higher percentage of HIV incidence than women, respectively 64.7% and 35.3%. Free sex is the most common risk factor found in research subjects by 52.94%. There was a significant relationship between CD4 levels and the incidence of oesophageal candidiasis where patients with a CD4 level  $< 41.82 \text{ cell/mm}^3$  would be 5.25 times more likely to suffer from esophageal candidiasis than patients with a CD4 level  $\geq 41.82 \text{ cell/mm}^3$ , with a p value of 0.035. The mean absolute CD4 cell count in patients with Esophageal Candidiasis was  $41.82 \text{ cell/mm}^3$  (SD  $\pm 35.47$ ). The Albida Candida fungus (29.4%) is the most common species that causes esophageal candidiasis in HIV patients. The pattern of resistance and antifungal sensitivity in patients with Esophageal Candidiasis shows that in general antifungals still have a good sensitivity to Candida fungus including Flusitocin (100%), Micafungin (100%), Ampotericin (100%), Caspofungin (100%), but at Flusitocin (100%), Micafungin (100%), Ampotericin (100%), Caspofungin (100%), but at Fluconazole and Voriconazole antifungals have begun to show a resistance rate of 10%.

**Conclusion.** There was a significant relationship between CD4 levels and the incidence of esophageal candidiasis in HIV patients at H. Adam Malik General Hospital. Fluconazole which is the first choice routinely used for antifungal has begun to show resistance value, but still has a good sensitivity value.

**KEYWORDS :** Human Immunodeficiency Virus, opportunistic infections, Candidiasis, CD4.

### INTRODUCTION

HIV is a virus that attacks the human immune system so that a person is easily absorbed by disease. People who are infected with HIV will sooner or later suffer from AIDS (Acquired Immuno Deficiency Syndrome) if they are not treated regularly. AIDS is a collection of symptoms of a disease characterized by severe immune deficiency and is a manifestation of the end-stage HIV infection. The natural course of untreated HIV infection causes a decrease in the immunity of the host to continue to cause opportunistic infections (OIs) which indicate AIDS. Clinically used to count the number of lymphocytes Cluster of differentiation 4 (CD4) as a marker of the emergence of opportunistic infections in people with AIDS. In people with HIV / AIDS CD4 cell counts will decrease and cause opportunistic infections<sup>1</sup>. In patients with HIV / AIDS, Candida Sp infection is an opportunistic infection that can be fatal in sufferers. The spectrum of Candida Sp infections is very diverse, ranging from asymptomatic to pathological colonization<sup>1</sup>. Esophageal candida infection is an opportunistic infection in people with HIV / AIDS and is classified as an invasive candida infection<sup>1</sup>.

Severe EC conditions can cause esophageal bleeding or develop strictures or fistula formation, accompanied by a significant reduction in quality of life. Early diagnosis and treatment are very important things that can affect the quality of life of patients<sup>2</sup>. Therefore researchers in this case more specifically identify the relationship of CD4 T lymphocyte cell numbers in patients with HIV AIDS with OI esophageal candidiasis in the hope of identifying earlier and preventing delays in diagnosis and providing HIV / AIDS management with faster and more accurate opportunistic infections and more cheap in terms of cost.

### METHODS

This type of research is analytic research. The researcher will measure the independent and dependent variables, then will analyze the data collected to find the relationship between the variables. In this study using a case control approach to see the relationship between levels of CD4 T lymphocytes on the incidence of esophageal candidiasis in HIV / AIDS sufferers at Adam Malik Hospital in Medan. The research will begin in June 2019 until the research subjects are fulfilled. Collection

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and examination of blood samples, endoscopy and culture are carried out by the Clinical Pathology Laboratory, Microbiology Laboratory and Integrated Diagnostic Installation at HAM General Hospital. The population in this study were all sufferers of HIV / AIDS infections who came to Medan HAM Hospital both as outpatients or inpatients. Minimum sample size for HIV patients with Esophageal Candidiasis and non Esophageal Candidiasis is 34 people. This sample size also considers the limitations of the tool and the subject which is still likely to be limited. The criteria included in the study were adult subjects, both men and women who had HIV infection and who had upper gastrointestinal symptoms and oropharynx, received information and gave consent to participate in voluntary and written research (informed consent), and CD4 counts below 200 cell / mm. The criteria issued in the study (exclusion) were HIV sufferers who had received antifungal and unconscious or mental disorders as well as those who were not cooperative in following the research process. Anamnesis was taken to obtain data: age, sex, occupation, marital status, sexual behavior habits, drug users and needles and the use of tattoos and things not previously known to be at high risk of HIV infection. Perform Absolute CD4 cell counts. Receive informed consent and approval for endoscopy. A culture examination was performed to identify fungi in the esophageal area and antifungal resistance tests. Data analysis was performed using a computer using the SPSS version 23 program. This analysis was used to find relationships and examine the relationship between two ordinal variables. Then the data analysis uses Chi-Square test.

**RESULT**

Characteristics of respondents include age, gender, occupation, education, and risk factors are as follows:

**Table 1. Frequency Distribution of Research Subjects Based on Characteristics**

| Characteristics | Category           | Case |      | Control |      |
|-----------------|--------------------|------|------|---------|------|
|                 |                    | n    | %    | n       | %    |
| Age             | 20-40 years        | 13   | 76,5 | 12      | 70,5 |
|                 | 41-60 years        | 4    | 23,5 | 5       | 29,5 |
| Sex             | Male               | 11   | 64,7 | 14      | 82,3 |
|                 | Female             | 6    | 35,3 | 3       | 17,7 |
| Education       | Junior High School | 2    | 11,8 | 3       | 17,7 |
|                 | Senior High School | 10   | 58,9 | 10      | 58,9 |
|                 | Diploma            | 4    | 23,5 | 3       | 17,7 |
|                 | Bachelor           | 1    | 5,8  | 1       | 5,8  |
| Occupation      | Self Employed      | 2    | 11,8 | 1       | 5,8  |
|                 | Private Employee   | 3    | 17,7 | 4       | 23,5 |
|                 | Employee           | 1    | 5,8  | 1       | 5,8  |
|                 | IRT                | 3    | 17,7 | 2       | 11,8 |
|                 | Labor              | 2    | 11,8 | 5       | 29,5 |
|                 | Driver             | 4    | 23,5 | 3       | 17,7 |
|                 | Student            | 2    | 11,8 | 1       | 5,8  |
| Risk Factor     | Free Sex           | 9    | 52,9 | 7       | 41,1 |
|                 | Syringe            | 5    | 29,5 | 6       | 35,3 |
|                 | Tattoo             | 1    | 5,8  | 2       | 11,8 |
|                 | Husband            | 2    | 11,8 | 2       | 11,8 |

The table above shows that, age 20-40 years is an age that is becoming relatively more frequent in the occurrence of HIV / AIDS infection compared to 41-60 years of age, as well as male sex having a higher percentage of HIV / AIDS events than women, respectively, 64.7% and 35.3%, while for

**Table 6. Candida Resistance Patterns Against Anti-Fungal HIV Patients in H. Adam Malik General Hospital.**

| Type of Candida | Amount of Isolat | Result of Resistance | FCN  | FKZL | VKN  | AMP  | CSP  | MKFN |
|-----------------|------------------|----------------------|------|------|------|------|------|------|
| C. Albican      | 10               | Sensitive            | 100% | 90%  | 90%  | 100% | 100% | 100% |
|                 |                  | Resistance           | 0    | 10%  | 10%  | 0    | 0    | 0    |
| C. Tropicalis   | 3                | Sensitive            | 100% | 100% | 100% | 100% | 100% | 100% |
|                 |                  | Resistance           | 0    | 0    | 0    | 0    | 0    | 0    |
| C. Lusitaniae   | 1                | Sensitive            | 100% | 100% | 100% | 100% | 100% | 100% |
|                 |                  | Resistance           | 0    | 0    | 0    | 0    | 0    | 0    |

education the majority of research subjects received their most recent high school (SLTA) education. Driver's occupation occupies the highest percentage of 23.5% followed by Private Employees and Housewives (IRT) of 17.7% for HIV / AIDS infections. Risk Factors for HIV / AIDS can occur through a variety of risks, free sex is the most common risk factor encountered in the study subjects by 52.94%, followed by the use of syringes by 29.5%.

**Table 2. Endoscopic Results Report**

| Mucosa Layer                         | n  | %    |
|--------------------------------------|----|------|
| Mucosal Break                        | 7  | 20,5 |
| White Patch                          | 27 | 79,5 |
| Conclusion                           | n  | %    |
| Candidiasis Esophageal and Gastritis | 9  | 26,4 |
| Candidiasis Esophageal               | 25 | 73,6 |

**Table 3. Mean CD4 counts in patients with Esophageal Candidiasis**

| Parameter | Cases |       |        |      |        | Control |       |        |      |        |
|-----------|-------|-------|--------|------|--------|---------|-------|--------|------|--------|
|           | Mean  | SD    | Median | Min  | Max    | Mean    | SD    | Median | Min  | Max    |
| Cd4 Level | 41.82 | 35.47 | 41.00  | 2.00 | 120.00 | 91.05   | 49.47 | 103.00 | 1.00 | 164.00 |

The table above shows that the mean absolute CD4 count in Esophageal Candidiasis patients was 41.82 cells / mm<sup>3</sup> (SD ± 35.47). Whereas the mean absolute CD4 cell that did not experience Esophageal Candidiasis was 91.05 cells / mm<sup>3</sup> (SD ± 49.47).

**Table 4. Relationship of CD4 value to Esophageal Candidiasis**

| CD4          | Cases     |              | Control   |              | Total     |               | P value | OR (95%CI)        |
|--------------|-----------|--------------|-----------|--------------|-----------|---------------|---------|-------------------|
|              | N         | %            | n         | %            | n         | %             |         |                   |
| <41.82       | 9         | 75.0%        | 3         | 25.0%        | 12        | 100.0%        | 0.035   | 5.25 (1.09-25.21) |
| ≥41.82       | 8         | 36.4%        | 14        | 63.6%        | 22        | 100.0%        |         |                   |
| <b>Total</b> | <b>17</b> | <b>50.0%</b> | <b>17</b> | <b>50.0%</b> | <b>34</b> | <b>100.0%</b> |         |                   |

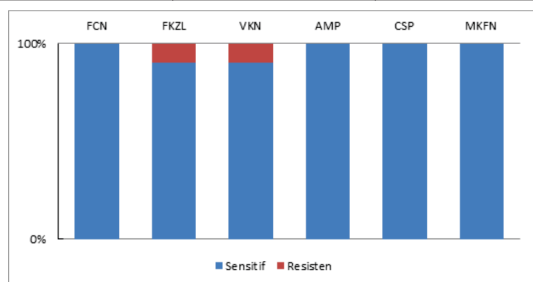
There was a significant relationship between CD4 levels and the incidence of oesophageal candidiasis where patients with a CD4 level < 41.82 cells / mm<sup>3</sup> would be 5.25 times more likely to suffer from oesophageal candidiasis than patients with a CD4 level ≥ 41.82 cells / mm<sup>3</sup>, with a p value 0.035.

**Table 5. Results of Fungal Culture in Esophageal Candidiasis of HIV / AIDS Patients**

| Mushroom type  | Frequency | Validity (%) |
|----------------|-----------|--------------|
| C.Albicans     | 10        | 29.4         |
| C.Tropicalis   | 3         | 8.8          |
| C.Lucitaniae   | 1         | 2.9          |
| C.Glabrata     | 1         | 2.9          |
| C.Parapsilosis | 1         | 2.9          |
| C.Krusei       | 1         | 2.9          |
| Stephanoascus  | 5         | 14.7         |
| No growth      | 12        | 35.3         |
| <b>Total</b>   | <b>34</b> | <b>100.0</b> |

The table above shows that the Candida fungus is the most genus occupying the incidence of mycosis in the esophageal canal in HIV / AIDS patients, where Candida Albican (29.4%) is the most species that causes the incidence of esophageal candidiasis in HIV / AIDS patients.

|                 |   |            |      |      |      |      |      |      |
|-----------------|---|------------|------|------|------|------|------|------|
| C.Parapsiliosis | 1 | Sensitive  | 100% | 100% | 100% | 100% | 100% | 100% |
|                 |   | Resistance | 0    | 0    | 0    | 0    | 0    | 0    |
| C. Glabrata     | 1 | Sensitive  | 100% | 100% | 100% | 100% | 100% | 100% |
|                 |   | Resistance | 0    | 0    | 0    | 0    | 0    | 0    |
| C. Krusei       | 1 | Sensitive  | 100% | 0    | 100% | 100% | 100% | 100% |
|                 |   | Resistance | 0    | 100% | 0    | 0    | 0    | 0    |



**Figure 1. Pattern of Candida Albican Mushroom Resistance to some Anti-Fungus in H. Adam Malik General Hospital Medan**

Information : FCN( Flucitosin), FKZL ( Flukonazol), VKN ( Vorikonazol), AMP ( Ampoterisin B), CSP ( Caspofungin), MKFN (Mikafungin)

**DISCUSSION**

The first step in the development of candida infections is mucocutaneous surface colonization. HIV / AIDS infection is not only associated with an increase in the level of colonization but also with the progression of the disease. During the course of HIV / AIDS infection, candidiasis infection is inversely proportional to the subject's CD4 cell count. This study analyzed the relationship between candida infection and immunological status by displaying CD4 cell counts and patterns of resistance of Candida fungi to antifungals<sup>3</sup>.

In the descriptive description of the characteristics above it is found that middle age is the age that is more dominant for the incidence of HIV / AIDS infection, namely the age of 20-40 years (Table 1). Male sex is more likely to have an esophageal candidiasis compared to women, 64.7% and 35.3%, respectively. This is consistent with studies that have been done by Khan et al., Stating that the incidence of male esophageal candidiasis is greater than that of women by 56% and 44%.<sup>3</sup> When viewed from the level of education, high school is the most common level of education characteristics for the incidence of candidiasis infection in HIV / AIDS (Table 1), this is consistent with research conducted by Matthew et al, that the lack of understanding of knowledge about risk factors for HIV / AIDS infection and handling it in the age of primary education is a major factor in the infection of this virus<sup>4</sup>.

In terms of employment, drivers are jobs that have a major impact on the transmission of HIV / AIDS through free sex that is not a partner. But not many people know that the work of the driver itself has an adverse effect on the neurocognitive function of the HIV / AIDS patient (Table 1). This is consistent with studies conducted by Gouse et al, where HIV positive patients use the driver's simulator compared with HIV negative patients with the same simulator. Significant neurocognitive reduction results were found in patients with HIV positive. This can explain that the condition of neurocognitive disorders causes worsening in HIV patients which will ultimately lead to an increased risk of opportunistic infections<sup>5</sup>.

It is common knowledge, that the highest risk factor for transmission of HIV infection is from unsafe sexual relations (Table 1), between an infected husband and wife or vice versa, or sexual relations that are not partners, followed by the use of

non-disposable syringes , It may also be in the provision of unsafe medical measures or it could also be in making tattoos that often use alternating syringes. In accordance with a study conducted by Sandra G et al (2006), it was stated that the biggest risk factor for HIV infection was sexual and vaginal sexual behavior, followed by repeated use of syringes<sup>6</sup>. Likewise, Pei R et al (2018), states that sex education is very lacking and patterns of behavior or habits of unsafe sexual activity cause transmission of HIV infection to increase<sup>7</sup>.

The increasing increase in HIV infection is not matched by adequate understanding and management of people with HIV / AIDS. This has an adverse effect on the mortality rate of patients infected with the virus. We already know that there is an inverse relationship between CD4 cell counts that are markers of immunological status in HIV patients and the incidence of opportunistic infections that are often the cause of death (Table 4). One of them is esophageal candidiasis, which in this study we tried to link the mean CD4 value in the incidence of oesophageal candidiasis in patients infected with HIV / AIDS, it was found that the mean CD4 absolute value was 41.8 cells / mm3 (SD ± 35.4) (Table 3). From this mean value can be interpreted through statistical tests found that there is a significant relationship between CD4 levels with the incidence of oesophageal candidiasis, where patients with CD4 levels <41.82 cells / mm3 will be 5.25 times more likely to suffer from esophageal candidiasis than patients with CD4 levels ≥ 41.82 cells / mm3, with a p value of 0.035 (Table 4). This is consistent with research conducted by Suzzane et al (1991), reporting that the mean of HIV patients with esophageal candidiasis is at an absolute CD4 level of ± 66 cells / mm<sup>3,8</sup>. Likewise Vazquez AJ et al (2010), reported that the incidence of esophageal candidiasis in HIV patients was in the CD4 range between 10-110 cells / mm<sup>3,1</sup>.

These results cannot be separated from the bias and control obtained from the inclusion criteria contained in this study. There are still a number of factors that can influence CD4 cell decline itself, but in this study researchers limited other factors that affect CD4 cell decline to the extent of subjects with HIV sufferers.

In this study also obtained the results of fungal isolation performed on HIV patients who have esophageal candidiasis, where specimens are taken through endoscopic action and fungal culture. Obtained several types of Candida and non Candida mushrooms. From the Candida fungus species, it was found that Candida Albican (10 isolates) around 29.4% which occupied the most mushroom obtained from the results of mucosal brushing in the esophagus of HIV / AIDS patients (Table 5). This result is supported by the study of Khan et al (2012), reporting that from Candida and Non Candida fungi isolates, 40% of Candida Albican of the Candida species were obtained. This study was also supported by Olga H et al (2018), who stated that the type of candida fungus in HIV / AIDS patients in RSUP.H. Malam Medan was the most Candida Albican type around (66.7%)<sup>8</sup>. Similarly, Vazquez et al (2010) concluded that Candida Albican is the most common species of Candida fungus in the incidence of esophageal candidiasis<sup>1</sup>.

The pattern of resistance and antifungal sensitivity in patients with Esophageal Candidiasis shows that in general antifungals still have a good sensitivity to Candida fungus including Flusitocin (100%), Micafungin (100%), Amphotericin

(100%), Caspofungin (100%), but at Flusitocin (100%), Micafungin (100%), Ampotericin (100%), Caspofungin (100%), but at Fluconazole and Voriconazole antifungals have begun to show a resistance rate of 10% (Figure 1). This can occur due to the use of antifungal fluconazole which is the first choice most often used in antifungal treatment. This is consistent with the report stated by Elizabeth R et al., 2017), that the first choice of standard therapy most often given to patients with esophageal candidiasis is fluconazole which can also affect the level of resistance<sup>10</sup>. According to the results of a research report conducted by Vazquez et al (2010), it is said that fluconazole provides a faster response to relieve the symptoms of esophageal candidiasis in HIV / AIDS patients<sup>11</sup>.

## CONCLUSION

1. There is a significant relationship between absolute CD4 levels and the incidence of esophageal candidiasis in patients with HIV / AIDS at H. Adam Malik General Hospital where HIV patients with CD4 levels <41.82 cells / mm<sup>3</sup> will be 5.25 times more likely to suffer from esophageal candidiasis compared with patients with a CD4 level ≥ 41.82 cells / mm<sup>3</sup> with a p value of 0.035.
2. There is an average absolute CD4 cell count in Esophageal Candidiasis patients in this study at 41.82 cells / mm<sup>3</sup> (SD ± 35.47).
3. Candida Albican species are the most species found in patients with Esophageal Candidiasis. Fluconazole which is the first choice routinely used for antifungals has begun to show a resistance value of 10%. Whereas the antifungal flucitosin, Ampotericin B, Caspofungin, Micafungin still have very good sensitivity values.

## Suggestion

1. Further research needs to be done with a larger number of samples, large locations and other variables and minimize bias in this study
2. It is recommended for people with HIV / AIDS with CD4 levels <50 cells / mm<sup>3</sup>, so that endoscopy can be considered

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