

Relationship between CD4 levels and mucocutaneous manifestations in HIV-AIDS patients at Dr. Soetomo General Academic Teaching Hospital, Surabaya, Indonesia



Citra Dwi Harningtyas¹, Damayanti¹, Maylita Sari¹, Muhammad Yulianto Listiawan¹,
Diah Mira Indramaya¹, Linda Astari¹, Budi Utomo², Dwi Murtiastutik¹,
Setyana Widyantari¹, Astindari¹, Afif Nurul Hidayati^{1*}

ABSTRACT

Background: CD4 can assess the immune status of a patient with HIV, and this is considered the standard way of assessing and characterizing the severity of HIV-related immunodeficiency. CD4 cell counts are associated with increased mucocutaneous manifestations. This study aims to explain the relationship between CD4 and mucocutaneous manifestations in HIV-AIDS patients.

Methods: This study is analytical with a retrospective cross-sectional design. The data of the present study was obtained from a number of 614 HIV-AIDS patients with mucocutaneous manifestations, but only 149 patients met the inclusion criteria, including the CD4 level data.

Results: The majority of the patients in this study were male (74.5%), which includes patients under the age group of 25-49 years (70.5%). The most common risk factor was heterosexuality (48.3%). Most CD4 levels were in the CD4 group < 200 (64.4%). Based on the distribution of mucocutaneous manifestations, the various cases were reported as infections (55.8%). Pyoderma and syphilis were significantly associated with CD4 counts ≥ 200 cells/mm³ with a risk of 3.7 and 7.8 times than CD4 cells < 200 cells / mm³. On the other hand, candidiasis was higher in CD4 count < 200 cells/mm³ with a significant difference and a risk of 0.3 times compared to CD4 count ≥ 200 cells/mm³.

Conclusion: Several mucocutaneous manifestations can be considered predictors of advanced immunosuppression (low CD4 level), which were pyoderma, syphilis, and candidiasis in this study.

Keywords: AIDS/HIV, CD4, mucocutaneous, immune status.

Cite This Article: Harningtyas, C.D., Damayanti., Sari, M., Listiawan, M.Y., Indramaya, D.M., Astari, L., Utomo, B., Murtiastutik, D., Widyantari, S., Astindari., Hidayati, A.N. 2022. Relationship between CD4 levels and mucocutaneous manifestations in HIV-AIDS patients at Dr. Soetomo General Academic Teaching Hospital, Surabaya, Indonesia. *Bali Medical Journal* 11(1): 216-222. DOI: 10.15562/bmj.v11i1.3385

¹Department of Dermatology and Venereology, Universitas Airlangga, Dr. Soetomo General Academic Teaching Hospital, Universitas Airlangga Teaching Hospital, Surabaya, Indonesia;

²Department of Public Health Sciences, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia;

*Corresponding author:

Afif Nurul Hidayati; Department of Dermatology and Venereology, Universitas Airlangga, Dr. Soetomo General Academic Teaching Hospital, Universitas Airlangga Teaching Hospital, Surabaya, Indonesia;
afif_nurulhidayati@fk.unair.ac.id

Received: 2022-01-08

Accepted: 2022-04-03

Published: 2022-04-13

INTRODUCTION

Human immunodeficiency virus (HIV) is a retrovirus that attacks and destroys CD4 T lymphocytes (cluster of differentiation 4) and other immune cells with CD4 receptors.^{1,2} Acquired immunodeficiency syndrome (AIDS) is a collection of symptoms or diseases caused by decreased body infection due to HIV and is the final stage of HIV infection.³ The main target of HIV is a subset of lymphocytes originating from the thymus, namely helper T cells, causing deficiency of cellular immunity, which is deficient in T helper lymphocytes (CD4+ cells). The immune status of

children and adults with HIV can be assessed by measuring the absolute (per mm³) or proportion of CD4+ cells, and this is considered the standard way of assessing and characterizing the severity of HIV-related immunodeficiency.^{1,2} Mucocutaneous manifestations were found in 80-95% of HIV-infected patients. Changes in patient status and low CD4 cell counts are associated with an increased frequency of mucocutaneous manifestations. It is because CD4 cells are also present in skin tissue, such as Langerhans cells. Langerhans cells (LCs) are antigen-presenting cells. LC is located

within the epithelium of the skin and mucosa.⁴⁻⁷

Knowledge and awareness of various mucocutaneous manifestations in HIV/AIDS patients are important for doctors because it is very helpful in diagnosing and monitoring the patient's immune status, which is objectively described by CD4 levels. The purpose of this study was to determine the pattern and frequency of mucocutaneous manifestations and their relationship with CD4 levels in HIV/AIDS patients. This analytical study aims to explain the relationship between CD4 and mucocutaneous manifestations in

HIV-AIDS patients at UPIPI RSUD Dr. Soetomo Surabaya in 2019 with secondary data from medical records. The results of this study provide data on the number of cases, gender, age, CD4 levels and types of mucocutaneous manifestations in HIV AIDS patients that can be used as a basis and reference in further studies related to CD4 levels in HIV AIDS patients who have mucocutaneous manifestations. However, knowing the relationship between CD4 levels and mucocutaneous manifestations in HIV patients can be a clinical guide in determining the diagnosis and prognosis of advanced stages of HIV so that adequate therapy can be given and may help to reduce morbidity and mortality in HIV patients.

METHODS

This study was an analytical study with a retrospective cross-sectional design. The subjects were patients with a diagnosis of HIV-AIDS who had mucocutaneous manifestations. Mucocutaneous manifestations are clinical manifestations of skin and mucosa. There are 3 types of mucocutaneous manifestation that was evaluated in this study; the first was dermatoses infections, which can be caused by bacteria such as pyoderma and syphilis, caused by a virus such as herpes, varicella-zoster, molluscum contagiosum and human papillomavirus, caused by fungal such as candidiasis, dermatophytosis and systemic fungal infection. The second was non-infection dermatoses such as psoriasis vulgaris, drug eruption, xerosis, eosinophilic folliculitis, popular pruritic eruption and seborrheic dermatitis. The third was cutaneous malignancies, such as Kaposi sarcoma, squamous cell carcinoma, basal cell carcinoma and melanoma.

The data of the present study was obtained from a number of 614 HIV-AIDS patients with mucocutaneous manifestations who were treated at UPIPI RSUD Dr. Soetomo Surabaya in 2019, but only 149 patients met the inclusion criteria. Total sampling was used in this study. The inclusion criteria in this study were all patients diagnosed with HIV-AIDS (using Rapid Test of HIV) with mucocutaneous manifestations (new and controlled patient, with or without HAART), which were treated in the inpatient and outpatient

installations of the Intermediate Care and Infectious Diseases of Dr. Soetomo General Academic Hospital Surabaya in 2019, which had CD4 count data. The exclusion criteria were missing medical records. The CD4 count is an assessment test that measures the ratio of CD4 cells in the human body. The purpose of the CD4 count was to determine the health of immune system levels in patients affected with HIV (Human immunodeficiency virus) infection. The diagnosis was established by symptom-direct examination and laboratory findings. The data was only taken once, and there were no follow conducted.

The statistical relationship was identified and analyzed using the SPSS version 17 program. The data were categorized and arranged in an SPSS sheet for result analysis and tabulation. The test used Chi-Square and Spearman, and it was declared significant if < 0.05 . The research was conducted on the inpatient and outpatients of the Intermediate and Infectious Diseases Treatment Unit (UPIPI) RSUD Dr. Soetomo Surabaya, Indonesia. The duration of the study was

carried out starting from April 2020 to April 2021. The present research was approved and reviewed by the Ethical Committee (Reference no. 0032/LOE/301.4.2/VI/202) of Dr. Soetomo General Teaching Hospital situated in Surabaya, Indonesia.

RESULTS

The results of this study provide data on the number of cases, gender, age, CD4 levels and types of mucocutaneous manifestations in HIV AIDS patients that can be used as a basis and reference in further studies related to CD4 levels in HIV AIDS patients who have mucocutaneous manifestations. Out of the 149 patients who participated in the study, the highest CD4 cell count was 1,161 cells/mm³, and the lowest was 1 cell/mm³. Table 1 shows the baseline characteristic of this study. Distribution of CD4+ levels, there were CD4+ less than 200 in 96 patients (64.4%), CD4+ 200-500 in 42 patients (28.1%), CD4+ more than 500 in 11 patients (7.3%). The distribution of sex in this study is reported in Table 2. The majority of the cases were male, 111 patients (74.5%),

Table 1. Baseline Characteristics of subjects.

Characteristic	Frequency & Percentage (%)
CD4 (cell/mm³)	
< 200	96 (64.4)
200-500	42 (28.2)
> 500	11 (7.4)
Total	149 (100)
Gender	
Man	111 (74.5)
Woman	38 (25.5)
Total	149 (100)
Age (years)	
< 4	2 (1.3)
5 - 14	2 (1.3)
15 - 19	2 (1.3)
20 - 24	14 (9.4)
25 - 49	105 (70.5)
> 50	24 (16.2)
Total	149 (100)
Risk Factor	
Heterosexual	72 (48.3)
Homosexual	31 (20.8)
Bisexual	1 (0.7)
Injecting Drug User (IDU)	1 (0.7)
Maternal	3 (2.0)
No data	41 (27.5)
Total	149 (100)

while the female was 38 patients (25.5%). The male and female ratio is about 2.92:1. The majority of the cases were male, 111 patients (74.5%), while the female was 38 patients (25.5%). The male and female ratio is about 2.92:1. According to the age

division determined by the Indonesian Ministry of Health, the average age of the patients was 36 ± 10.87 years. The youngest patient was one year old, and the oldest was 65 years old. Most cases of HIV with mucocutaneous manifestations were found in the age group of 25-49 years, as many as 105 patients (70.5%). Based on the distribution of risk factors for HIV and AIDS patients with mucocutaneous manifestations, most of them were heterosexual, as many as 72 patients (48.3%), homosexual 31 patients (20.8%), bisexual one patient (0.7%), parenteral three patients (2.0%) and injecting drug user one patient (0.7%).

It was found that 149 patients had one or more skin manifestations. There are three groups of mucocutaneous manifestations: infectious, non-infectious, and malignancy, and there are 12 types of mucocutaneous manifestations. The most common infection found in this study was a fungal infection, with 30.2%, followed by non-infectious cases were PPE (23.3%). In this study, only two cases of malignancy were found in the form of lymphoma, but because they did not have data on CD4 levels and were not included in the inclusion criteria (Table 2).

In the CD4 category < 200 and 200-500, mostly found in the infectious group (72.5% and 23.3%), while for the CD4 category > 500 , in the non-infectious manifestation group (9.5%). Distribution for the type of disease from

Table 2. Distribution of mucocutaneous manifestations.

Category of Mucocutan manifestation	Diseases	Total n (%)
Infections		120 (55.8)
Bacterial	Pyoderma	10 (4.7)
	- Furuncles: 1	
	- Carbuncle: 1	
	- Secondary infection: 8	
Syphilis	Syphilis	12 (5.5)
	- Secondary: 6	
	- Latency: 6	
Fungal	Mucocutaneous candidiasis	65 (30.2)
	- Cutaneous candidiasis: 1	
	- Oral Candidiasis: 64	
	Dermatophytosis	8 (3.7)
	- Tinea corporis: 3	
	- Tinea pedis: 2	
- Tinea barbae: 1		
- Tinea cruris: 2		
Virus	Human papillomavirus infection	15 (6.9)
	- Condyloma Acuminata: 14	
	- Verruca: 1	
	Herpes simplex virus infection	1 (0.5)
	- Herpes Genital: 1	
Herpes Zoster	8 (3.7)	
Molluscum contagiosum	1 (0.5)	
Non-infections		95 (44.2)
	Seborrheic Dermatitis	15 (6.9)
	Pruritic Papular Eruption (PPE)	50 (23.3)
	Xerosis	15 (6.9)
	Drug reactions	15 (6.9)
	- Steven Johnson Syndrome: 2	
	- Morbiliform exanthem: 1	
	- Other drug eruptions (no specific data): 12	

Table 3. Distribution of CD4+ counts in each type of mucocutaneous manifestation of HIV and AIDS patients with mucocutaneous manifestations at Dr. Soetomo General Teaching Hospital Surabaya during 2019.

No.	Type of mucocutaneous manifestation	CD4 levels (cells/mm ³)			Total
		< 200 (%)	200-500 (%)	>500 (%)	
1	Pyoderma	4 (2.7)	4 (7.8)	2 (14.3)	10 (4.7)
2	Syphilis	3 (2.0)	7 (13.7)	2 (14.3)	12 (5.5)
3	Human papillomavirus infection	10 (6.7)	4 (7.8)	1 (7.1)	15 (6.9)
4	Herpes simplex virus infection	1 (0.7)	0 (0)	0 (0)	1 (0.5)
5	Herpes Zoster	7 (4.6)	1 (2.0)	0 (0)	8 (3.7)
6	Molluscum contagiosum	1 (0.7)	0 (0)	0 (0)	1 (0.5)
7	Mucocutaneous candidiasis	54 (36.0)	11 (21.6)	0 (0)	65 (30.2)
8	Dermatophytosis	7 (4.6)	1 (2.0)	0 (0)	8 (3.7)
9	Seborrheic Dermatitis	8 (5.3)	3 (5.9)	4 (28.6)	15 (6.9)
10	Pruritic Papular Eruption (PPE)	36 (24.0)	12 (23.5)	2 (14.3)	50 (23.3)
11	Xerosis	9 (6.0)	4 (7.8)	2 (14.3)	15 (6.9)
12	Drug reaction	10 (6.7)	4 (7.8)	1 (7.1)	15 (6.9)

the opportunistic infection group in the CD4 group, CD4 levels < 200, was found to be the most in the manifestations of mucocutaneous candidiasis and PPE, are 36.0% and 24.0%, respectively. CD4 levels of 200-500 were also the most common in the manifestations of mucocutaneous candidiasis and PPE, obtained at 21.6% and 23.5%, respectively. The CD4 level group > 500 was found the most in manifestations of seborrheic dermatitis (28.6%) (Table 3).

Analysis of the relationship was carried out between the infectious and non-infectious mucocutaneous manifestations on CD4 levels using the chi-square statistical test. The result obtained a p-value of 0.447, which indicates the value is > 0.05, meaning there is no significant/significant relationship between CD4 and mucocutaneous manifestations in the infectious and non-infectious groups (Table 4).

One hundred forty-nine data can be analyzed related to the relationship between CD4 levels and the type of mucocutaneous manifestations; of the 149 data obtained, 215 types of disease manifestations can be analyzed for the relationship. There was a significant relationship between CD4 levels in patients with syphilis infection ($P = 0.002$; Contingency coefficient 0.231), mucocutaneous candidiasis ($P = 0.006$; Contingency coefficient 0.213), and seborrheic dermatitis ($P = 0.005$; Contingency coefficient 0.218). Analysis of the ratio of the risk of mucocutaneous manifestations to CD4 levels showed that pyoderma and syphilis infections were significantly related to the condition of CD4 cell count of 200 cells/mm³ with a risk of 3.7 times and 7.8 times compared to CD4 < 200 cells/mm³. On the other hand, candidiasis infection was higher in conditions of CD4 count < 200 cells/mm³ with a significant difference and 0.3 times risk than CD4 200 cells/mm³.

DISCUSSION

Several studies have been conducted regarding skin disorders in HIV-positive patients, but the relationship between mucocutaneous lesions and CD4 cell counts has rarely been studied.⁸ The main target of HIV is the CD4 cell population. The progressive decline in the number

and function of the CD4 cell population is one of the most striking and consistent immunological features of HIV-associated disorders. In general, CD4 cell counts decreased as HIV disease progressed.^{9,10} Atypical features and severity of skin disease are what generally lead to the diagnosis of HIV infection.⁵ In a country like Indonesia, it is essential to identify skin markers that will predict the degree of immune suppression, as CD4 counts may not be possible in all patients regularly.

In this study, men made up 74.5%, while women made up 25.5% of patients. They were dominated by a male compared to females, with a male: female ratio of 2.92:1. The majority of patients in this study were 25-49 years age group, as many as 105 patients (70.5%). It is in line with data from the Directorate General of P2P sourced from the HIV, AIDS, and STI Information System (SIHA) in 2019. The fourth quarter stated that cases of HIV and AIDS in men were higher than in women. This is probably due to the increasing number of men who have sex with men (MSM) by practicing unsafe sex and the use of intravenous drugs (IVDU), which men dominate.⁷

HIV is spread through sexual contact with an infected person, contact or transfusion with infected blood, from mother to child, and sharing contaminated needles. In this study, the most frequent transmission mode was heterosexual (48.3%), followed by a homosexual (20.8%). This result may be due to patient reluctance to disclose precise information due to social and cultural differences in our region. Kamat et al. also reported heterosexuality as the most common mode of transmission, as much as 67.7%.¹¹ In fact, the heterosexual route continues to be the most common route of transmission reported worldwide.¹²

A decrease in the CD4 count is a sign of disease progression in HIV/AIDS. Mucocutaneous manifestations may increase with HIV progression and a decrease in CD4 cell count.¹³ It is thought that the incidence and severity of skin disorders increase with decreased immune function.⁹ In this study, 149 patients (24.3%) were examined for CD4+, obtained CD4+ less than 200 as many as 96 patients (64.4%), CD4+ 200-

500 as many as 42 patients (28.1%), CD4+ more than 500 as many as 11 patients (7.3%). Following the study of Britto et al., it has a higher incidence of skin manifestations in the advanced and severe immunosuppression categories.⁵

Mucocutaneous manifestations of HIV can be found in cases of infection, not infection, and tumors.¹⁴⁻²² In developed countries, non-infectious are more common in HIV patients.¹³ Mucocutaneous manifestations in HIV/AIDS patients in Indonesia may be different from those in other countries because of differences in skin pigmentation, climate, hygiene, genetics, environment, demographics, and behavioral patterns cause clinical manifestations and epidemiological patterns, which differ from developing countries such as Indonesia. In this study, the group with the most mucocutaneous manifestations was infection as many as 120 cases (55.8%); the second most was the inflammatory or non-infectious group, with 95 cases (44.2%). In this study, 2 cases of malignancy were found in the form of lymphoma, but because they did not have data on CD4 levels, they were not included in the study inclusion criteria.

In this study, from 3 groups of mucocutaneous manifestations that had CD4 data, there were 12 types of mucocutaneous manifestations: pyoderma infection, syphilis, human papillomavirus infection, herpes simplex (herpes labialis or genital herpes), herpes zoster, molluscum contagiosum, candidiasis, dermatophytosis, dermatosis seborrheic, PPE, xerosis, and drug eruptions. From the infection group, it was found that most cases were fungal infections which were dominated by mucocutaneous candidiasis (30.2%). These results agree with the study reported by Mirnezami et al. and Pudjiati et al.^{8,13} It can be due to Indonesia's tropical climate with relatively high humidity levels, making various germs, including fungal infections, easy to breed.¹³ The most non-infectious cases in this study were PPE in 50 patients (23.3%). This figure is more significant than the research results by Abhinandan and colleagues, who also showed that PPE was the most common non-infectious manifestation (13%).¹⁹

HIV infection impairs the immune system, leaving people infected with

Table 4. Analysis of CD4 Relationship Test with Types of Mucocutaneous Manifestations of HIV and AIDS patients with mucocutaneous manifestations at Dr. Soetomo General Academic Hospital Surabaya during 2019.

Mucocutan manifestations	N (%)	CD4 levels (n)			r***	p-value
		< 200	200-500	> 500		
Pyoderma	10 (4.6%)	4	4	2	0.157	0.066
Syphilis	12 (5.6%)	3	7	2	0.231	0.002**
Human papillomavirus infection	15 (6.9%)	10	4	1	0.020	0.960
Herpes simplex virus infection	1 (0.5%)	1	0	0	0.045	0.804
Herpes Zoster	8 (3.7%)	7	1	0	0.079	0.507
Molluscum contagiosum	1 (0.5%)	1	0	0	0.045	0.804
Mucocutaneous candidiasis	65 (30.2%)	54	11	0	0.213	0.006*
Dermatophytosis	8 (3.7%)	7	1	0	0.079	0.507
Seborrheic Dermatitis	15 (7.0%)	8	3	4	0.218	0.005**
Pruritic Papular Eruption (PPE)	50 (23.3%)	36	12	2	0.056	0.712
Xerosis	15 (7.0%)	9	4	2	0.081	0.489
Drug reaction	15 (7.0%)	10	4	1	0.020	0.960

*Test used Chi-Square is declared significant if <0.05 . ** test used Spearman is declared significant if <0.05 . *** r = strength of the relationship

HIV susceptible to various infections. Opportunistic infectious conditions in HIV patients are a significant cause of mortality and morbidity. The effect of HIV on the immune system is monitored by measuring the number of CD4 lymphocytes in the blood.^{13,22} In this study, the distribution of CD4 < 200 and 200-500 categories were more common in the infectious group (72.5% and 23.3%), while for the > 500 CD4 categories, more occurred in the non-infectious manifestation group (64.3%). HIV patients with high CD4 cell counts have an excellent immune response to respond the specific pathogens.^{9,13,22}

CD4 levels < 200 were found the most in mucocutaneous candidiasis and PPE, 36.0% and 24.0%, respectively. CD4 levels of 200-500 were also found the most in the manifestations of candidiasis and PPE, namely 21.6% and 23.5%, respectively. The CD4 level group > 500 was found the most in manifestations of seborrheic dermatitis (28.6%). Fungal infections are most common at low CD4 cell counts. HIV infection can change the course of the fungal disease so that the lower the CD4 count causes, the higher the fungal infection.¹³ PPE constitutes the majority of cases in inflammatory or non-infectious dermatoses.¹² In A study conducted in Thailand, Wichai et al. found PPE as the most common skin finding. Another study in Iran reported an incidence of

36.7%.²⁰ PPE may appear as an early skin disease with a high CD4 cell count and is described as a stage II disease by WHO.¹² Several studies have reported widespread atypical seborrheic dermatitis in patients ranging from 15.62% to 83%. The cause of seborrheic dermatitis is unknown, but many researchers believe that changes in the immune system in HIV-AIDS, altering the skin's response to the fungus *Pityrosporum ovale*, lead to higher infection rates.²⁰

HIV-AIDS patients experience immunologic dysfunction, and with the diversification of therapeutic drugs, the incidence of drug eruptions among these patients is usually higher than that of the general population.²¹ In our study, drug eruption was found in 6.9% of patients, with the most having a CD4 count < 200, this result is lower than reported in the literature.²¹ Drug reactions include maculopapular, urticarial rash, and Stevens-Johnson syndrome. The principal causative agent noted was Nevirapine. The lower incidence in our study can be explained by the fact that ARV itself improves the general condition of the patients. The current principle of ARV is to use three types of drugs, all three of which must be absorbed and in therapeutic doses in the blood, known as highly active antiretroviral therapy (HAART) and often shortened to antiretroviral therapy (ART). It has been shown that patients with

CD4+ cell count < 200 are more likely to have a drug eruption, which is associated with immune function status. Therefore, patients should evaluate the risk when using different hypersensitivity drugs.²¹

The results showed the analysis of the relationship between the group of infectious and non-infectious mucocutaneous manifestations with CD4 levels based on the Chi-Square Test and obtained a p-value of 0.447. The p-value is > 0.05, which means there is no significant relationship between CD4 and the group of infectious and non-infectious mucocutaneous manifestations; this is the same as reported in a study in Pakistan. Wichai et al. even reported an inverse relationship between CD4 cell count and skin disease incidence and severity. Therefore, this correlation is still controversial.⁴

We carried out the further analysis in this study by looking for the relationship between CD4 levels and each of the 12 types of mucocutaneous manifestations in this study, such as pyoderma infection, syphilis, human papillomavirus infection, herpes simplex, herpes zoster, molluscum contagiosum, candidiasis, dermatophytosis, seborrheic dermatitis, PPE, xerosis, and drug eruptions. Found a significant relationship between CD4 cell count and mucocutaneous candidiasis ($P = 0.003$) and has a weak relationship strength of 21% ($r = 0.213$). It is in line with

a similar study conducted by Abihandan et al. and Mirnezami et al. A CD4 cell count of fewer than 200 cells/mm³ was significantly associated with a higher number of mucocutaneous disorders and the development of candidiasis.¹⁹ Another study also found candidiasis as a mucocutaneous disorder with a significant association with low CD4 cell count, which is also in line with previous studies.⁸

The odds ratio was calculated to determine the level of risk of mucocutaneous disease in HIV/AIDS patients by changing the CD4 group into two categories, namely < 200 and 200 cells/mm³. Pyoderma infection was significantly associated with a CD4 cell count of 200 cells/mm³ with a risk of 3.7 times compared to CD4 < 200 cell/mm³. Likewise, syphilis has a significant relationship with a CD4 cell count of 200 cells/mm³ with a risk of 7.8 times compared to CD4 < 200 cells/mm³. On the other hand, mucocutaneous candidiasis infection was higher in conditions of CD4 count < 200 cells/mm³ with a significant difference and 0.3 times risk compared to CD4 200 cells/mm³. These results are different from similar studies conducted by other researchers. Pudjiati et al. reported that a lower CD4 cell count (< 200 cells/mm³) increased the risk of fungal infection by 3.8-fold. A higher CD4 cell count (> 200 cells/mm³) increases the risk of viral infection by about 2.5-fold and parasitic infection by 5-fold.¹³ Goh et al. found that the risk of developing PPE was three times higher in patients with CD4 counts below 200 cells/mm³. Sanchez et al. found that 80% of their patients had CD4 counts <100 cells/mm³. The higher mean CD4 cell count in the current study may be because 90% of patients with PPE are on ART and may be due to IRIS.¹⁹

Lowe and others reported that PPE and molluscum contagiosum was most commonly seen in patients with lower CD4 cell counts. According to Noruka's study, PPE was most commonly found at CD4 counts < 200, and seborrheic dermatitis was observed in patients with CD4 counts between 200 and 500. In Goh's study, CD4 cell count < 200 was strongly associated with psoriasis and drug reactions.⁸ However, a significant association between PPE and seborrheic

dermatitis on CD4 levels was not found in our study. The differences in the results of these different studies can be explained by variations in sample size, disease stage, route of infection, and regional patterns of reported disease.

HIV/AIDS patients are at high risk for malignancies, such as Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical carcinoma. These three malignancies are often called AIDS-defining conditions. If one of the three malignancies is found, it can indicate the course of HIV infection has reached the AIDS stage. The relationship between HIV infection and certain types of malignancy is still unexplained, possibly related to a decrease in the immune system.¹³ In this study, only two lymphoma cases were found; this could be due to other malignancies in patients who were not screened for HIV. In addition, no data were obtained regarding CD4 levels in patients, so an analysis of the relationship could not be carried out.

This study has some limitations because it was conducted in a tertiary care hospital, so the manifestation may be different from patients in hospitals in primary and secondary services. It is important to plan and carry out research using larger sample sizes in different areas, which will help in better interpretation of the population. The small number of patients who have CD4 levels checked is also a limitation in this study, so the monitoring of immune status through CD4 level examinations needs to be further improved so that it can provide guidelines for possible interventions and better prognostics.

CONCLUSION

Manifestations of mucocutaneous disorders occur throughout the course of HIV infection. Several mucocutaneous manifestations can be considered as predictors of advanced HIV infection (low CD4 level), which were infections, syphilis, and in this study. According to the distribution of CD4 results with mucocutaneous manifestations, it was found that CD4 < 200 cells/mm³ and 200-500 cells/mm³ in HIV/AIDS patients mostly related to infections categorized diseases, especially as mucocutaneous candidiasis. Moreover, CD4 > 500 cells/mm³ were also found in non-

infectious categorized diseases, with the most manifestations being seborrheic dermatoses. This study has some limitations because it was conducted in a tertiary care hospital, and there was no follow-up to observe the development or deterioration of dermatoses. It is important to plan and carry out research using larger sample sizes in different areas, which will help in better interpretation of the population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

This study did not receive a specific grant from any institution.

ETHICAL CLEARANCE

The present research was approved and reviewed by the Ethical Committee (Reference no. 0032/LOE/301.4.2/VI/202) of Dr. Soetomo General Teaching Hospital situated in Surabaya, Indonesia.

AUTHOR CONTRIBUTION

All authors contributed to the study, including conceptual framework, design, data collection, and data analysis to report study results for publication.

REFERENCES

- Lipworth AD, Freeman EE, Saavedra AP. Cutaneous Manifestations of HIV and Human T-Lymphotropic Virus. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS. eds. *Fitzpatrick's Dermatology, 9e*. McGraw Hill; 2019.
- Chopra S, Arora U. Skin and Mucocutaneous Manifestations: Useful Clinical Predictors of HIV/AIDS. *J Clin Diagn Res*. 2012;6(10):1695-1698. doi:10.7860/JCDR/2012/4615.2633.
- Raju PV, Rao GR, Ramani TV, Vandana S. Skin disease: clinical indicator of immune status in human immunodeficiency virus (HIV) infection. *Int J Dermatol*. 2005;44(8):646-649. doi:10.1111/j.1365-4632.2004.02067.x.
- Azfar NA, Khan AR, Zia MA, Humayun A, Malik LM, Jahangir M. Frequency of mucocutaneous manifestations in HIV positive Pakistani patients. *J Pak Assoc Dermatol*. 2011;21(3):149-153. doi: 10.20473/bikk.V33.3.2021.156-161.
- Botting RA, Rana H, Bertram KM, et al. Langerhans cells and sexual transmission of HIV and HSV. *Rev Med Virol*. 2017;27(2):10.1002/rmv.1923. doi:10.1002/rmv.1923.

6. Shoko C, Chikobvu D. A superiority of viral load over CD4 cell count when predicting mortality in HIV patients on therapy. *BMC Infect Dis.* 2019;19(1):169. Published 2019 Feb 15. doi:10.1186/s12879-019-3781-1.
7. Crum-Cianflone N, Hullsiek KH, Satter E, et al. Cutaneous malignancies among HIV-infected persons. *Arch Intern Med.* 2009;169(12):1130-1138. doi:10.1001/archinternmed.2009.104.
8. Mirnezami M, Zarinfar N, Sofian M, Botlani Yadegar B, Rahimi H. Mucocutaneous Manifestations in HIV-Infected Patients and Their Relationship to CD4 Lymphocyte Counts. *Scientifica (Cairo).* 2020;2020:7503756. Published 2020 Aug 11. doi:10.1155/2020/7503756.
9. Moustaid K, Nassiri A, BayBay H, Gallouj S, Rabhi S, Mernissi FZ. Profile of dermatological manifestations in seropositive patients correlated with CD4 count sample of a Moroccan population. *Yumed Text.* 2019;1(1):1-6.
10. Adewole OE, Olagundoye OA, Ajumobi IO. Depression and its associated factors among people living with HIV/AIDS attending the HIV/AIDS CLINIC in Southwest Nigeria. *Family Medicine & Primary Care Review.* 2021;23(1):7-12. doi:10.5114/fmPCR.2021.103149.
11. Agrawal M, Sharma P, Saxena A, A study of sexually transmitted infections among HIV – infected patients in correlation with their CD4 T cell counts. *IP Indian J Clin Exp Dermatol* 2020;6(3):257-260. <https://doi.org/10.18231/j.ijced.2020.052>.
12. Khat N, Kudligi C, Rathod RM, Kuntoji V. A clinical study of mucocutaneous manifestation of HIV/AIDS and its correlation with CD4 count. *Journal of Pakistan Association of Dermatologists.* 2020;30(4):550-557.
13. Pudjiati SR, Dewi NA, Palupi SSA. Correlation between CD4 cell counts with mucocutaneous manifestations: study of HIV patients in Dr. Sardjito General Hospital, Yogyakarta. *J the Med Sci.* 2018;50(1):42–9. <https://doi.org/10.19106/JMedSci005001201805>.
14. Khondker L. Dermatological manifestations of HIV/AIDS patients. *J Enam Med Coll.* 2018;9(3):185–8. doi:<https://doi.org/10.3329/jemc.v9i3.43249>.
15. Fernandes MS, Bhat RM. Spectrum of mucocutaneous manifestations in human immunodeficiency virus-infected patients and its correlation with CD4 lymphocyte count. *Int J STD AIDS.* 2015;26(6):414-419. doi:10.1177/0956462414543121.
16. Titou H, Ebongo C, Hjira N. Dermatologic manifestations among human immunodeficiency virus patients in Morocco and association with immune status. *Int J Dermatol.* 2018;57(2):156-161. doi:10.1111/ijd.13864.
17. Boushab BM, Malick Fall FZ, Ould Cheikh Mohamed Vadel TK, et al. Mucocutaneous manifestations in human immunodeficiency virus (HIV)-infected patients in Nouakchott, Mauritania. *Int J Dermatol.* 2017;56(12):1421-1424. doi:10.1111/ijd.13737.
18. Harnanti DV, Hidayati AN, Miftahussurur M. Concomitant Sexually Transmitted Diseases In Patients With Diagnosed Hiv/ Aids: A Retrospective Study. *Afr J Infect Dis.* 2018;12(1 Suppl):83-89. Published 2018 Mar 7. doi:10.2101/Ajid.12v1S.12.
19. Abhinandan HB, Suresh KJ, Asha N, Ramesh K, Manali J, Jitendra B et al. Cutaneous manifestations of HIV-infection in relation with CD4 cell counts in Hadoti region. *J Evol Med Dent Sci.* 2013;2(36):6703-14. doi:10.14260/jemds/1246.
20. Tahir K., Alam F, Hussain I, Ashraf S. Frequency of mucocutaneous manifestations in HIV positive patients. *J Pak Assoc Dermatol.* 2018;28(4):420–5.
21. Li YY, Yang SH, Wang RR, Tang JT, Wang HM, Kuang YQ. Effects of CD4 cell count and antiretroviral therapy on mucocutaneous manifestations among HIV/AIDS patients in Yunnan, China. *Int J Dermatol.* 2020;59(3):308-313. doi:10.1111/ijd.14725.
22. Bayu R, Indrawan I, Sukarni N, Sridana M. Profil pasien baru HIV di poliklinik VCT BRSU Tabanan Bali pada tahun 2009 sampai 2017. *Intisari Sains Medis.* 2018;9(1). doi:10.15562/ism.v9i1.145.



This work is licensed under a Creative Commons Attribution