

## Correlation of mucocutaneous manifestations of HIV infected patients with CD4 count during antiretroviral therapy

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### ABSTRACT

**Background:** Human Immunodeficiency Virus (HIV) infection produces a wide range of infectious and noninfectious dermatoses which correlate with the degree of immunodeficiency. Cluster of Differentiation 4 (CD4) count is used as a marker of immunodeficiency in case of HIV infection.

**Objective:** To identify the mucocutaneous manifestations in HIV infected patients, and to find out their correlation with CD4 cell count.

**Materials & Methods:** This cross-sectional study included ninety-seven HIV positive patients from the ART center and the Department of Dermatology & Venereology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. Patients were examined for mucocutaneous manifestations and CD4 cell counts of patients were extracted from their medical records. Data was analyzed and calculated using the Statistical Package for Social Sciences (SPSS version 26). Correlation of number of mucocutaneous manifestations with CD4 count was done by Pearson's correlation test.

**Result:** The common infectious diseases were Dermatophytosis 53.6%, Scabies 13.4%, Oral Candidiasis 10.3%, Pityriasis Versicolor 5.2%, Onychomycosis 4.1%, Paronychia 3.1%, Wart 2.1% and Herpes Simplex 1%. Among the noninfectious diseases Seborrhoeic Dermatitis 16.5%, Melanonychia 5.2%, Acne 2.1%, Aphthous stomatitis in 2.1%, Cheilitis 2.1%, Oral pigmentation in 1.0% and Eczema 1.0% were found. Statistically significant association with CD4 count were seen in Dermatophytosis ( $p < 0.001$ ), Seborrhoeic Dermatitis ( $p < 0.001$ ), Onychomycosis ( $p < 0.002$ ), Oral Candidiasis ( $p < 0.003$ ), Herpes Simplex ( $p < 0.005$ ). Pearson's correlation test showed negative correlation between CD4 count and number of mucocutaneous manifestations ( $r = -0.337$ ,  $p = 0.001^*$ ).

**Conclusion:** Significant negative correlation was found between number of mucocutaneous manifestations and CD4 count in HIV patients. Statistically significant association with the CD4 count was seen in Dermatophytosis, Seborrhoeic Dermatitis, Onychomycosis, Oral Candidiasis and Herpes Simplex.

KEY WORDS: HIV infection, antiretroviral therapy, mucocutaneous findings of HIV, CD4 count of HIV infection

### INTRODUCTION

Human immunodeficiency virus (HIV) is an enveloped ribonucleic acid (RNA) retrovirus from the lentivirus family. HIV infection is acquired sexually from blood or blood products or vertically from an infected mother during pregnancy, birth or breastfeeding.<sup>1</sup> HIV infect cells bearing

Cluster of Differentiation (CD4) receptors and causes their destruction.<sup>2</sup> The normal absolute CD4 count in adolescents and adults ranges from 500 to 1500 cells per mm<sup>3</sup> of blood. In general, the CD4 count progressively decreases as HIV disease advances. Low CD4 cell count is associated with a moderately higher risk for disease

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progression among HIV positive patients.<sup>3</sup> Acquired immune-deficiency syndrome (AIDS) is a fatal illness which breaks down the immune system of the body, leaving the victim vulnerable to a host of life-threatening opportunistic infections.<sup>1</sup> In Bangladesh estimated people living with HIV is 14,000. Approximately 1600 people were newly infected with HIV and 580 people died due to AIDS related illness in Bangladesh in 2018.<sup>4</sup>

Skin manifestations of HIV infection not only act as markers, but also reflect the underlying immune status and help to determine the stage of the disease.<sup>5</sup> Skin conditions may indicate progression of HIV disease and they can be disabling, disfiguring, or even life-threatening.<sup>3</sup> Some dermatological manifestations are good markers of HIV infection such as generalized prurigo, herpes zoster of the young adult, oral hairy leukoplakia, others have a prognostic value such as Kaposi sarcoma. Oral hairy leukoplakia are good indicators of the diagnosis, stage, and prognosis of HIV infection.<sup>6</sup>

HIV contributes significantly to patient morbidity in terms of quality of life and may also reflect the progress of HIV disease.<sup>7</sup> If CD4 T cell count  $>500$  cell/mm<sup>3</sup>, the common mucocutaneous manifestations are Acute retroviral syndrome, Herpes zoster infection (nondisseminated), Seborrhoeic dermatitis. If CD4 T cell count 200-500 cells/mm<sup>3</sup>, the common mucocutaneous manifestations are recurrent or persistent dermatophyte infections, oral candidiasis, oral hairy leukoplakia, disseminated herpes zoster infection. If CD4 T cell count  $<200$  cells/mm<sup>3</sup>, the common mucocutaneous manifestations are bacillary angiomatosis, cutaneous miliary tuberculosis, hyperkeratotic scabies, eosinophilic folliculitis, herpes

simplex virus infection ( $>1$  month's duration), idiopathic pruritus, invasive fungal infections, papular pruritic eruption.<sup>8</sup>

Mucocutaneous lesions in HIV patients have been correlated with CD4 counts in many studies. Serial CD4 counts have a prognostic significance, and are used as markers for assessing progression from HIV infection to AIDS.<sup>9</sup> Mucocutaneous manifestations are one of the most important clinical markers, and may be the first clue of HIV infection and disease progression. A wide range of infectious, noninfectious and neoplastic skin lesions develop during the course of the disease. The CD4 cell plays an important role in the immune system, and CD4 count is used as a marker for assessing progression from HIV infections to AIDS. So, these mucocutaneous manifestations may indicate the worsening of immune status and the need for regular monitoring with periodical CD4 counts. But currently there is no data regarding the mucocutaneous manifestation in HIV patient with CD4 count in Bangladeshi population. This study may open the door as a reference for future studies.

## MATERIALS & METHODS

A cross sectional study was conducted during the period of January 2020 to June 2021. Adult HIV infected patients attending ART center and the Department of Dermatology & Venereology at Bangabandhu Sheikh Mujib Medical University were included in the study. Consecutive type of sampling technique was applied to collect the sample from the study population during the study period, and a total of 97 patients were taken as sample in this study. Inclusion criteria were adults living with HIV infection, aged  $\geq 18$  years, patients with mucocutaneous finding,

patients with medical record of CD4 cell count (within 1 month), patients on the treatment with antiretroviral therapy. Exclusion criterias were HIV infected patients without medical record of CD4 cell count and patients having mucocutaneous finding but without medical record of CD4 cell count. Semi-structured questionnaire was used as research instrument.

**Study Procedure:** All eligible patients were informed about the whole process of the study at the beginning. And, only those consenting to take part in the study, were enrolled. Informed written consent was obtained from each participant. Relevant history was taken regarding present illness regarding mucocutaneous manifestations, duration of the disease, duration of HIV infection and duration of ART treatment. Mucocutaneous manifestations of all the patients were clinically diagnosed. The most recent CD4 cell counts of patients were collected from their medical records. All the information regarding mucocutaneous findings and CD4 cell count were collected from each patient and was recorded in preformed data collection sheet.

**Data Processing and Analysis:** Data was analyzed and calculated using the Statistical Package for Social Sciences (SPSS version 26). Absolute and relative frequency of mucocutaneous manifestation was computed. Chi-square test ( $\chi^2$  test) was used to analyze the qualitative data. A p-value  $<0.05$  was considered as statistically significant. Correlation of CD4 count with number of mucocutaneous manifestations was done by Pearson's correlation test.

**Ethical Issues:** Ethical clearance for the study was taken from the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University(BSMMU). Permission for the study

was taken from ART center and the department of Dermatology and Venereology, BSMMU from where study subjects were selected. All the subjects were thoroughly appraised about the nature, purpose and implications of the study, as well as entire spectrum of benefits and risks of the study. Subjects were assured about the confidentiality of data and freedom to withdraw from the study anytime.

## RESULTS

This cross-sectional study was conducted in the department of Dermatology and Venereology and ART center, Bangabandhu Sheikh Mujib Medical University, during the period of January 2020 to June 2021. A total of ninety-seven HIV patients were included in this study.

Table I: Showed age group distribution with CD4

**Table I** Distribution of age group with CD4 count (n=97)

Age group (years)	CD4				P-value
	<200 (n=3)	200-349 (n=7)	350-500 (n=23)	>500 (n=64)	
<20	0(0.0%)	0(0.0%)	0(0.0%)	1(1.6%)	0.776
21-30	1(33.3%)	1(14.3%)	8(34.8%)	17(26.6%)	
31-40	2(66.7%)	4(57.1%)	8(34.8%)	22(34.4%)	
41-50	0(0.0%)	0(0.0%)	4(17.4%)	17(26.6%)	
51-60	0(0.0%)	2(28.6%)	3(13.0%)	7(10.9%)	
Total	3(100.0%)	7(100.0%)	23(100.0%)	64(100.0%)	

p value  $\leq 0.05$  considered as significant

count. Most of the patients were from age group 31-40 years. Where, 66.7% had CD4 count  $<200$ , 57.1% had CD4 count 200-349, 34.8% had CD4 count 350-500 and 34.4% had CD4 count  $>500$ . No statistically significant differences were seen between the different age group and CD4 count (p $<0.776$ ).

Table II: Showed that infectious disease were more common where 87% had CD4 count 350-500, 75% had CD4 count >500 and 71.4% had CD4 count 200-349. Statistically significant association were seen between the different disease group and CD4 count ( $p < 0.001$ ).

Table-II: CD4 cell count in relation with infectious and non-infectious disease (n=97)

Disease type	CD 4 count				p-value
	<200 (n=3)	200-349 (n=7)	350-500 (n=23)	>500 (n=64)	
Infectious	0(0.0%)	5(71.4%)	20(87.0%)	48(75.0%)	0.001
Non-infectious	1(33.3%)	0(0.0%)	3(13.0%)	12(18.8%)	
Both	2(66.7%)	2(28.6%)	0(0.0%)	4(6.3%)	
Total	3(100.0%)	7(100.0%)	23(100.0%)	64(100.0%)	

Chi-squared Test ( $\chi^2$ ) was done to analyze the data. p value  $\leq 0.05$  considered as a level of significant

Table III: Showed that statistically significant association were found between CD4 count and dermatophytosis ( $p < 0.001$ ), onychomycosis ( $p < 0.002$ ), oral candidiasis ( $p < 0.003$ ), herpes simplex ( $p < 0.005$ ) and seborrhoeic dermatitis ( $p < 0.001$ ).

Table-III: Relation of mucocutaneous manifestations with different grade of CD4 count (n=97)

Mucocutaneous manifestations	CD4				p-value
	<200 (n=3)	200-349 (n=7)	350-500 (n=23)	>500 (n=64)	
Dermatophytosis	0(0.0%)	7(100.0%)	19(82.6%)	26(40.6%)	0.001*
Tinea Corporis	0(0.0%)	4(57.1%)	13(56.5%)	23(35.9%)	0.122
Tinea cruris	0(0.0%)	3(42.9%)	4(17.4%)	3(4.7%)	0.008
Tinea pedis	0(0.0%)	0(0.0%)	2(8.7%)	0(0.0%)	0.087
Onychomycosis	0(0.0%)	2(28.6%)	2(8.7%)	0(0.0%)	0.002*
Pityriasis versicolor	0(0.0%)	0(0.0%)	1(4.3%)	4(6.3%)	0.866
Oral Candidiasis	2(66.7%)	2(28.6%)	2(8.7%)	4(6.3%)	0.003*
Herpes Simplex	0(0.0%)	1(14.3%)	0(0.0%)	0(0.0%)	0.005*
Wart	0(0.0%)	0(0.0%)	0(0.0%)	2(3.1%)	0.788
Scabies	0(0.0%)	0(0.0%)	0(0.0%)	13(20.3%)	0.052
Paronychia	0(0.0%)	0(0.0%)	0(0.0%)	3(4.7%)	0.660
Folliculitis	0(0.0%)	0(0.0%)	0(0.0%)	2(3.1%)	0.788
Seborreic Dermatitis	3(100.0%)	1(14.3%)	4(17.4%)	8(12.5%)	0.001*
Eczema	0(0.0%)	0(0.0%)	0(0.0%)	1(1.6%)	0.914
Acne	0(0.0%)	0(0.0%)	1(4.3%)	1(1.6%)	0.829
Melanonychia	0(0.0%)	1(14.3%)	0(0.0%)	4(6.3%)	0.429
Aphthous stomatitis	0(0.0%)	1(14.3%)	0(0.0%)	1(1.6%)	0.121
Cheilitis	0(0.0%)	0(0.0%)	1(4.3%)	1(1.6%)	0.829
Oral pigmentation	0(0.0%)	0(0.0%)	0(0.0%)	1(1.6%)	0.914
Alopecia	0(0.0%)	0(0.0%)	1(4.3%)	1(1.6%)	0.829

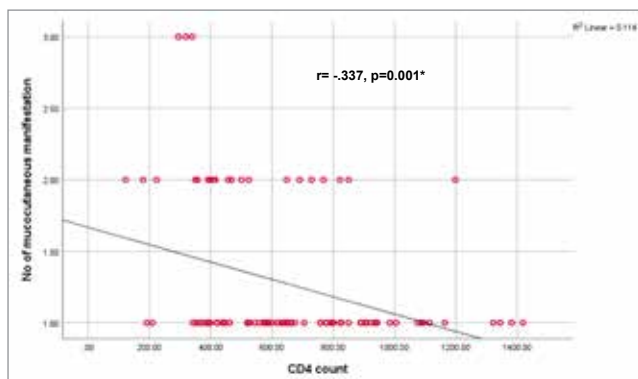
Figures in the parentheses indicate corresponding percentage; Chi-squared Test ( $\chi^2$ ) was done to analyze the data. p value  $\leq 0.05$  considered as a level of significant

**Table IV** Comparison of CD4 count among single, double and triple lesion (n=97)

	Single lesion (n=74) Mean±SD	Double lesion (n=20) Mean±SD	Triple lesion (n=3) Mean±SD	p-value
CD4 count	707.1±276.0	525.0±260.7	317.7±23.02	0.003

Data were expressed as mean±SD, ANOVA test was performed to compare among group p value  $\leq 0.05$  considered as a level of significant

**Table IV** Showed statistically significant association among single, double, triple lesion and CD4 count. ( $p < 0.003$ ).



Pearson's correlation test, \*significant

**Fig. 1** Correlation of CD4 count with number of mucocutaneous manifestations

The scattered diagram in figure 4 and the Pearson's correlation test showed negative correlation between CD4 number and number of mucocutaneous manifestations. ( $r = -.337$ ,  $p = 0.001^*$ ).

## DISCUSSION

This cross-sectional study was conducted on ninety-seven patients attending in the ART center and the department of Dermatology & Venereology at Bangabandhu Sheikh Mujib Medical University, from January 2020 to June 2021 to find out the correlation of mucocutaneous manifestations of HIV infected patients with CD4 count during Antiretroviral Therapy.

Majority of the patients in this study belonged to the age group between 31- 40 years (37.1%)

where 66.7% had CD4 count  $< 200$ , 57.1% had CD4 count 200-349, 34.8% had CD4 count 350-500 and 34.4% had CD4 count  $> 500$ . HIV infection can occur in any age but is more common in young adult patient. Khat et al. reported majority of the patients belonged to the age group between 31-40 years (42%).<sup>1</sup> Chandrakala et al. 2017, reported majority of the patients were in the age group of 31-40 years (36%).<sup>10</sup> Malkud et al. 2016, reported majority of the patients 43.3% were in the age group of 30-39 years.<sup>11</sup> Kore et al. 2013, reported majority of the patients were in the age group of 31-40 years (49.7%).<sup>12</sup> Singh et al. 2009, reported higher prevalence age group of 30-39.<sup>13</sup> These findings were almost similar to the current study.

In this study, infectious diseases were more common where 87% had CD4 count 350-500, 75% had CD4 count  $> 500$ , 71.4% had CD4 count 200-349 and 66.7% had CD4 count  $< 200$ . Statistically significant differences were seen between the different disease group and CD4 count ( $p < 0.001$ ). Surprisingly, all the infectious and noninfectious skin diseases were seen in patients with a higher CD4 count. This is an important finding as it suggests and proves that starting ART in the early stages of HIV prevents mucocutaneous manifestations. In contrast to the study by Davarpanah et al. 2018, they found no association between CD4 cell count and infectious or noninfectious dermatologic manifestations ( $p < 0.274$ ).<sup>14</sup>

Most common fungal infections were dermatophytosis with a frequency of 53.6% in this study. The most common dermatophytosis was Tinea corporis 41.2% number followed by Tinea cruris 10.3% and Tinea pedis 2.1%. Khat et al. 2020, reported the most common fungal infection was dermatophytosis (59.1%) with a mean

CD4 count of  $489.69 \pm 260.13$  cells/mm<sup>3</sup>.<sup>1</sup> Similar results were found in study by Titou et al, where dermatophytic infections were seen in 67% out of the total 170 patients.<sup>6</sup> The presentation of dermatophytoses were very much similar to non-HIV patients and hot climate in this region was considered as an important factor for the higher prevalence of dermatophytosis in immunosuppression associated condition. Statistically significant association were found between CD4 count and dermatophytosis ( $p < 0.001$ ) in this study. Similar result was found in the study of Kore et al, where statistically significant association found between immunological stage of HIV infections and dermatophytosis ( $p < 0.008$ ).<sup>12</sup> Khat et al. 2020, reported statistically significant association between CD4 count and dermatophytosis ( $p < 0.05$ ).<sup>1</sup> Chandrakala et al. 2017, reported statistically significant association between CD4 count and dermatophytosis ( $p < 0.046$ ).<sup>10</sup> Oral candidiasis was found in 10.3% cases in this study. Similar results were found in the study of Boushab et al, where oral candidiasis was reported in 11.6%.<sup>15</sup> Ashrif et al, reported oral candidiasis in 16%.<sup>16</sup> Halder et al reported oral candidiasis in 17% cases.<sup>17</sup> Statistically significant association was found in oral candidiasis ( $p < 0.003$ ) in this study. Titou et al, reported statistically significant association in oral candidiasis with lower CD4 count ( $p < 0.01$ ).<sup>6</sup> Mirnezami et al, reported oral candidiasis ( $p < 0.002$ ) was significantly associated with low CD4 cell count.<sup>18</sup> Li et al, reported oral candidiasis was statistically significant ( $p < 0.001$ ).<sup>19</sup> Sud et al reported statistically significant association of oral candidiasis ( $p < 0.002$ ).<sup>20</sup> Singh et al reported statistically significant association of oral candidiasis ( $p < 0.0001$ ).<sup>13</sup> These findings were almost similar

to the current study.

In this study, pityriasis versicolor 5.2% was found in immunocompetent condition (CD4 >500). This prevalence was more common in general population. Similar result found in the study of Vijaya et al, reported six cases of pityriasis versicolor infection among 125 patients, where mean CD4 count was  $366.17 \pm 201.324$ .<sup>21</sup> Khat et al. 2020, reported pityriasis versicolor 2.3%.<sup>1</sup>

Onychomycosis 4.1% was found in this study. Similar result was found in the study of Rajput et al, where onychomycosis reported in 3.8% cases.<sup>5</sup> Statistically significant association was found in Onychomycosis ( $p < 0.002$ ) in this study. Khat et al, reported statistically significant association with Onychomycosis ( $p < 0.032$ ).<sup>1</sup> In this study, Folliculitis 2.1% was found in immunocompetent patient (CD4 >500). Similar result was found in the study of Vijaya et al, reported four cases of folliculitis where mean CD4 count  $621.50 \pm 188.878$ .<sup>21</sup>

In this study one case of herpes simplex virus infection was found in advanced immunosuppression condition (CD4 count 340). Viral infections were more common in immunosuppression condition. Similar result was found in the study of Vijaya et al, reported one case of herpes simplex virus infection among 125 patients where CD4 count 301.<sup>21</sup> Khat et al, reported herpes simplex virus infection 3.8%, which is slightly higher than this study.<sup>1</sup> Statistically significant association was found in herpes simplex ( $p < 0.005$ ) in this study. Similar result was found in the study of Khat et al, where herpes simplex was statistically significant ( $p < 0.012$ ).<sup>1</sup> In this study, wart 2.1% was found where mean CD4 count  $878.5 \pm 40.3$  and range 850.0-907. All these patients were im-

munocompetent and CD4 count >500. Khat et al. in 2020 reported wart 5.4%.<sup>1</sup>

In this study, Scabies 13.4% was found in immunocompetent patient (CD4 count above 500). No crusted scabies was found in this study because this occurred in immunosuppressive condition. The high percentage of patients in this study may correspond to its higher prevalence in general population. Malkud, et al., 2016, reported scabies in 11.6% among 120 HIV patient.<sup>11</sup> No statistically significant association was found in scabies ( $p < 0.052$ ) in this study. Similar result was found in the study of Khat et al. 2020, where scabies was statistically significant ( $p < 0.012$ ).<sup>1</sup> Seborrheic dermatitis 16.5% was the most common noninfectious manifestations encountered in this study. In severe immunosuppression condition, seborrheic dermatitis was found 100% cases. Seborrheic dermatitis was considered early clinical marker for HIV infection. Alteration in the immune system in HIV-AIDS, changes the response of the skin to the yeast, *Pityrosporum ovale*, leading to a higher rate of infection. Similar result was found in the study of Kore et al. 2013, found seborrheic dermatitis 22% patient among 352 patients.<sup>12</sup> Shikur et al found 11% seborrheic dermatitis patients among 572 patients.<sup>22</sup> Williams et al reported seborrheic dermatitis in 30.6% among 36 patients.<sup>23</sup> In this study, statistically significant association was found between CD4 count and seborrheic dermatitis ( $p < 0.001$ ). Titou et al reported statistically significant association in seborrheic dermatitis ( $p < 0.007$ ).<sup>6</sup> Chandrakala et al. 2017, reported statistically significant association with CD4 count in seborrheic dermatitis ( $P < 0.041$ ).<sup>10</sup> These findings were almost similar to the current study. In this study, melanonychia was found in 5.2%

cases, where mean CD4 count  $773.4 \pm 305.5$  and range 340-1199. Zidovudine may produce melanonychia. Khat et al, reported melanonychia in 6.9% patients among total of 130 patients.<sup>1</sup>

In this study, triple mucocutaneous manifestations were found in mean CD4 count  $317.7 \pm 23.02$ . Increase in the number of mucocutaneous manifestations related to decreased CD4 count. Significant negative correlation was found between number of mucocutaneous manifestations and CD4 count in HIV patients ( $r = -0.337$ ,  $p = 0.001^*$ ). In immunosuppressive condition number of mucocutaneous manifestations increased. Similar result was found in the study of Kore et al. 2013, where negative correlation was found between number of mucocutaneous manifestations and CD4 count in HIV patients ( $r = -2.33$ ,  $p = 0.001$ ).<sup>12</sup>

## CONCLUSION

Significant negative correlation was found between number of mucocutaneous manifestations and CD4 count in HIV patients. Statistically significant association with the CD4 count was seen in dermatophytosis, seborrheic dermatitis, onychomycosis, oral candidiasis and herpes simplex.

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