

# Pattern of mucocutaneous manifestations in human immunodeficiency virus-positive patients in North India

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## Abstract

**Background:** Mucocutaneous diseases are among the first-recognized clinical manifestations of acquired immune deficiency syndrome. They function as visual markers in assessing the progression of human immunodeficiency virus (HIV) infection. Given the relative ease of examination of skin, its evaluation remains an important tool in the diagnosis of HIV infection. **Objective:** To determine the pattern of mucocutaneous manifestations in HIV-positive patients and to correlate their presence with CD4 counts. **Materials and Methods:** This cross-sectional study included 352 HIV-infected patients seen at PGIMER, Chandigarh, India, over a period of 1 year. The patients were screened for mucocutaneous disorders by an experienced dermatologist. The patients were classified into different stages according to the World Health Organization clinical and immunological staging system. **Results:** The most prevalent infection was candidiasis, seen in 57 patients (16.2%). Prevalence of candidiasis, dermatophytosis, herpes simplex, herpes zoster, molluscum contagiosum (MC), seborrheic dermatitis, adverse drug reaction, nail pigmentation, xerosis and diffuse hair loss differed statistically according to the clinical stages of HIV infection. There was a statistically significant association between immunological stages of HIV infection and dermatophytosis. **Conclusion:** Results of our study suggest that mucocutaneous findings occur throughout the course of HIV infection. Dermatoses like MC and dermatophytosis show an inverse relation with CD4 cell count, and these dermatoses can be used as a proxy indicator of advanced immunosuppression to start highly active anti-retroviral therapy in the absence of facilities to carry out CD4 cell count.

**Key words:** Acquired immune deficiency syndrome, CD4 count, human immunodeficiency virus, India, mucocutaneous manifestation of AIDS

## INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is a chronic, infective disorder caused by a single stranded RNA retrovirus, human immunodeficiency virus (HIV). Though India is a country with low

HIV prevalence, it has the third largest number of people living with HIV/AIDS because of its huge population. As per HIV estimates 2008-09, there are an estimated 2.39 million people living with HIV/AIDS in India, with an adult prevalence of 0.31% in 2009.<sup>[1]</sup> The Post Graduate Institute of Medical Education and Research, Chandigarh, is a regional institution as indicated by the National AIDS Control Organisation, and caters the needs of the states of Haryana, Himachal Pradesh, Jammu and Kashmir, Punjab and Chandigarh. Alarmingly, the states of Chandigarh and Jammu and Kashmir are showing rising trends in adult HIV prevalence in the last 4 years. In spite of low prevalence of HIV

### Access this article online

Quick Response Code:



Website:

www.ijstd.org

DOI:

10.4103/0253-7184.112865

### How to cite this article:

Kore SD, Kanwar AJ, Vinay K, Wanchu A. Pattern of mucocutaneous manifestations in human immunodeficiency virus-positive patients in North India. Indian J Sex Transm Dis 2013;34:19-24.

in Punjab and Haryana, they have a large number of people living with HIV infection due to the large population size.<sup>[2]</sup> These features highlight the urgent need for quality data regarding clinical manifestation and local epidemiological trends of HIV.

Mucocutaneous diseases are among the first-recognized clinical manifestations of AIDS. In developed countries, CD4 lymphocyte count, detection of viral load and viral culture are being used for the assessment of HIV disease. Lack of these facilities in developing countries necessitates dependence on clinical markers. Given the relative ease of examination of skin, and because most skin disease are amenable to diagnosis by inspection and biopsy, evaluation of skin remains an important tool in the diagnosis of HIV infection. However, studies pertaining to mucocutaneous manifestation in HIV/AIDS patients are mostly available from western countries. There are only few such reports from India. Therefore, this study was conducted to determine the pattern of mucocutaneous manifestations in HIV-positive patients and to correlate their presence with CD4 counts.

## MATERIALS AND METHODS

This cross-sectional study included 352 HIV-infected patients seen at the HIV Clinic and Dermatology Outpatient Department and wards of Nehru Hospital PGIMER, Chandigarh, India, over a period of 1 year.

Inclusion criteria were HIV-positive (three successive reactive ELISA sera) adult patients regardless of stage of disease and in whom all clinical and investigative information including CD4 counts were available. Patients were classified into different stages according to the World Health Organization (WHO) clinical and immunological staging system,<sup>[2]</sup> and were also grouped into those who had and who had not initiated highly active anti-retroviral therapy (HAART).

All the patients were screened for mucocutaneous disorders by an experienced dermatologist. The clinical diagnosis was confirmed with laboratory procedures like microscopy (KOH preparations, Tzanck smear) and histopathological evaluation whenever necessary. CD4 counts were recorded in all the patients.

### Statistical methods

Prevalence of each diagnosis during our study was calculated. Data were analyzed by unpaired Student's *t* test. The Chi-square test was used to evaluate for significance between categorical groups. A *P* value of less than 0.05 was considered significant.

## OBSERVATIONS AND RESULTS

Of the 352 HIV-seropositive patients screened, 235 (66.8%) were males and 117 (33.2%) were females, with a sex ratio of 2:1. Majority of the patients (175, 49.7%) were in the age group of 31-40 years [Figure 1]. The demographic characteristics of the study population are shown in Table 1. Most of the patients were in WHO clinical stage 2 and 3 [Figure 2a] and had severe immunosuppression, defined as CD4 cell count <200 cells/mm<sup>3</sup> [Figure 2b]. Two hundred and seventy patients (76.7%) had mucocutaneous manifestations. Mean number of dermatoses per patient was 1.2. Number of dermatoses per patients increased as the CD4 count decreased ( $r = -2.33$ ,  $P: 0.001$ ). Only 30.9% of the WHO clinical stage 1 patients had associated dermatoses compared with 93.6% of the WHO clinical stage 4 patients [Figure 2a]. Proportion of patients having dermatoses increased with immunological worsening; 58.4% of patients with CD4 count >500/mm<sup>3</sup> had a

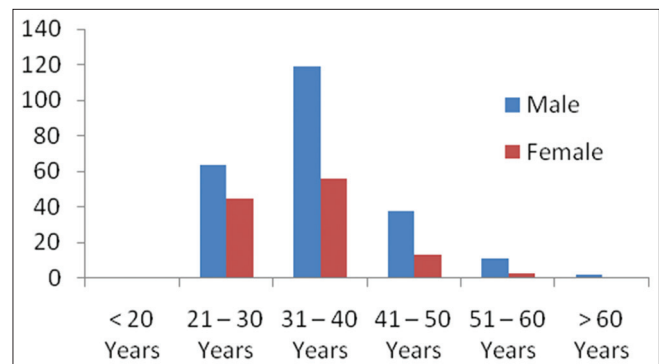


Figure 1: Age distribution of 352 human immunodeficiency virus-infected patients

Table 1: Demographic characteristics of 352 HIV-infected patients

Males (M) (%)	235 (66.8)
Females (F)	117 (33.2)
M:F	2:1
Mean age	35.37 years (range 20-66 years)
Routes of transmission (%)	
Heterosexual	315 (89.5)
Homosexual	2 (0.6)
Intravenous drug abuse	5 (1.4)
Blood transfusion	15 (4.3)
Unknown	15 (4.3)
Partner affected	211 (59.9)
Dead (%)	46 (13.06)
Alive (%)	165 (46.8)
Partner not affected (%)	87 (24.7)
Not tested\unknown (%)	27 (7.7)
Unmarried (%)	27 (7.7)
Number of patients on HAART* (%)	174 (49.4)
Mean CD4 count of patients	249.2/mm <sup>3</sup> (range 13-1119)

\*HAART-Highly active anti-retroviral therapy. The most common regimen was a combination of stavudine, lamivudine and nevirapine

dermatoses compared with 83.2% of patients with CD4 count  $<200/\text{mm}^3$  [Figure 2b]. When patients were grouped into those with CD4 cell counts of less than 200 cells/ $\text{mm}^3$  or above, the average number of skin disorders per patient was significantly higher in patients with CD4<sup>+</sup> cell count less than 200 cells/ $\text{mm}^3$  (1.7 vs. 1.1;  $P = 0.001$ ).

### Infective dermatoses

The most prevalent infection seen was candidiasis in 57 patients (16.2%). Other infective dermatoses seen were: dermatophytosis (11.9%), herpes simplex (HS) infection (10.2%), herpes zoster (HZ) (8.0%),

pyoderma (8.0%), human papilloma virus (HPV) infection (7.5%), scabies (5.1%) and molluscum contagiosum (MC) (4%) [Table 2]. The prevalence of candidiasis, dermatophytosis, HS, HZ and MC differed statistically according to clinical stages of HIV infection [Table 3]. There was a statistically significant association between immunological stages of HIV infection and dermatophytosis ( $P = 0.008$ ) [Table 3]. When the mean CD4 counts of each mucocutaneous manifestation was compared with the mean CD4 counts of patients not having similar manifestation, significant difference was seen in only four of the infectious dermatoses;

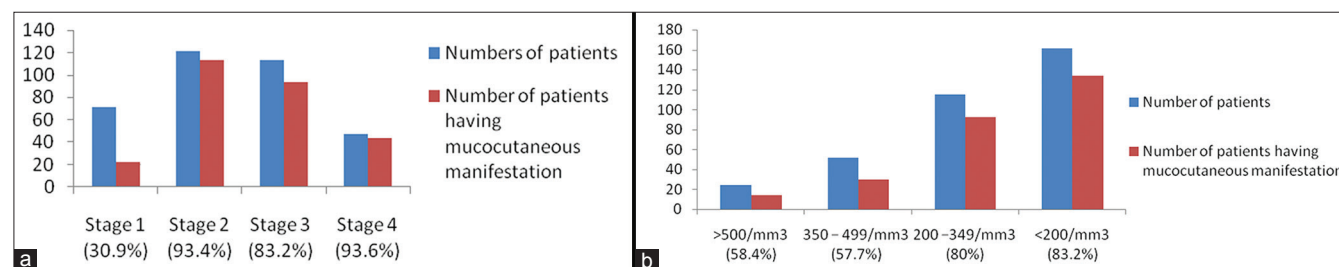


Figure 2: The prevalence of mucocutaneous manifestation in various World Health Organization clinical (a) and immunological stages (b)

Table 2: Prevalence of infectious manifestation according to the WHO clinical stage of HIV infection

Infections	1* n=71 (%)	2* n=121 (%)	3* n=113 (%)	4* n=47(%)	Total n=(%)	P value
Candidiasis	-	11 (9.1)	36 (31.9)	10 (21.2)	57 (16.2)	0.001
Dermatophytosis	-	18 (14.9)	19 (16.8)	5 (10.6)	42 (11.9)	0.001
Herpes virus infection	-	11 (9.1)	11 (9.7)	14 (29.8)	36 (10.2)	0.001
Herpes zoster	-	15 (12.4)	10 (8.8)	3 (6.4)	28 (8.0)	0.02
Pyodermas	-	17 (14.0)	8 (7.1)	3 (6.4)	28 (8.0)	0.06
HPV infection	-	12 (9.9)	7 (6.2)	4 (8.5)	23 (7.5)	0.05
Scabies	-	9 (7.4)	4 (3.5)	5 (10.6)	18 (5.1)	0.10
Molluscum contagiosum	-	2 (1.6)	5 (4.4)	5 (10.6)	14 (4)	0.04
Pityriasis versicolor	-	3 (2.5)	3 (2.7)	-	6 (1.7)	0.3
Syphilis	-	3 (2.5)	-	-	3 (0.9)	0.35
Deep fungal infection	-	-	-	1 (2.1)	1 (0.3)	-
Mycobacterial infection	-	-	-	1 (2.1)	1 (0.3)	-

\*WHO clinical stage. HPV=Human papilloma virus; WHO=World health organization

Table 3: Prevalence of infectious manifestation according to the WHO immunological stage of HIV infection

Infections	>500/ $\text{mm}^3$ n=24 (%)	350-500/ $\text{mm}^3$ n=52 (%)	200-350/ $\text{mm}^3$ n=115 (%)	<200/ $\text{mm}^3$ n=161 (%)	Total n=352 (%)	P value
Candidiasis	3 (12.5)	5 (9.61)	19 (16.05)	30 (18.63)	57 (16.2)	0.45
Dermatophytosis	-	3 (5.7)	10 (8.7)	29 (18.01)	42 (11.9)	0.008
Herpes simplex virus infection	1 (4.1)	4 (7.69)	17 (14.9)	14 (8.7)	36 (10.2)	0.22
Herpes zoster	2 (8.3)	6 (11.5)	9 (7.8)	11 (6.8)	28 (8.0)	0.75
Pyodermas	-	2 (3.8)	11 (9.6)	15 (9.3)	28 (8.0)	0.25
HPV infection	1 (4.1)	-	8 (6.9)	14 (8.7)	23 (7.5)	0.16
Scabies	1 (4.1)	1 (1.9)	6 (5.2)	10 (6.2)	18 (5.1)	0.67
Molluscum contagiosum	-	-	3 (2.6)	11 (6.8)	14 (4)	0.067
Pityriasis versicolor	1 (4.1)	1 (1.9)	2 (1.7)	2 (1.2)	6 (1.7)	0.78
Syphilis	1 (4.1)	1 (1.9)	-	1 (0.6)	3 (0.9)	0.17
Deep fungal infection	-	-	1 (0.8)	-	1 (0.3)	-
Mycobacterial infection	-	-	1 (0.8)	-	1 (0.3)	-

HPV=Human papilloma virus; WHO=World health organization

dermatophytosis, MC, HPV infection and pyodermas [Table 4]. When patients were grouped into those with CD4 cell counts of less than 200 cells/mm<sup>3</sup>, significant association was seen only in the prevalence of dermatophytosis and MC. There was no significant difference in the mean number of diagnoses in those who had and those who had not initiated HAART (1.4 vs. 1.6; *P* = 0.2). Most infectious dermatoses were higher in the group who did not receive HAART. However, this was significant in case of candidiasis (11.5% vs. 20.8%, *P*: 0.02) and dermatophytosis only (7.92% vs. 15.42%, *P*: 0.03). Tuberculids, atypical mycobacterial infections and leprosy can occur as a manifestation of immune restoration disease (IRD). However, we did not find any patients of these diseases in our study.

### Noninfective dermatoses

Seborrheic dermatitis (SD) was the most common noninfectious disorder, which was present in 29 (8.2%) patients. Other dermatoses were pigmentary disorders (6.3%), adverse reaction to drugs (6.3%),

nail discoloration (5.4%), xerosis (5.1%) and diffuse hair loss (3.4%) [Table 5]. There was a statistically significant difference between prevalence of SD, adverse drug reaction, nail pigmentation, xerosis and patients with diffuse hair loss according to the WHO clinical stage of HIV infection [Table 5]. Prevalence of noninfectious manifestation did not differ statistically according to immunological stages of HIV infection. When mean CD4 counts of each mucocutaneous manifestation was compared with the mean CD4 counts of patients not having similar manifestation, significant difference was not seen in any of the dermatoses. Prevalence of SD (12.8 vs. 4.2, *P*: 0.03) and adverse cutaneous reaction to drugs (10.9 vs. 2.1, *P*: 0.001) were significantly higher in the HAART group than in those who were not on HAART.

### Sexually-transmitted infections

The incidence of Sexually-transmitted infections (STIs) in the patients studied was 22.15%, herpes genitalis (34 patients 9.65%) being the most common STI. Recurrent herpes genitalis was seen in eight

**Table 4: CD4 cell count and mucocutaneous findings (infectious)**

Infections	Number of patients <i>n</i> (%)	Mean CD4/mm <sup>3</sup> of those having infections±SD	Mean CD4/mm <sup>3</sup> of those not having infections±SD	<i>P</i> value
Candidiasis	57 (16.2)	211.2 (±189.1)	256.6 (±169.7)	0.07
Dermatophytosis	42 (11.9)	168.5 (±12.0)	260.8 (±177.5)	0.001
Herpes simplex virus infection	36 (10.2)	244.3 (±166.9)	249.8 (±174.2)	0.85
Herpes zoster	28 (8.0)	265.3 (±167.1)	247.1 (±174.1)	0.63
Pyodermas	28 (8.0)	177.9 (±110.3)	255.4 (±176.6)	0.023
HPV infection	23 (7.5)	192.8 (±103.2)	253.2 (±176.7)	0.016
Scabies	18 (5.1)	193.1 (±139.8)	252.3 (±174.7)	0.159
Molluscum contagiosum	14 (4)	136.4 (±74.3)	253.9 (±174.8)	0.001
Pityriasis versicolor	6 (1.7)	413 (±369.3)	216 (±167.8)	0.019
Syphilis	3 (0.9)	479.3 (±298.1)	247.3 (±171.4)	0.021
Deep fungal infection	1 (0.3)	281	245.2 (±173.4)	-
Mycobacterial infection	1 (0.3)	343	249 (±173.6)	-

HPV=Human papilloma virus

**Table 5: Prevalence of non-infectious manifestation according to the WHO clinical stage of HIV infection**

Mucocutaneous findings	1 <i>n</i> =71 (%)	2 <i>n</i> =121 (%)	3 <i>n</i> =113 (%)	4 <i>n</i> =47 (%)	Total <i>n</i> =352 (%)	<i>P</i> value
Seborrheic dermatitis	-	24 (19.8)	4 (3.5)	1 (2.1)	29 (8.2)	0.001
Pigmentary disorder	7 (9.9)	9 (7.4)	6 (5.3)	-	22 (6.3)	0.2
Adverse reaction to drugs	-	6 (4.9)	9 (7.9)	7 (10.6)	22 (6.3)	0.01
Nail discoloration	2 (2.9)	2 (1.6)	13 (11.5)	2 (4.2)	19 (5.4)	0.006
Xerosis	1 (1.4)	9 (7.3)	4 (3.5)	4 (8.5)	18 (5.1)	0.04
Diffuse hair loss	2 (2.9)	4 (3.3)	-	6 (12.8)	12 (3.4)	0.001
PPD	-	5 (4.1)	4 (3.5)	1 (2.1)	10 (2.8)	0.4
Psoriasis	1 (1.4)	1 (0.8)	1 (0.9)	1 (2.1)	4 (1.2)	0.9
EPF	-	1 (0.8)	2 (1.8)	-	3 (0.9)	0.5
Graying of hairs	-	-	-	2 (4.2)	2 (0.6)	0.005
Aphthae	-	1 (0.8)	-	1 (2.1)	2 (0.6)	0.3
Beau's lines	-	1 (0.8)	1 (0.9)	-	2 (0.6)	0.8

PPD=Pigmentary purpuric dermatosis; EPF=Eosinophilic pustular folliculitis; WHO=World health organization



patients in spite of adequate antiviral therapy. Other STIs seen were genital warts (5.68%), MC (3.97%) and vulvovaginal candidiasis (1.2%).

## DISCUSSION

During the 12-month study period, 352 patients were seen. The male to female ratio of 2.01:1 was more than that reported previously.<sup>[3]</sup> This could be attributed to the increased awareness among the female population leading to voluntary testing and detection. Overall, candidiasis was the most prevalent dermatological disorder, seen in 57 patients (16.2%). In our study, candidiasis was found to be more common in patients with clinical stage 3 and 4 and in patients with CD4 count <350 cells/mm<sup>3</sup>. There was a statistically significant lower prevalence of candidiasis in patients who were on HAART. This is in line with the previous study by Ulrich *et al.*,<sup>[4]</sup> in which the authors found a decrease in the prevalence of oral candidiasis, from 36.8% to 20.2% after HAART administration. These features reflect the importance of cell-mediated immunity in candidiasis. Prevalence of dermatophytosis (42, 11.9%) in our study was similar to that reported previously.<sup>[3]</sup> The most common dermatophyte infection was onychomycosis, seen in 22 (6.25%) patients. The prevalence of dermatophytosis correlated inversely with the CD4 cell count, and was significantly more common in patients with severe immunosuppression. Like candidiasis, there was a statistically significant lower prevalence of dermatophytosis in patients on HAART. Hence, it can be inferred that dermatophytosis might be considered as a marker of disease progression in HIV-infected patients, and its presence might indicate advanced immunosuppression.

A diagnosis of HS was made in 10.2% patients. It was the most common viral infection in our study. HIV in our subjects was commonly transmitted through sexual activity; therefore, it is not surprising that genital herpes was one of the most prevalent disorders identified. This finding is consistent with previous studies.<sup>[5]</sup> The incidence of HZ was 8.0% in our study. Interestingly, we found HZ to be less frequent among those patients who had initiated HAART. This is in contrast with other reports, where an increasing prevalence of HZ with HAART has been reported due to immune reconstitution.<sup>[6]</sup> Genital warts were seen in 23 (7.5%) patients, which was comparable to previous studies.<sup>[3,5]</sup> We noticed a significant correlation between the increasing incidence of condyloma and advancement through stages of HIV infection. The incidence of pyoderms (8.0%) in our study was lower than that reported by Kumarasamy *et al.*<sup>[3]</sup> In our patients, impetigo and folliculitis were recurrent and persistent, and more resistant to

treatment, requiring higher doses of antibiotics and for a longer period.

The mean CD4 count of patients with dermatophytosis, MC, HPV infection and pyoderms were statistically lower than in patient without these dermatoses. Halder *et al.*<sup>[7]</sup> also found a lower mean CD4 cell count in patients with MC. This signifies the occurrence of these dermatoses with decreasing CD4 counts. However, when patients were grouped into those with CD4 cell counts of less than 200 cells/mm<sup>3</sup> or above, significant association was seen only in the prevalence of dermatophytosis and MC. Hence, presence of dermatophytosis and MC in asymptomatic patients not on HAART can be considered as a proxy indicator for initiating HAART when facilities for CD4 count are not available.

SD has been described as the most common skin condition affecting HIV-infected patients, being observed in 85% of patients during their lifetime.<sup>[8]</sup> SD was found in 22% of our study patients, in contrast to the study by Sharma *et al.*,<sup>[9]</sup> who found a lower prevalence of 4.2% among 200 HIV patients screened. In contrast to the previous reports,<sup>[10]</sup> the incidence of SD was higher in patients who were on HAART; few of them may be explained by IRD. The prevalence of pigmentary disorder in our study was 6.3%. An increase in pigmentation was noted in the oral mucosa, skin and the nails. Some of the cases of hyperpigmentation have been related to zidovudine therapy. However, such pigmentation was noticed in many HIV-positive patients who had never been given zidovudine. Immunohistochemical studies have suggested that there is stimulation of increased pigment production in melanocytes, and other studies have shown increased levels of  $\alpha$ -melanocyte-stimulating hormone in HIV-positive patients.<sup>[11]</sup>

The prevalence of xerosis in our study was 5.1%, in contrast to the very high prevalence reported by Smith *et al.* (75%).<sup>[12]</sup> Involvement of nails in our study was either due to infection or adverse effect of drug or may be idiopathic. We found onychomycosis in 22 (6.3%) patients. This data was similar as in various previous studies.<sup>[5]</sup> But, there was a low incidence of proximal subungual onychomycosis compared with a previous study (1.2% vs. 4.3%).<sup>[13]</sup> Discoloration of nails was seen in 19 (5.4%) patients. The most common pattern of discoloration was longitudinal melanonychia, followed by diffuse nail involvement. Diffuse hair loss was present in 15 (4.3%) patients. Graying of hair was also seen in two patients. None of the patients had straightening of hairs, curly hairs, elongation of eyelashes and hypertrichosis of body

hairs. These are mainly side-effects of zidovudine, and majority of our patients were taking stavudine as first choice among nucleoside reverse transcriptase inhibitor. There was a positive correlation between the stage of HIV and prevalence of xerosis, nail pigmentation, graying of hairs and diffuse hair loss. This may be due to malnutrition and cachexia that is associated with late stages of HIV infection. Cutaneous drug reactions were seen in 6.3% patients, which caused substantial morbidity. Morbilliform rash secondary to nevirapine was the most common type of drug-related eruption, followed by rash secondary to anti-tubercular therapy.

The incidence of STIs in the patients studied (22.15%) was relatively high, herpes genitalis being the most common STI seen in 9.65%. Sarna *et al.*<sup>[14]</sup> in their study of 200 HIV patients found an evidence of genital herpes in 18% of the study subjects. Interestingly, in an earlier study on non-HIV patients from Chandigarh, herpes genitalis was the most common STI observed.<sup>[15]</sup> Other studies from India however showed chancroid or syphilis to be the most common STI in HIV patients.<sup>[16]</sup> This difference could be due to the fact that ours is a tertiary care center and most of the patients referred to us had already been given multiple courses of antibiotics, which take care of bacterial STIs.

Our study was different from most of the previous studies reported from India for the fact that we correlated mucocutaneous manifestation with CD4 counts. The patients were divided in both clinical and recently introduced immunological classification by the WHO, and we tried to stratify the patients according to staging of HIV disease. As half of patients were on HAART, we could analyze the data regarding dermatoses in patients who were on HAART and those who were not on anti-retroviral therapy. A higher proportion of patients taking HAART also explains the lower incidence of infective and malignant disorder in our patients compared with previously reported studies from India.

## CONCLUSION

Results of our study suggest that mucocutaneous findings occur throughout the course of HIV infection. Some of the infectious dermatoses like candidiasis, MC and dermatophytosis are useful clinical predictors for advanced immunosuppression. Dermatoses like MC and dermatophytosis show an inverse relation with CD4 cell count, and these dermatoses can be used as a proxy indicator of advanced immunosuppression to start HAART in the absence of facilities to carry out CD4 cell count. The presentations of mucocutaneous manifestations in HIV patients may be atypical and

less responsive to treatment. Given the relative ease of examination of skin, and because most skin disease are amenable to diagnosis by inspection and biopsy, evaluation of skin remains an important tool in the diagnosis of HIV infection.

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Source of Support: Nil. Conflict of Interest: None declared.