"OVIDIUS" UNIVERSITY OF CONSTANȚA

DOCTORAL MEDICAL SCHOOL

MEDICAL DOCTORAL FIELD

**PhD Thesis**

# DERMATOLOGICAL PATHOLOGY IN HIV INFECTION FROM THE PERSPECTIVE OF THE PREVALENCE, THE ASSOCIATION WITH DEPRESSION, AND THE INFLUENCE OF HIV ON THE QUALITY OF THE SKIN IN SEROPOSITIVE PATIENTS

## Resume

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**TABLE OF CONTENTS**

**Key words:** ***HIV, dermatological diseases, depression, skin quality***

**News and particular aspects of mucocutaneous disorders in HIV infection**

The skin is one of the target organs at all stages of HIV infection. Mucocutaneous diseases are among the top clinical aspects of AIDS, and in some patients these may be the first and only sign of HIV infection, therefore being considered markers of immunosuppression, leading to early diagnosis of HIV infection and the establishment of good management of patients living with HIV / AIDS.

HIV-associated mucocutaneous manifestations are common throughout the evolution of HIV infection and include disorders associated to early HIV disease, infectious (bacterial, viral, fungal, parasitic), and non-infectious disease etiology. The highest frequency of dermatological diseases has been reported in HIV at a CD4 + count <200/ $mm^3$ (1,2)**.**

With the introduction of ART therapy a decline of HIV associated opportunistic skin diseases was reported, as well as an increase in frequency of adverse drug reactions and non-infectious diseases (3,4).

For dermatologists or infectious disease doctors, these clinical manifestations are a diagnostic and therapeutic challenge due to the particularities of dermatoses in HIV+ patients, thus necessitating ongoing investigation of skin diseases related to HIV and the development of clinical-therapeutic correlations.

## STUDY I: Prevalence of mucocutaneous manifestations in patients with HIV infection

## Main objective

The present study aimed to describe the prevalence of skin manifestations in HIV positive patients.

## Secondary objectives

1. To estimate the status of skin diseases in HIV positive patients and to correlate data with CD4 + cell count, viral load and WHO clinical stage of HIV;
2. Evaluation of the frequency of skin manifestations depending on demographics;

3. Determination of the number of dermatological manifestations per HIV+ patient;
4. Investigation of the skin disease frequency according to the ART treatment;

## Material and methods

Between 01.11.2011 - 31.12.2014 an observational study was prospectively conducted on a group of 145 HIV + patients with mucocutaneous manifestations, hospitalized in the Adults HIV Department of the Infectious Diseases Hospital in Constanta, or investigated as outpatients.

**Inclusion criteria**

1. HIV infection confirmed by positive Western-Blot test.
2. Presence of dermatological diseases, diagnosed by the dermatologist.
3. Age $\geq$ 18 years.

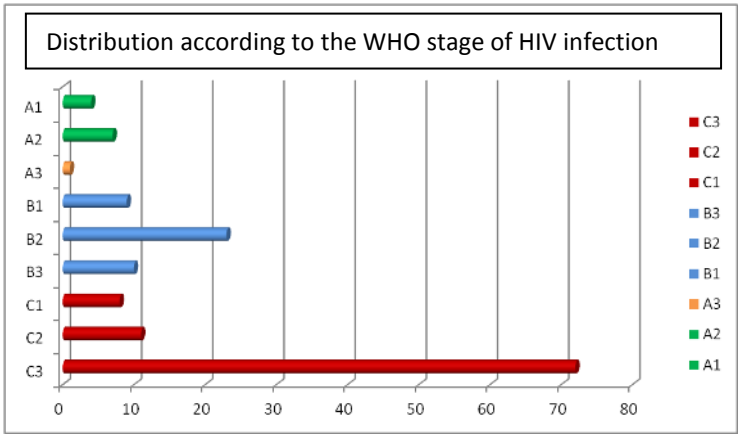
# Results

**General characteristics of the group**

Of the 145 patients with HIV infection and dermatological disorders, enrolled in the study during the considered period, 66 patients (45.51%) were women and 79 (54.48%) men. Of these, the majority of patients, 74 (51.03%) was in the age group 20-30 years old (40 women and 34 men), the category with the highest feminine prevalence. Most patients come from urban areas (96 patients, 66.20%).

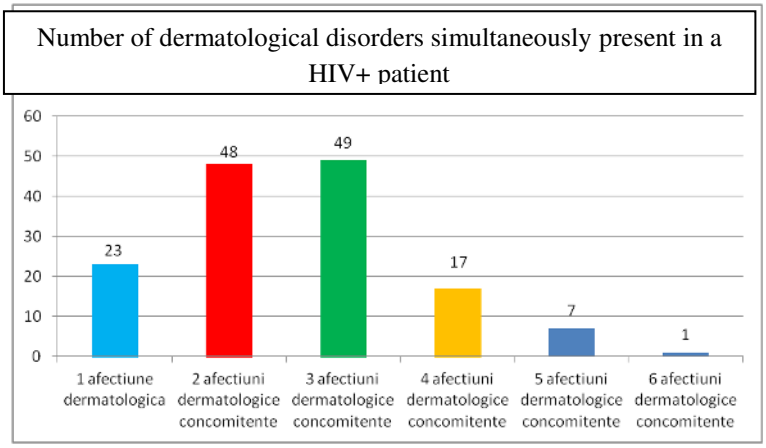
Most patients are classified in clinical stage of disease C (91 patients, 85.10%), especially C3 (49.65%) (Chart 1), and are receiving ARV (81.37%). There is a male predominance in the studied group (54.48%). The main route of HIV transmission was parenteral (46.20%). In addition, most patients come from urban areas (66.20%), do not have a steady job (68.96%) are unmarried (63.44%) and have a low educational level (only 44.13% completed secondary school).

Chart 1. Distribution of patients according to WHO clinical stage of HIV infection




Overall, in this study 375 dermatological diagnoses were established. The number of cutaneous manifestations present in a single patient ranges from 1-6 dermatological diseases with an average of 2 conditions / patient (Chart 2).

Chart 2. Number of dermatological disorders simultaneously present in a HIV+ patient




The prevalence of mucocutaneous manifestations of this study is similar to data reported in medical literature. The spectrum of mucocutaneous manifestations diagnosed in this study is shown in the table, depending on the category of disease and CD4 + count (Table 1).

Table 1. Mucocutaneous manifestations diagnosed in HIV+ patients

| **Category of disease** | **Dermatological disease** | **Total number of patients** | **Prevalence (%)** | **CD4<200** | **CD4 200 - 499** | **CD4 ≥500** |
|---|---|---|---|---|---|---|
| Infections<br>• Fungal | Oral candidiasis<br>Genital candidiasis<br>Tinea corporis | 98<br>9<br>7 | 67,58<br>6,20<br>4,82 | 34<br>3<br>3 | 28<br>2<br>1 | 36<br>4<br>3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Onicomycosis | 6 | 4,13 | 2 | 3 | 1 |
| • Viral | Herpes Zoster | 23 | 15,86 | 11 | 3 | 9 |
| | Varicella | 1 | 0,68 | 0 | 1 | 0 |
| | Herpes simplex | 2 | 1,37 | 2 | 0 | 0 |
| | Molluscum contagiosum | 4 | 2,75 | 1 | 1 | 2 |
| | Warts | 7 | 4,82 | 2 | 4 | 1 |
| | Flat warts | 1 | 0,68 | 0 | 1 | 0 |
| | Epidermodysplasia verruciformis | 4 | 2,75 | 1 | 2 | 1 |
| • Bacterial | Ectima | 1 | 0,68 | 1 | 0 | 0 |
| | Impetigo | 2 | 1,37 | 1 | 0 | 1 |
| | Celulitis | 7 | 4,82 | 2 | 2 | 3 |
| • Parasitic | Scabies | 2 | 1,37 | 2 | 0 | 0 |
| Non-infectious inflammatory diseases | Seborrheic dermatitis | 46 | 31,72 | 14 | 13 | 19 |
| | Contact dermatitis | 3 | 2,06 | 0 | 0 | 2 |
| | Papular pruritic eruption | 1 | 0,68 | 0 | 0 | 1 |
| | Psoriasis | 2 | 1,37 | 1 | 0 | 1 |
| Sexually transmitted diseases | Syphilis | 9 | 6,20 | 2 | 4 | 3 |
| | Condylomatosis | 8 | 5,51 | 4 | 3 | 1 |
| Neoplasia | Kaposi Sarcoma | 3 | 2,06 | 1 | 1 | 1 |
| Other diseases | Cutaneous xerosis | 44 | 30,34 | 10 | 16 | 18 |
| | Acne | 8 | 5,51 | 1 | 3 | 4 |
| | Pruritus | 14 | 9,65 | 3 | 6 | 5 |
| | Melasma | 5 | 3,44 | 1 | 1 | 3 |
| | Postinflammatory hyperpigmentations | 4 | 2,75 | 2 | 2 | 0 |
| | Insect bite | 2 | 1,37 | 0 | 1 | 1 |
| | Sebaceous cyst | 1 | 0,68 | 0 | 0 | 1 |
| | Lipodystrophy | 38 | 26,20 | 12 | 11 | 16 |
| | Lipoatrophy | 27 | 18,62 | 12 | 6 | 9 |
| | Lipohypertrophy | 11 | 7,58 | 0 | 5 | 6 |
| | Urticaria | 10 | 6,89 | 3 | 4 | 3 |
| | Photodermatoses | 2 | 1,37 | 1 | 1 | 0 |
| | Recurrent oral aphthae | 1 | 0,68 | 0 | 1 | 0 |

The most common dermatological manifestations associated with HIV infection, occurred in patients enrolled in the study were oral candidiasis (98 patients, 67.58%), seborrheic dermatitis (46 patients, 31.72%), cutaneous xerosis (44 patients, 30.34 %), lipodystrophy (38 patients, 26.20%) and herpes zoster (23 patients, 15.86%).

The presence of oral candidiasis is statistically associated with the value of CD4+ T lymphocytes <200 cells / $mm^3$ ($p = 0.028$) and levels of CD4 + T lymphocytes under 200 cells / $mm^3$ increase the risk of developing oral candidiasis by 1.3 times (95% CI: 1.1 - 1.6).

For patients with detectable viral load statistically significant differences were observed depending on the presence of oral candidiasis (Median 25,600 copies / ml, P25% 3313-291237 -

P75% in patients with oropharyngeal candidiasis, as opposed to patients without oral candidiasis; p = 0.042, non-parametric Mann Whitney test U).

Seborrheic dermatitis shows a male predominance in HIV+ patients, highly statistically significant (p <0.00001) and the relative risk of having seborrheic dermatitis is 2.3 times (95% CI: 1.7 to 3.0) higher in HIV + men against women.

The average age varies significantly in HIV patients with seborrheic dermatitis (40.21 ± 13.69 years) and those without seborrheic dermatitis (33.62 ± 10.61 years). In seropositive patients with seborrheic dermatitis a statistically significant difference was observed, according to the initiation of antiretroviral therapy, respectively between naive patients and those who had at least one ARV regimen (p = 0.002). Thus, the relative risk of seborrheic dermatitis is 2.4 times (95% CI 1.5-3.7) increased in patients who are not on ARV therapy.

Applying the T test for equality of means showed a highly statistically significant difference regarding the duration of HIV infection (p = 0.001) between patients with lipodystrophy (14.06 ± 7.10 years) and those which do not present with the lipodystrophy syndrome (9.92 ± 7.52 years). In addition, the percentage of those with lipodystrophy who initiated antiretroviral therapy (29.7%) is significantly higher than the percentage of naïve patients (0%), p = 0.006 (Fisher exact test). The relative risk of lipodystrophy increases of 1,189 times after initiation of antiretroviral therapy (95% CI: 1.095 to 1.291).

There is a statistically significant difference according to the stage of HIV among patients with dry skin and those without xerosis (p = 0.005 likelihood ratio), the percentage of patients with dry skin in HIV stage A or B being significantly higher than in those in clinical stage C (40.7% vs. 24.2%, p = 0.036, Chi Square test).

Regarding antiretroviral treatment, percentage of patients with dry skin who are receiving antiretroviral treatment is significantly lower than that of patients who have not started or stopped antiretroviral therapy (24.6% vs. 55.6%; p = 0.002, Chi Square test), and administering ARV is a protective factor for developing cutaneous xerosis (RR: 0.442, 95% CI: 0.279 to .702).

Regarding shingles, a significant difference (p <0.0001) was highlighted among HIV + patients with herpes zoster depending on the presence of HBV coinfection (53.8% versus 12.1% without HBV coinfection).

## Discussions

According to recent medical data (5,6) seborrheic dermatitis and candidiasis are the most common oral mucocutaneous manifestations in HIV+ patients. In our study, the prevalence of these conditions was similar to that reported worldwide, the most common dermatological pathology registered being oral candidiasis (67.58%), followed by seborrheic dermatitis (31.72%). Interestingly, the 3rd in order of frequency was cutaneous xerosis, with a percentage of 30.34%, almost double than that reported in other studies (4). In addition, the results showed that 26.20% of patients had lipodystrophy and 15.87% had herpes zoster.

The prevalence of oral candidiasis in HIV-infected patients in the present study (67.58%) was higher compared to other studies (44.2% (7), 32.22% (8), 53.1% (9) 32 25% (10) 37.8% (11) 11.11% (12)). The emergence of oral candidiasis was statistically associated in this study to CD4 + cell levels below 200 cells/ $mm^3$, which was reported in other recent studies (7,9,10,13,14,15) where the CD4+ level was inversely proprotional to the frequency of oral candidiasis, most HIV+ patients with oral candidiasis having CD4 + values <200 cells /$mm^3$. In addition, the results of the current study highlight that CD4 + T lymphocyte values <200 cells /$mm^3$ are a risk factor for developing candidiasis, increasing the risk 1.3 times.

The present study indicates a high prevalence of seborrheic dermatitis in HIV + patients, 31.72%, compared to the general population (16,17); also, the male predominance is still maintained (n = 46, M: F = 41: 5). Male gender proved to be a risk factor in the development of seborrheic dermatitis, the relative risk being 2.3 times higher in HIV+ men than in women.

According to the literature, the average age of HIV+ patients with seborrheic dermatitis (40.21 ± 13.69 years) is significantly higher than in HIV+ patients without seborrheic lesions (33.62 ± 10.61 years), seborrheic dermatitis occuring in adults with a peak incidence between 40-70 years (16,17).

In terms of ARV therapy, the absence of ARV treatment is considered a risk factor for the occurrence of seborrheic dermatitis, increasing the risk 2.4 times ($p = 0.002$).

Referring to cutaneous xerosis, the prevalence of dry skin is 30.34%, which is commonly seen in clinical stages A and B (WHO). Moreover, it is interesting to note that the presence of HBV coinfection is associated with dry skin development, a percentage of 53.8% HIV-HBV coinfected patients having dry skin, against 28% of the patients only with HIV infection.

However, if we consider the relationship between ARV treatment and the presence of dry skin, HAART administration is a protective factor for developing dry skin conditions, reducing the risk of xerosis of 0.44 times. Mean CD4 + count in patients with dry skin in this study was higher than that reported in other studies (497 cells/ $mm^3$ vs. 376 cells/$mm^3$) (4).

According to the data published so far, about 40% of HIV+ patients develop lipodystrophy in 1-2 years after initiation of HAART (17), and the prevalence of lipodystrophy syndrome varies between 10-80% (18,19). Similarly, in this study there was a prevalence of the lipodystrophy syndrome of 26.20%. In addition, the duration of HIV infection was significantly higher in patients with lipodystrophy (14.06 ± 7.1 years) than in those without this syndrome (9.92 ± 7.52 years), which supports previously reported data, that state that the long duration of ARV therapy with PIs and / or NRTIs causes lipodystrophy. In this study, most ARV schemes (4 of 6) comprise at least one IP and one NRTI. Moreover, the initiation of ARV therapy is a risk factor for the development of lipodystrophy, increasing the risk 1.2 times.

According to the literature, about 25% of HIV+ patients had at least one episode of herpes zoster, described as an early indicator of HIV infection (20). In our study, the prevalence was lower (15.87%). Statistically, it was highlighted an association between the presence of HBV-shingles coinfection that could be further explored in subsequent studies aimed to precisely determine the virus level and the impact of concomitant HBV antiviral treatment.

Of specific AIDS markers were reported 3 cases of Kaposi's sarcoma and a case of papular pruritic eruption, dermatoses which have a much higher prevalence in other studies (16,21,22). Although the incidence of STDs is rising in HIV+ patients, almost 70% of them having at one point positive serology for syphilis (4), syphilis prevalence in our study was only 6.20%. However, there were 8 cases of warts (5.51%). Important to note is the presence of acquired epidermodysplasia verruciformis in 4 patients (2.75%), which is a rare genodermatosis (23).

## STUDY II: Comparative study of depression in HIV+ patients with associated dermatological diseases and in HIV+ patients without mucocutaneous manifestations

### Main objective

The aim of this study is to determine the prevalence of depression in HIV + patients with associated dermatological pathology compared with HIV+ patients without mucocutaneous manifestations, and to identify risk factors associated with the risk of depression.

### Secondary objectives

1. Determining correlations between the most common dermatological disorders in HIV + patients and the final score of the Beck scale of depression (average, major items).
2. Establishing differences between the degree of depression in patients with dermatological disorders associated with HIV infection and HIV + patients without mucocutaneous manifestations.

### Material and methods

During 01.01.2014 - 31.12.2014 we conducted a prospective cross-sectional, controlled (control group) study, on a group of 29 HIV + patients with associated dermatological pathology (Group A) and a control group of 37 HIV + patients without mucocutaneous manifestations (Group B).

**Inclusion criteria group A:**

- age ≥ 18 years;
- positive HIV serology;
- signing informed consent;
- HIV transmission route – parenteral;
- undergoing ARV tratament;
- presence of dermatological diseases diagnosed by a dermatologist;

**Inclusion criteria group B:**

- age ≥ 18 years;

- signing informed consent;
- HIV transmission route – parenteral;
- undergoing ARV tratament;

For depression screening and evaluating the degree of depression, study participants completed the Beck Depression questionnaire, with 21 questions. Each answer corresponds to a score ranging from 0-3, and the total amount is within the range of 0 - 63. A final score between 14-19 indicates mild depression, while a score between 20-28 shows moderate depression, and over 28 severe depression. For values less than 14 is considered that the patient does not show signs of depression.

## Results

### General features

**Group A** consisted of 29 patients with HIV infection and dermatological disorders, predominantly female (58.62%) (F: M = 5:12 p.m.), the age group 20-30 years being best represented (25 patients, 86. 20%). Regarding HIV status, all subjects were diagnosed with stage C WHO, mostly assigned to stage C3 (72.41%). In terms of viral load 51.72% of patients had undetectable values and 48.27% of patients had detectable viral load, ranging between 134-1657723 copies/ml. The CD4+ level in the day of the examination was <200 cells /$mm^3$ for 10 patients (34.48%), between 200-499 cells / $mm^3$ for 6 patients (20.68%), and > 500 cells/ $mm^3$ in 13 patients (44.82%). Five patients had HBV coinfection. In terms of socio-economical status, most patients are unmarried (89.65%) and do not have a stable job (79.31%) and in terms of educational level the last school graduated was secondary school (44.82%) or high school (51.72%). All patients had been HIV infected parenterally and were currently on ARV treatment.

**Group B** consisted of 37 HIV+ patients without dermatological manifestations, with a slight male predominance (56.75%) (F: M = 16:21), the age group 20-30 years being best represented (35 patients, 94.59%). Most patients were in WHO stage B and C of HIV infection, and the most prevailing was stage C3 (70.27%). Viral load was undetectable in 27 patients (72.97%) and only 10 patients were reported with values between 50-171376 copies /ml. CD4+ counts <200 cells/$mm^3$ were recorded in 5 patients (13.51%), between 200-499 cells/$mm^3$ in 15 patients (40.54%) and 17 patients (45.94%) had a the level of CD4+ higher than 500 cells/$mm^3$.

Ten patients had HBV coinfection and one patient was HCV coinfected. Most patients do not have a job (54.05%), are unmarried (97.29%) and had graduated 12 classes (48.64%). The route of HIV transmission was parenteral for all subjects. All patients were under ARV therapy.

The main mucocutaneous manifestations diagnosed in group A patients were, in order of frequency: oral candidiasis, lipoatrophy, lipohypertrophy, seborrheic dermatitis, dry skin and pruritus. In total, 79 dermatological diagnoses were established.

The percentage of HIV + patients with oral candidiasis and depression was significantly higher than that of patients without depression (68.4% versus 19.1%, $p < 0.0001$) and risk of depression in these patients was 4.3 times higher (95% CI: 1.9 to 9.8). A statistical correlation between the presence of seborrheic dermatitis and depression in patients with HIV was also identified.

Lipodystrophy syndrome increases the risk of depression by 2.3 times (RR = 2.308; 95% CI: 1.125 to 4.735; $p = 0.039$). The results show the existence of a relative risk of depression 3.9 times higher among patients with herpes zoster, as opossed to HIV+ patients without shingles (95% CI: 2.579 to 6.012; $p = 0.021$).

Overall, the percentage of patients with dermatological pathology and depression was significantly higher ($p < 0.0001$) than that of patients with depression alone, without skin diseases (94.7% vs. 23.4%).

Regarding oral candidiasis, there is a statistically significant difference ($p = 0.002$) between the percentage of patients with oral candidiasis and the results of Beck score, specifically among those without signs of depression (19.1%) and those with severe depression (75%).

There was a highly significant statistical difference ($p < 0.0001$) between the average value of Beck score in HIV+ patients with associated dermatosis ($16.07 \pm 10.74$) and in HIV+ patients without skin pathology ($5.08 \pm 5.08$ ).

The mean value of Beck score was significantly higher in patients with oral candidiasis ($15.5 \pm 10.76$,), than in those without ($7.11 \pm 7.86$) ($p = 0.003$). Seborrheic dermatitis patients experienced a higher Beck score average ($20.83 \pm 10.94$) than patients without seborrheic lesions ($8.82 \pm 8.96$) ($p = 0.003$).

A statistically significant difference (p = 0.044) was identified in the lipodystrophy syndrome, between the average Beck score in patients with lipodystrophy (15.27 ± 12.28) and in patients without the syndrome (8.84 ± 8 85).

In terms of sexual activity, there was a statistically significant difference (p <0.0001) in HIV+ patients with associated dermatological pathology, depending on the answer to “sex” item, among those without affected sexual activity (23.3%) and those in whom sexual activity was severely affected (100%). Similarly, the presence of oral candidiasis was significantly associated (p = 0.005) to the response on the ”sex” item, with differences being reported between patients without affected sexual activity (18.6%) and those in which sexual activity was slightly (66.7 %) or moderately affected (62.5%).

Furthermore, in patients with HIV-associated skin diseases, a statistically significant association (p <0.0001) with responses to the item "sleep" was shown, between patients without sleep disorders (23.7%) and those with moderate ( 100%) or severe (100%) disturbance of the sleep.

In HIV+ patients with dermatological diseases there is a statistically significant difference between the average CD4 + count in patients with depression (356 ± 346 cells/$mm^3$) and the average count in those without depression (661 ± 422 cells/$mm^3$) (p = 0.043). Also, in the group of HIV + patients with skin pathology there was a significantly statistic difference between the mean value of CD4 + and Beck score value (p = 0.05), a CD4+ level below 200 cells /$mm^3$ being associated with an average Beck score value of 21.4 ± 10 as oppossed to 10.2 ± 13.26, registered at levels of CD4+ above 200 cells/$mm^3$.

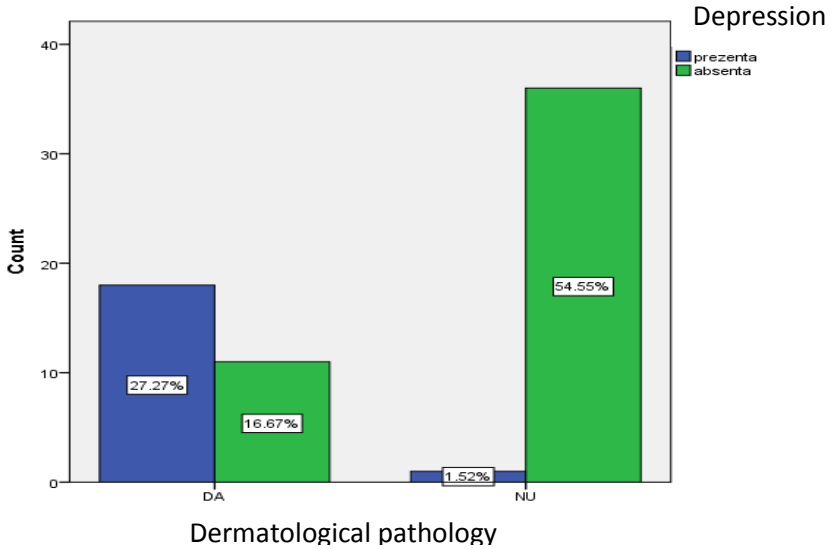
For the group of HIV+ patients with skin diseases there is a significant difference between the average Beck scores in patients with detectable viral load (20 ± 12) and in patients with undetectable viremia (12.4 ± 8.1) (p = 0.05) .

## Discussions

According to the medical literature, depression is the most common neuropsychiatric comorbidity among HIV+ patients and can occur at all stages of HIV infection, being considered a negative prognostic factor in terms of quality of life, adherence and response to treatment, disease progression and mortality (24) .

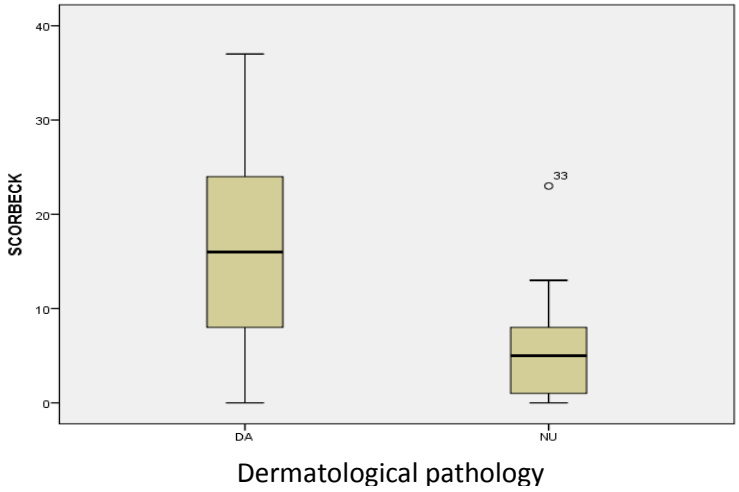
The prevalence of depressive symptoms remains high (14.2% -47%), for both patients on ARV therapy, and naïve (25, 26, 27, 28). According to a meta-analysis, the frequency of major depressive episodes is 2 times higher in HIV + patients vs. HIV- persons (29). In agreement with these observations, prevalence of depression in HIV+ patients with dermatological pathology in this study was 27.27%, significantly higher than that recorded in HIV+ patients without mucocutaneous disorders (Chart 3).

Chart 3. Prevalence of depression in HIV+ patients with associated dermatological pathology




Mean Beck score values differ significantly between patients with dermatological pathology (16.07 ± 10.74) and those without mucocutaneous manifestations (5.08 ± 5.08) ($p < 0.0001$, t test for equality of means), indicating that the presence of skin diseases associated with HIV infection have a strong impact on psychological status, being involved in the occurrence of depression (Chart 4).

Chart 4. Average values of Beck score based on the presence of dermatological pathology




In addition, this study underlines the important association between moderate depression and the presence of dermatological diseases associated to HIV infection. We have also determined a series of risk factors for developing depression. Thus, the risk of developing depression is 4.3 times higher in patients with oral candidiasis, and the presence of herpes zoster involves a relative risk of depression 3.9 times higher for these patients.

According to a study on relationship between lipodystrophy and quality of life, the lipodystrophy syndrome in HIV+ patients lowers self-esteem, causes psychological distress and may lead to depression (30). Our results support these data, lipodystrophy syndrome increasing the risk of depression by 2.3 times in HIV+ patients. Moreover, the average Beck score in patients with lipodystrophy (15.27 ± 12.28) was significantly higher compared to the values registered in patients without lipodystrophy (8.84 ± 8.85), indicating a greater degree of depression in patients with lipodystrophy.

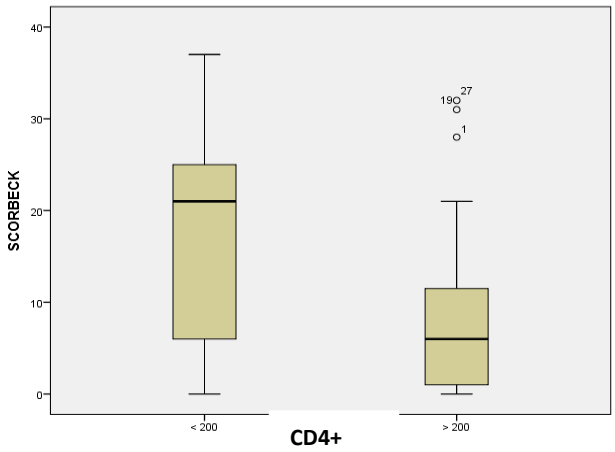
Similarly, the average Beck score in the presence of oral candidiasis (15.5 ± 10.76) was higher than the average values for patients without candidiasis (7.11 ± 7.86) ($p = 0.003$). Regarding seborrheic dermatitis, patients with seborrheic lesions showed higher mean values of Beck score (20.83 ± 10.94), than those without seborrheic dermatitis (8.82 ± 8.96).

Overall, in this study, dermatological pathology related to HIV infection was associated with higher mean values of Beck score, thus being correlated with a higher degree of depression compared to HIV+ patients without skin diseases, which confirms the study hypothesis.

In previous studies, the presence of depression in HIV+ individuals is associated with advanced stages of disease (31) and with low CD4+ counts, thus being more frequent in patients

with baseline CD4 + counts <150 cells / $mm^3$ (25, 28). Similarly, in our study, HIV + patients with skin diseases and depression show a mean CD4+ count lower (356 ± 346 cells/$mm^3$) than those the mean value in those without depression (661 ± 422 cells /$mm^3$). In addition, CD4+ counts less than 200 cells/$mm^3$ were correlated with a higher average Beck score (21.4 ± 10) compared to Beck score values associated with CD4 + levels of less than 200 cells/$mm^3$ (13.26 ± 10.2) (Chart 5). Also, the average Beck score value in patients with detectable viremia is higher than in those with undetectable viral load (20 ± 12 vs. 12.4 ± 8.1) for HIV+ patients with associated dermatological diseases. These observations indicate that the association between depression and dermatological pathology is not random, being influenced by low immune status, due to both HIV infection and associated skin diseases.

Chart 5. Mean value of Beck score depending on the CD4+ count (cells/$mm^3$)




According to a recent study, sleep disorders were reported in 47% of HIV+ patients, predominantly women with moderately severe symptoms of depression. Other factors associated with sleep disorders have included the lack of a stable job and absence of a life partner (32). Similarly, in the present study, the results for the item "sleep" on the Beck score revealed the presence of sleep disorders in 68.96% of HIV+ patients with dermatological pathology. In addition, there were significant differences in the degree of sleep disturbances in these HIV+ patients with dermatological disorders, predominantly moderate or severe sleep disorders.

As indicated by data from the medical literature, there is a significant correlation in all areas between depression and decreased quality of life of HIV+ patients, including sexual

activity, in which decreased libido and ejaculation disorders are commonly reported (33). The current study reveals a significant impairment (moderate and severe) of sexual activity in 34.48% of HIV + patients with dermatological diseases (n = 29) versus those without mucocutaneous lesions. Interestingly, a considerable proportion of patients with oral candidiasis (59%, n = 22) recorded a statistically significant (p = 0.005) impairment of sexual activity, mild and moderate.

## STUDY III: Skin quality evaluation in HIV-infected patients, compared to HIV- control group, in terms of level of skin hydration, transepidermal loss of water and sebum quantity

### Main objective

The objective of the study is to assess the quality of skin in HIV positive patients compared to a control group of healthy participants, HIV negative, in terms of the level of skin hydration, transepidermal water loss and the quantity of sebum.

### Secondary objectives

1. Identification of risk factors that distort the balance of skin in HIV+ patients.
2. Establishing correlations between clinical diagnoses of cutaneous xerosis and seborrheic dermatitis and skin hydration level, namely sebum level in HIV+ patients.

### Material and methods

Between 04.01.2015 – 30.06.2015 we conducted an experimental, prospective, non-invasive study, controlled (control group), on a group of 54 HIV+ patients (group A) and a control group of 54 healthy participants, HIV- (group B).

**Inclusion criteria group A:**

- age ≥ 18 years;
- HIV positive serology;
- signed informed consent;

**Inclusion criteria group B:**

- age ≥ 18 years;
- signed informed consent;

Skin quality testing was performed with non-invasive medical devices CK-MPA 580 manufactured by Courage-Khazaka Electronic GmbH, Germany, using the following probes:

- ✓ Corneometer probe CM 825 to measure skin hydration;
- ✓ Tewameter probe TM 300 to measure transepidermal water loss (TEWL);
- ✓ Sebumeter box for SM 815 measurements of sebum;

Measurements were performed under optimal and constant ambient temperature and humidity ($T^0$ = $20^0$C, humidity 40-60%) after an interval of 10-20 minutes of rest for every participant, the necessary time for adjustment to the ambient.

The principle of the Corneometer method of measuring skin hydration, internationally recognized, is the capacitance method , based on the difference between the dielectric constant of water (81) and other substances, by recording the capacitance of a dielectric medium. Interpretation of results from testing with Corneometer is shown in Table 2.

Table 2. Interpretation of the results obtained with the probe Corneometer CM 825

| Registered values – Corneometer (UA) | Interpretation of the results – evaluation of skin hydration |
|---|---|
| **< 30** | Very dry |
| **30-45** | Dry |
| > 45 | Sufficiently hydrated |

The principle of measurement with Tewameter is based on the Law of diffusion, from physics. Inside the probe there are two pairs of sensors (temperature and relative humidity) which allow indirect measurement of the density gradient, which is then analyzed by a microprocessor. Interpretation of results from testing with Tewameter is shown in Table 3.

Table 3. Interpretation of results obtained with the probe Tewameter TM 300

| Registered values – Tewameter (g/h/m2) | Interpretation of the results – evaluation of transepidermal water loss |
|---|---|
| **< 10** | Very good condition |
| **10-15** | Good condition |
| 15-25 | Normal condition |
| 25-30 | Bad condition |
| >30 | Very bad condition |

Sebumeter measuring principle is based on the photometric method, an internationally recognized method which uses a photometer with oil stain and is not sensitive to moisture. The results are interpreted in Table 4.

Table 4. Interpretation of results obtained by SM Sebumeter Box 815

| Registered values – Sebumeter µg/cm2 | Interpretation of the results – sebum measurement |
|---|---|
| **< 70** | dry |
| **70-140** | normal |
| > 140 | oily |

## Results

### General features

**Group A** consisted of 54 patients with HIV infection, predominantly females (57.40%) (M: F = 31:23), the age group 20-30 years being best represented (29 patients, 53.70% ). Regarding HIV status, most subjects are classified as stage C (64.81%), especially C3 (53.70%). In terms of viral load the majority of patients had undetectable levels (36 patients, 66.66%), only one third of patients presenting with detectable viral load, with values between 37-1053491 copies /ml. The CD4 + level at the moment of clinical examination was <200 cells/$mm^3$ for 12 patients (22.22%), between the 200-499cells/$mm^3$ for 26 patients (48.14%), and > 500 cells/ $mm^3$ for 16 patients (29.62%).

**Group B** consisted of 54 healthy subjects HIV- with a female predominance (53.70%) (M: F = 29:25), age group 20-30 is best represented (30 patients, 55.55%).

The results indicate a statistically significant difference between the average values obtained at the Corneometer measurement in HIV+ patients (36.87 ± 17.97) and the mean values for HIV- patients (51.72 ± 16.89) (p = 0.0001 test t for equality of means). The percentage for the Corneometer index differs significantly according to HIV status, thus, 63% of the HIV- patients have hydrated skin as compared to 20.4% of HIV+ patients (p <0.0001).

Regarding the degree of hydration of the skin, measured by Corneometer, there is a statistically highly significant difference (p <0.0001) in people with dry skin, "corneometer <45", between HIV + patients (79.6%) and HIV- persons (37%). Thus, the relative risk of having dry skin is 2.79 times higher in HIV + patients (95% CI: 1.626 to 4.794).

After testing with Tewameter, there is a statistically significant difference (p = 0.001) between TEWL median in HIV+ patients [median: 9.7; (P25% -P75%: 7.75 to 15.70)] and in HIV- patients [median: 7.8; (P25% -P75%: 5.4 to 9.2)]. At the same time, there is a statistically

significant low positive correlation between the age of the patients and TEWL value (r = 0.372, n = 108, p = 0.0001).

The presence of HIV infection was statistically associated with Tewameter index value (interpreted as "very good skin condition : <10", "good condition: 10-15", "normal skin: 15-25", "bad skin condition: 25 -30 "," very bad skin condition> 30 "), and this association is more important for " bad skin condition " and "very bad skin condition" in HIV + patients (100%) than in HIV- patients (0 %) (p = 0.006).

T-test for Equality of Means (Equal variances assumed) shows a statistically significant difference (p = 0.002) between the mean values of the Corneometer index in HIV+ patients with dry skin (19.38%) and HIV+ patients without dry skin (39.91%).

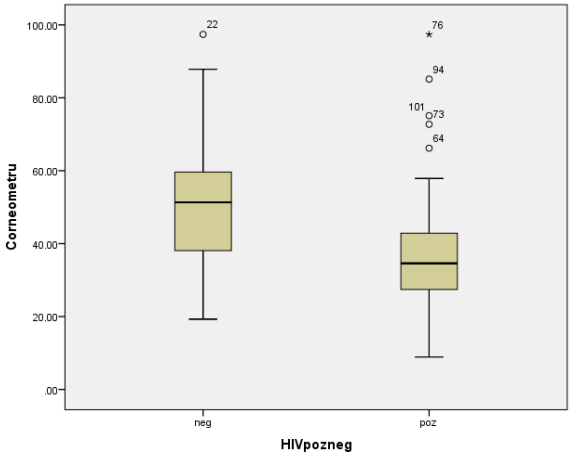
In HIV+ patients tested with the Sebumeter Box there is a statistically significant difference (p = 0.001) between the average sebum index in patients with seborrheic dermatitis (157.11 ± 43.02) and those without seborrheic lesions (92.73 ± 51.90 ).

## Discussions

Cutaneous xerosis is one of the most common skin disorders in patients with HIV infection, as it was highlighted in study I (30.34%) and in the medical literature (34,35,36) being associated with impaired barrier function of the stratum corneum of the skin (37).

Results show that the average Corneometer index in HIV+ patients is lower than the average value in HIV- individuals (36.87 ± 17.97 vs. 51.72 ± 16.84, p = 0.0001) (Chart 6).

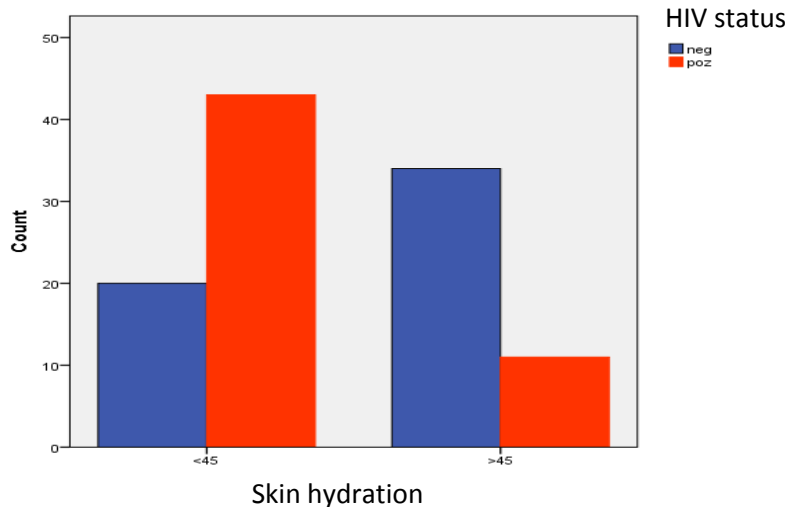
Chart 6. Average Corneometer index based on HIV status




In addition, only 20.4% of HIV patients have normal skin hydration, as compared to 63% in the control group, which means that HIV positive patients have a higher degree of cutaneous

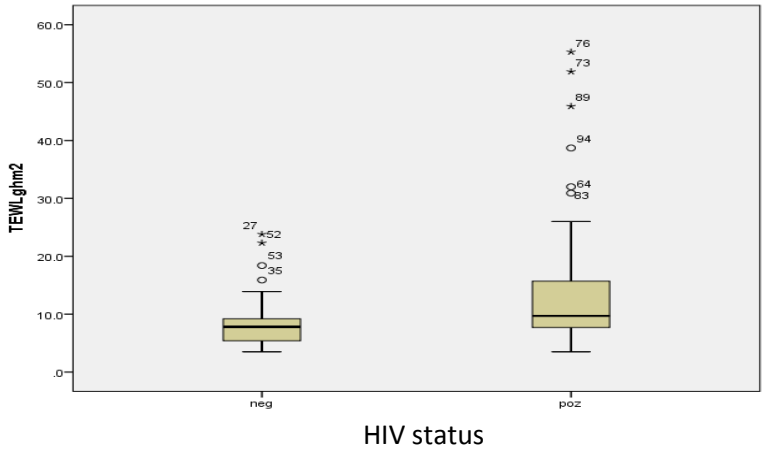
xerosis as compared to HIV- (p <0.0001) (Chart 7). Moreover, HIV infection is a risk factor for dry skin, increasing the risk of cutaneous xerosis by 2.8 times.

Chart 7. The degree of skin hydration based on HIV status



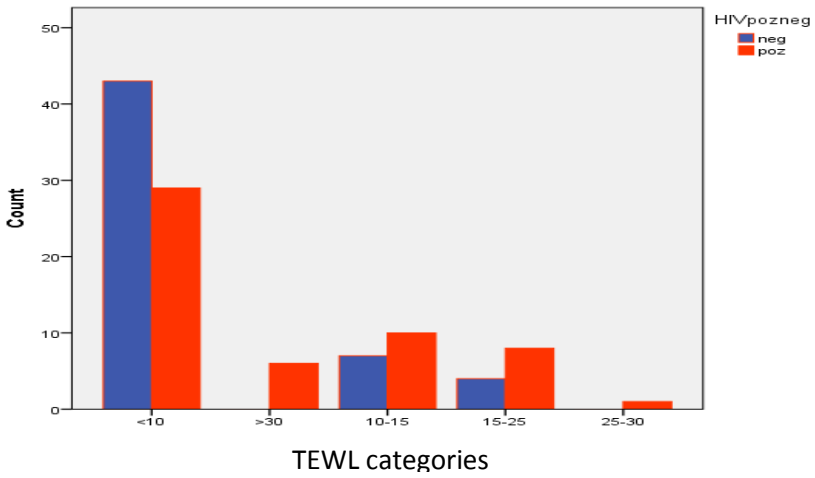

Thus, regarding Tewameter tests, the median value of TEWL for HIV+ patients is significantly higher than that of the control group (9.7 vs. 7.8, p = 0.001), indicating a higher transepidermal water loss in HIV+ patients compared with HIV- persons (Chart 8).

Chart 8. Mean index of Tewameter based on HIV status



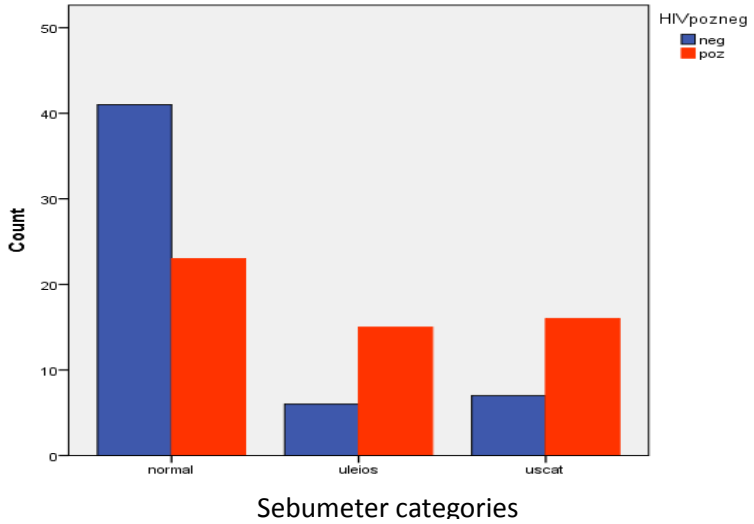

Transepidermal water loss test results, plotted by categories, reveal that the percentage of HIV+ patients who have a very good skin quality index (<10) is lower than that of HIV- individuals. Also, a more significant transepidermal water loss (translated by elevated index TEWL) was reported in HIV+ than in HIV- individuals, and TEWL values showing poor and very poor skin quality were only noted in HIV+ patients (Chart 9).

Chart 9. Tewameter test results based on HIV status




The association between HIV infection and the value of the Sebumeter index (interpreted as "normal skin", "oily skin", "dry skin") was plotted, this association being more important for "oily skin" in HIV+ patients (71.4% ) than in HIV- patients (28.6%) (p = 0.002) (Chart 10).

Chart 10. Sebumeter test results based on HIV status




Regarding the average Corneometer index in HIV+ patients with clinical diagnosis of dry skin, it is significantly smaller than that identified in HIV+ patients without clinically evident xerosis (19.38 ± 9.72 vs. 39.91 ± 17 37). Also, HIV+ patients with cutaneous xerosis were registered with skin hydration values of less than 30, a significantly higher percentage than that seen in HIV- patients. This observation highlights the correlation between clinical diagnosis of cutaneous xerosis and Corneometer values of less than 30, indicating very dry skin.

Similarly, for HIV+ patients diagnosed with seborrheic dermatitis the average Sebumeter ratio is significantly higher than in HIV+ patients without seborrheic lesions (157.11 ± 43.02 vs. 92.73 ± 51.90), a result that supports the relationship between the presence of seborrhoeic dermatitis and increased levels of sebum.

For the HIV- control group a difference between gender and amount of sebum was demonstrated, healthy men having more oily skin than women; there is also a correlation between the degree of transepidermal water loss (expressed by an elevated TEWL index) and old age in HIV- patients.

## General conclusions and perspectives

This thesis aimed to study the dermatological pathology associated to HIV infection, in terms of prevalence, association with depression and HIV influence on the skin quality in HIV+ patients.

Although the medical progress in recent years offers new perspectives in HIV infection, particularly due to treatment options, dermatological diseases associated with HIV continue to have a major negative impact, as evidenced by decreased quality of life of these patients.

Dermatological conditions in patients with HIV infection are often neglected by patients, although they represent is a very common health problem with psychosocial impact. Also, mucocutaneous manifestations associated with HIV tend to have a more severe clinical aspect, longer evolution, burdened by frequent relapses, and are often rebellious to treatment. Thus, the need to study the clinical aspects of dermatoses in HIV+ patients becomes increasingly obvious, in order to identify risk factors involved and to establish clinical and therapeutic correlations or association with other pathologies. An important element contributing to an increased prevalence of mucocutaneous manifestations in HIV+ is the Romanian cohort, with specific characteristics (young patients with long-term evolution of HIV, commonly transmitted by iatrogenic means, often with HBC or HCV coinfection).

Therefore, this paper has proposed to establish the prevalence of current dermatological diseases associated with HIV and to determine the correlations between the status of skin diseases in HIV+ patients and the CD4 + cell count, viral load, clinical stage of HIV and ART. In addition, work has focused on the impact that the association of dermatological pathology and HIV infection has on the development of depression among HIV+ patients compared to HIV+

individuals without skin diseases. It was also desirable to compare the skin quality between patients HIV+ and HIV- individuals.

In the first study presented, the results showed that skin diseases occur with high prevalence among HIV+ patients, and therefore early detection and carefull follow-up are mandatory. Dermatological pathology with the highest prevalence is represented, in order of frequency, by oral candidiasis, seborrheic dermatitis, cutaneous xerosis, lipodystrophy and herpes zoster. It is interesting to mention that dry skin was evidenced by a frequency double than that reported in the medical literature.

This study confirms that skin diseases in HIV+ patients occur more frequently as HIV infection progresses to stage WHO C3, and the level of CD4 + cells falls below 500 cells /mm3, as described in the literature.

An important element highlighted by this study is the identification of the risk factors for dermatological diseases associated to HIV. Thus, the risk of oral candidiasis increases in the context of a CD4 + count lower than 200 cells/$mm^3$. Regarding seborrheic dermatitis, its main risk factors are male gender and lack of ARV administration. On the other hand, the initiation of ARV was shown to be a risk factor for lipodystrophy. Surprisingly, administration of HAART is a factor of protection for dry skin. Moreover, it is interesting to note that the presence of HBV-HIV co-infection is associated with the development of dry skin and herpes zoster, observation that could be further investigated in large studies aimed to monitor viremia and impact of concomitant treatment with HBV antivirals. Contrary to our expectations, and to the results from previous studies, the prevalence of sexually transmitted diseases was low, but we reported the presence of a rare genodermatoses, epidermodysplasia verruciformis.

Assuming that the quality of life in HIV+ patients is generally low, the second study confirmed that in the context of skin diseases associated to HIV infection,the prevalence of depression increases as compared with that recorded in HIV+ without mucocutaneous manifestations. Also, HIV+ patients with dermatological diseases associate moderate and severe depression, as confirmed by significant correlations with dermatological pathology for selected items of Beck scale. Furthermore, in patients with HIV associated dermatoses a significant disturbance of sexual activity was observed, as well as sleep disorders.

Particular attention should be paid to the risk factors for depression, namely, the presence of oral candidiasis, herpes zoster and lipodystrophy, which increase the risk of depressive

disorders in HIV+ patients. It is also important to mention that depression related to dermatological diseases associated with HIV infection correlates with advanced HIV disease or with low CD4 + counts and high viral load.

The originality of the second study consists in the evaluation of the features of depression in HIV+ patients in terms of association with dermatological pathology, association which so far was not explored in the medical literature.

The last part of the thesis aimed to evaluate through an original approach the skin quality in HIV+ patients compared with a control group of HIV- healthy participants, in terms of level of skin hydration, transepidermal water loss and quantity of sebum.

By using a noninvasive method, we evaluated the parameters that influence the quality of the skin, and it has been proven that HIV+ patients have a higher degree of cutaneous xerosis, compared with healthy individuals. In addition, HIV infection has been confirmed as a risk factor for the occurence of dry skin conditions.

Benchmarking HIV + and HIV- groups confirmed that the transepidermal water loss that occurs in HIV+ patients is higher than in healthy individuals. This loss of water is responsible for a poor quality or very poor quality of the skin, reported only in HIV+ patients.

Clinical diagnosis of cutaneous xerosis was confirmed by low values of the hydration index, the skin of HIV+ patients being very dry. At the same time, seborrhoeic dermatitis lesions are associated with an increased level of sebum. Contrary to out expectations, no correlation could be established between the degree of immunosuppression and the skin quality of HIV+ patients, requiring further studies on larger groups of patients to better evaluate the possible association.

Dermatological diseases associated with HIV infection, with a vast clinical picture and a powerful negative psychological impact, represent in modern medicine a topic of great interest to the international scientific medical community. In conclusion, considering the results of the three studies, this thesis can be a valuable tool in early diagnosis of dermatological manifestations in HIV+ patients and in decreasing the morbidity associated with HIV related dermatological pathology.

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