

# Perspectives on skin disorder diagnosis among people living with HIV in southeastern Romania

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**Abstract.** The beginnings of the human immunodeficiency virus (HIV) pandemic are closely linked to dermatological conditions. A large part of the population living with HIV (PLWH) has a series of skin conditions that determine at some point, a visit to the dermatologist. The introduction of highly active antiretroviral therapy (HAART) more than 20 years ago has diminished the range of dermatological conditions, with improved immunosuppression of CD4 lymphocytes. The study aimed to describe the prevalence of the diagnosed type of skin changes in PLWH receiving antiretroviral therapy and their stratification according to the degree of immunodeficiency. A prospective study was conducted on 57 PLWH evaluated monthly at an HIV outpatient clinic, from a tertiary hospital in southeastern Romania. Clinical examination and dermoscopy revealed the existence of a wide range of dermatological conditions; all 57 patients (100%) being diagnosed with one or more dermatological conditions. As our study shows, the prevalence of different dermatoses among PLWH varies depending on the geographical region. At the same time, under HAART, the image of dermatoses associated with decreased immunity from HIV infection has changed. The skin changes of PLWH no longer fully follow the classical staging, based on the degree of immunosuppression.

## Introduction

The skin follows the intestine and other mucous tissues, as one of the barriers against pathogens. The skin contains innate or acquired immune response effectors. At this level immune conflicts in the skin are also manifested as a result of an abnormal or exaggerated immune response. Along with non-specific immunity effectors, most of the specific immunity effectors in the dermis include various subsets of T lymphocytes, including regulatory T lymphocytes, a population of CD4 receptor-expressing lymphocytes. The major role of CD4 lymphocytes at the skin level is to determine the resolution of inflammatory processes produced by various pathogens as well as the prevention of autoimmune phenomena (1). CD4<sup>+</sup> lymphocytes are also heavily involved in human immunodeficiency virus (HIV) infection, being the primary and the favorite targets of the HIV virus. The action of HIV on this type of lymphocyte is clinically translated by the decrease in the absolute and the percentage number, which determines the decrease of the specific action at the skin level and the perpetuation of the inflammatory phenomena with clinical expression (2).

A large part of the population living with HIV (PLWH) has a series of skin conditions that at some point require treatment by a dermatologist. It is estimated that PLWH require over 15 times more visits to the dermatologist than non-infected patients (3). The beginnings of the HIV pandemic are closely linked to dermatological conditions including Kaposi's sarcoma, a rare onco-dermatological condition which has been reported to be common among young gay males. Along with the occurrence of acquired immunodeficiency syndrome (AIDS) other dermatological conditions such as extensive oral candidiasis, herpes zoster and oral hairy leukoplakia have been described as indicators for this syndrome (4). The introduction of highly active antiretroviral therapy (HAART) more than 20 years ago has diminished and altered the range of dermatological conditions, with improved immunosuppression of CD4 lymphocytes (5,6). However, PLWH still face a number of viral skin infections, chronic inflammation or various forms of skin cancer (5). Understanding the complex relationship between

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the immune system and dermatoses suffered by PLWH can lead to a better therapeutic approach and appropriate management.

There are no data available in Romania on the skin health of patients with HIV infection or the general population, neither globally nor regionally (southeastern region), except for various cases of malignancies (Kaposi' sarcoma, Paget's disease) reported for patients with HIV or manifestations of human papilloma virus (HPV) infection in the general population (7-11). Based on these grounds, we conducted this study to investigate the skin health of PLWH in the southeastern part of Romania.

The objective of this study was to describe the current skin disorders in PLWH receiving antiretroviral therapy (ARVT) to evaluate the prevalence of dermatoses diagnosed (type of skin changes), to stratify these changes according to the degree of immunodeficiency and to compare these skin disorders with those reported in the general population.

### Patients and methods

**Patients.** We conducted a prospective study on 57 PLWH, undergoing monitoring and treatment at the HIV Outpatient Clinic, of the Infectious Diseases Hospital Sf. Cuv. Parascheva', Galati, Romania, evaluated monthly, between 1/10/2019 and 31/03/2020. The study was conducted with the approval of the Ethics Commission of the Infectious Diseases Hospital Sf. Cuv. Parascheva', Galati, Romania (no. 65 from 30/09/2019). All patients signed informed consent to participate in this study.

**Examination.** Patients who gave their consent were clinically examined and by dermoscopy within a screening programme by an experienced dermatologist. Dermoscopy was performed with a Heine (Heine Optotekhnica) device. Bacterial, viral and fungal infections were diagnosed clinically without the involvement of laboratory investigations. Data on the mode of infection, place of residence, duration of disease and ARVT, level of CD4 lymphocytes and viral load (VL), treatment regimen and dermatological history were taken from the patient files. The most recent values of CD4 and VL lymphocytes were considered during the last 6 months. The CD4 count was performed by the flowcytometry method with the Cyflow (Partec) device and the VL load was determined by RT-PCR (real-time polymerase chain reaction) at the National Institute of Infectious Diseases 'Prof. dr. Matei Bals' of Bucharest, Romania.

**Statistical analysis.** Statistical analysis was performed with MedCalc 19.5.3 software (<https://www.medcalc.org>) (12). Statistical analysis of the demographic data was performed on the group of patients with skin disorders and HIV infection with antiretroviral therapy. The data are expressed as mean  $\pm$  SD (standard deviation) for continuous variables and in absolute frequency (relative frequency) for categorical variables.

### Results

The study group was composed mostly of female patients (57.9%), from rural areas (59.6%) with an average age of

Table I. Demographic characteristics of the PLWH study group.

Features	Data
Sex, n (%)	
Male	24 (42.1)
Female	33 (57.9)
Age in years, mean (range)	34.6 (16-70)
Environment of residence, n (%)	
Urban	23 (40.4)
Rural	34 (59.6)
Means of infection, n (%)	
Early in infancy	32 (56.1)
Sexually	21 (36.9)
Vertically	4 (7.0)
CD4 lymphocyte value (cells/mm <sup>3</sup> )	
Total, mean $\pm$ SD (range)	528 $\pm$ 292.8 (5-1,092)
CD4 >500, n (%)	32 (56.0)
CD4=499-200, n (%)	14 (24.5)
CD4 <200, n (%)	11 (19.5)
VL, mean $\pm$ SD (range), copies/ml	371 $\pm$ 1,879 (10-12,864)
<20, n (%)	47 (82.5)
>20, n (%)	10 (17.5)
Classification CDC, n (%)	
Stage A	8 (14.0)
Stage B	23 (40.4)
Stage C	26 (45.6)
Disease duration in years, mean $\pm$ SD (range)	14.9 $\pm$ 7.2 (1-26)
Disease duration according to the mode of infection	
Mean $\pm$ SD (range), years	
Early in infancy	17.8 $\pm$ 6.8 (1-26)
Sexually	7.6 $\pm$ 5.5 (1-20)
Vertically	14.2 $\pm$ 3.5 (10-16)
ARVT (% of patients)	100%
ARVT (duration in years), mean (range)	13.5 (1-25)

CD4, T-lymphocyte cell-bearing CD4 receptor; VL, viral load; PLWH, population living with HIV; CDC, United States Centers for Disease Control and Prevention (31); ARVT, antiretroviral treatment.

34.6 years (range 16-70 years). The average value of CD4 lymphocytes was 528 cells/mm<sup>3</sup> and the average VL was 371 copies/mm<sup>3</sup>. Most patients were in clinical-immunological stage C, the mean duration of the disease was 14.9 years and the mean duration of treatment was 13.5 years (Table I).

In regards to the manner of acquiring the infection, most of the PLWH (56%) came from the former 'pediatric cohort' of Romanian patients born between 1987 and 1990; all from seronegative parents, infected in the first months of life by parenteral care maneuvers. They have a long condition

Table II. Range of dermatological lesions identified in PLWH in the study in correlation with immune status.

Dermatological disease	Prevalence in PLWH (%)	General population prevalence (%)	CD <sub>4</sub> (cells/mm <sup>3</sup> ) Mean ± SD (range)	Age (years) Mean ± SD (range)
Bacterial	3.5	1.4-7.7	83±14.1 (75-90)	30.2±2.12 (29-32)
Folliculitis	1.75			
Impetigo	1.75			
Viral	5.25	3.2	404±313 (54-656)	27.3±5.5 (21-31)
Herpes simplex	3.5			
Vulgar warts	1.75			
Fungal pityriasis versicolor	8.8	1.1-50	816±116.6 (691-923)	32.3±2.5 (30-35)
Inflammatory psoriasis	1.75	2	47	57
Malignant/premalignant nevocellular nevi	30	4.4-60	486±279 (27-980)	29.8±6.9 (16-46)
Other	43.7		523±316.3 (59-1036)	33.2±8.06 (20-58)
Microangiomas	14	2.35-11.3		
Seborrheic dermatitis	10.5	9-10.3		
Acne	7	7.7		
Cutaneous xerosis	5.2	2.6		
Papular pruritic exanthemas	3.5	12.3		
Follicular keratosis	1.5	40.0		
Stretch marks	1.5	43.0 (for obesity)		
Papilloma	3.5	36.0		
Dermatofibroma	1.5	3.0		

PLWH, population living with HIV; CD<sub>4</sub>, T-lymphocyte cell bearing CD4 receptor.

duration, i.e. 17.8 years on average. This population has experienced the full range of specific therapies, being long-term survivors (13,14). More than 1/3 of the patients (36.9%) were sexually infected while vertical transmission from mother to newborn was the least common form of infection, as a result of the introduction in 1992 in Romania of mandatory testing to all pregnant women before giving birth. The results of clinical examination and dermoscopy are shown in correlation with immune status (Table II); all patients being diagnosed with one or more dermatological conditions. The most common diseases (43.7%) were skin changes that cannot be attributed to an obvious etiology and fall into the heterogeneous group of other dermatoses: Skin xerosis, seborrheic dermatitis, acne and keratoses followed by malignant/premalignant nevocellular nevi (30%). The percentages of the different dermatological diseases of the HIV patients in our study were compared with the data from literature about the prevalence of these diseases, in the general population (Table II). These percentages are comparable, which suggests that the compensated immune status of the HIV-infected patients with antiretroviral therapy has minimal impact on skin damage.

The dermatological pathology described classically in the literature, in PLWH (15,16), the bacterial and viral forms, was limited to sporadic cases of impetigo, herpes simplex or vulgar warts, and cases of pityriasis versicolor for the fungal etiology. In Table III, the dermatological conditions associated with various degrees of severity of HIV infection, were compared between two clinical studies from 2007 and 2019 and those pathologies diagnosed in patients in our group.

## Discussion

The present study revealed that even with restored immunity under antiretroviral therapy and normal or quasi-abnormal values of CD4<sup>+</sup> lymphocytes, the population living with HIV (PLWH) from southeast of Romania, showed a wide range of dermatological conditions with different prevalence. All 57 (100%) patients of the study had various skin changes and 54 (95%) of them had at least two combinations of dermatoses. The most common dermatosis was nevocellular nevi with a prevalence of 30%. Pigmented nevi were highlighted in the general adult population in a series of cohort studies where the prevalence ranged from 9 to 60% (17-20) to 100% of cohort members. Although this presence was described in the mentioned studies as being common in the majority of the general population, it was not reported as common among PLWH, perhaps due to its ignorance in various evaluations, as it was not a skin change evocative of HIV infection. This observation is the first time reported in our study to the best of our knowledge. The average age of those who presented such lesions among PLWH was significantly lower (29.8 years) compared to the average age of the general population (49-50 years) in the studies where they were found (18,20).

Infections have been opportunistic diseases associated with HIV-induced immunosuppression since the beginning of the HIV pandemic. In our study, skin, viral, bacterial, or fungal infections had a low prevalence compared to other studies (21,22) where infections were the most common

Table III. Dermatological manifestations described during the evolution of HIV infection depending on the stage of cellular immunity (15,16) compared to the dermatological manifestations found in the PLWH group.

Dermatological manifestations (ref) (year)	Value of CD4 <sup>+</sup> lymphocytes			
	>500 cells/mm <sup>3</sup>	500-200 cells/mm <sup>3</sup>	200-100 cells/mm <sup>3</sup>	<100 cells/mm <sup>3</sup>
Dermatological manifestations (15) (2007)	Acute retroviral syndrome	Seborrheic dermatitis Oral thrush Prurigo Xerosis Kaposi sarcoma	Kaposi sarcoma Disseminated herpes simplex Molluscum contagiosum Pruritic papular eruption Skin hyperpigmentation	Chronic cutaneous mucosal herpes Cutaneous cryptococcosis Histoplasmosis Disseminated cytomegalovirus Skin hyperpigmentation
Dermatological manifestations (16) (2019)	Acute retroviral syndrome Oral hairy leukoplakia Seborrheic dermatitis Psoriasis Kaposi sarcoma	Oral thrush Herpes zoster Herpes simplex Refractory psoriasis Tinea infection Verruca vulgaris	Disseminated herpes simplex Refractory seborrheic dermatitis Pruritic papular eruption Molluscum contagiosum Extensive Kaposi's sarcoma	Chronic extensive herpes simplex Cutaneous cryptococcosis Disseminated cytomegalovirus Acquire dactriosis Giant molluscum
Dermatological manifestations in the PLWH group of our study	Pityriasis versicolor Seborrheic dermatitis Herpes simplex Cutaneous xerosis Acne Nevocellular nevi Vascular abnormalities	Nevocellular nevi Seborrheic dermatitis Acne	Folliculitis Seborrheic dermatitis	Psoriasis Skin spots Vulgar warts Onychomycosis

CD4, T-lymphocyte cell bearing CD4 receptor, PLWH, population living with HIV.

dermatoses. Even in the case of a precarious immune status whereby the average value of CD4<sup>+</sup> lymphocytes was below 100 cells/mm<sup>3</sup>, bacterial infections represented by folliculitis and impetigo had a low prevalence. The viral infections diagnosed in our patients consisted of vulgar warts and herpes simplex, with a cumulative total of 5.25%. The prevalence of herpes simplex was close to that of the general population (23) but lower than that found in PLWH in Iran (6.7%) (22). The most common infection was represented by pityriasis versicolor, an external mycosis with a prevalence of 8.8%. In the general population, the prevalence is as high as 50% in tropical countries and as low as 1.1% in cold climates such as Sweden (24,25). Other types of fungal infections such as extensive or treatment-resistant candidiasis were not observed in patients in our group. As a peculiarity, patients with pityriasis had an immune status comparable to that of people not infected with HIV, with a mean CD4<sup>+</sup> lymphocyte >800 cells/mm<sup>3</sup> (Table II).

Inflammatory skin pathology, represented by psoriasis was found with a frequency of 1.75% comparable to that of the general population (18,19); the disease being diagnosed in

a patient completely non-adherent to antiretroviral treatment, with CD4 <100 cells/mm<sup>3</sup>.

The most common dermatological conditions diagnosed in PLWH in our group were those with polymorphic etiology, incompletely known with a cumulative prevalence of 43.7%. Of these, seborrheic dermatitis with a prevalence of 2.35-11.3% in the general population and 30-80% in PLWH (21,25,26) had a prevalence of 10.5% in our Romanian PLWH group, comparable to that in the general population and well below that reported in patients with HIV infection. Another dermatosis recently diagnosed and associated with HIV infection was cutaneous xerosis, with a prevalence of 5.2%; although some studies estimate that it has a prevalence of 20%, being a relatively common skin aspect in HIV infection (26). Xerosis is more common in the extremities, a fact found by our study. The causes of xerosis in PLWH are not fully elucidated but appear to worsen with the decrease in CD4<sup>+</sup> lymphocyte count (22,26,27). A less common cutaneous sign among PLWH but which we identified in 14% of patients was vascular malformation such as vascular angiomas/microangiomas.



Although approximately 1/5 of the patients had low levels of immunity ( $CD4 < 200$  cells/mm<sup>3</sup>) no case of Kaposi sarcoma was diagnosed. It should be mentioned that almost all patients (except for cases of psoriasis) were examined dermatologically for the first time in this study, because, although aware of some of the skin changes diagnosed on this occasion, they did not seek specialized advice. We could not make any correlation between the stage of immunity and the type of different dermatoses as the average CD4 lymphocyte count was in the range of 400-600 cells/mm<sup>3</sup> with two exceptions; in the case of bacterial and fungal infections. Even in the case of a precarious immunity ( $CD4 < 200$  cells/mm<sup>3</sup>) due to a low therapeutic adherence, we did not encounter these severe dermatoses, evocative of immunosuppression (e.g. molluscum contagiosum) which is a fact found by other authors (22). In addition, no cases of rosacea or cutaneous or palpebral demodicosis were identified (28). As our study shows, the prevalence of different dermatoses varies depending on the geographical region both in the general population (18-20,23,29,30) as well as in PLWH (17,21,22,26). At the same time, under highly active antiretroviral therapy (HAART), the image of dermatoses associated with decreased immunity from HIV infection was altered (Table III), a fact found and highlighted in this study. The study has some limitations due to the relatively small number of patients included; nevertheless, it remains relevant, in our opinion, for the current description of skin health in PLWH.

In conclusion, our study showed that all patients with HIV infection, regardless of age or how they acquired the infection, had various skin changes. Skin changes could not be stratified in correlation with the immune status, the most common being premalignant dermatoses and the heterogeneous group of dermatoses with uncertain etiology. Infectious bacterial, viral or fungal skin pathology characteristic of HIV infection, had a low prevalence. Restoration of immune competence under HAART has brought to the fore those obvious and frequent dermatoses in the general population, at similar degrees of prevalence.

From the perspective of diagnosis, in the presence of HIV-reminiscent dermatoses, such as Kaposi sarcoma or long-lasting extended candidiasis, any dermatologist should also request testing for that patient's HIV infection. However, as we have shown in this study, the skin changes of PLWH no longer fully follow the classical staging, based on the degree of immunosuppression, so that any patient with dermatosis could be potentially infected with HIV. The range of dermatological diseases is getting closer to that of the general population, so that the specification of HIV status is, in our opinion, a mandatory and useful diagnostic approach in conducting subsequent therapy.

In order to get a better insight into the current dermatological pathology in HIV-infected patients in the region, the pathological picture outlined in this study needs to be completed by extending clinical and dermoscopic examination to all HIV-positive patients in active surveillance.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

Conceptualization of the research and writing of the original draft preparation was carried out by MD. Methodology, writing-review and editing was conducted by GLF and LB. Data analysis was conducted by AI and CD. Investigation and clinical management was performed by DR, CB, EDP, ALT and EN. All authors read and approved the final manuscript to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work.

## Ethics approval and consent to participate

The present study was conducted with the approval of the Ethics Commission of the Infectious Diseases Hospital Sf. Cuv. Parascheva', Galati, Romania (approval no. 65 from 30/09/2019). All patients signed informed consent to participate in this study.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare no competing interests.

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