CLINICAL SPECTRUM OF DERMATOLOGICAL DISORDERS FOUND IN HIV POSITIVE PATIENTS AT HELEN JOSEPH HOSPITAL

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A research report submitted to the Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the degree of Master of Medicine in Dermatology.

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DECLARATION

I, Silindile Sibisi declare that this research report is my own work which is being submitted for the degree of Master of Medicine (in the submissible format with my protocol and an extended literature review) in the branch of Dermatology at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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………...day of……………..2017

DEDICATION

I dedicate this project to my creator, God Almighty, for the strength, inspiration and wisdom that He granted me to complete this work as He is the source of our strength.

To my family, my dear husband Thabani for all your technical and emotional support. My two adorable sons, Melokuhle (10 years) and Alakhe (4months) you gave me the reason to carry on through your unconditional love and patience.

In memory of my late father Themba Wiseman Sibisi, who was a loving father and as a result of the love you showed us I am a loving being. To my mom Mantu Rose Sibisi and my mother in-law Bethabile Faith Linda thank you so much for all the support and love. To all my siblings I really appreciate your ongoing support emotionally, spiritually and socially. To all my friends who supported me through this journey.

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ABSTRACT

Background

The human immunodeficiency virus (HIV) epidemic is one of the world's most significant health problems. Sub-Saharan Africa has the highest prevalence globally with an estimated 5.7- 6.7 million people in the region living with HIV (WHO, 2012). South Africa is the epicenter of the epidemic.

HIV/ acquired immunodeficiency syndrome (AIDS) affect many organ systems including the skin. More than 90% of HIV infected individuals will have cutaneous manifestations of HIV at some time during their infection. These HIV- related skin conditions are often atypical in presentation, may be severe and can be poorly or non-responsive to treatment when compared to HIV-uninfected individuals.

Limited studies have been conducted which describe the whole spectrum of cutaneous manifestations in HIV infected population and none have been done in Johannesburg.

Objectives

To describe the frequency and the spectrum of skin diseases in HIV positive patients, to correlate the clinical picture with CD4 counts and the use of antiretroviral therapy (ART).

Methods

This is a retrospective study. Files of 98 patients who attended the dermatology outpatient department from January 2014 to December 2014 with HIV infection were reviewed. Only 81 patients met the inclusion criteria. These were male and female adults, > 18 years of age; HIV- positive status was confirmed on antibody/ antigen tests; a CD4 cell count was

available within 3-6 months, at the time of, or 3-6 months after the initial clinic visit and a clinical diagnosis of the skin condition had been verified by the senior physician/ consultant. Both those on ART and not yet on ART formed part of the study. Skin punch biopsies were taken in those patients where clinical diagnosis was difficult to make.

Results

A total of 25 different skin disorders were documented. Inflammatory skin disorders constituted the largest percentage of skin disorders followed by malignancies. The most frequently diagnosed skin diseases were Kaposi sarcoma, seborrheic dermatitis, papular pruritic eruption of HIV/AIDS, dermatophyte infections and drug reactions. The majority (72.8%) of patients were on ART. The frequency of skin conditions was increased in patients with CD4 counts less than 200 cells/mm^3. Fifty-nine patients (72.8%) of the patients were on ART when they developed the skin diseases and twenty-two (27.2%) patients were not yet on therapy. 54.3% were females and 37% were males.

Conclusion

In our study, skin diseases were common in patients with HIV and their frequency increases with low CD4 counts. This is the first study according to the author's knowledge done in Johannesburg describing the spectrum of skin diseases found in patients with HIV infection.

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ABBREVIATIONS

HIV	Human immunodeficiency virus
AIDS	Acquired immunodeficiency syndrome
WHO	World Health Organization
HSV	Herpes simplex virus
HHV	Human herpes virus
PPE	Papular pruritic eruption of HIV
ART	Antiretroviral therapy
EF	Eosinophilic folliculitis
IRIS	Immune reconstitution inflammatory syndrome
KS	Kaposi’s sarcoma
UTT	Universal test and treat
NRTI	Nucleoside reverse transcriptase inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitors
HB	Hemoglobin
ALT	Alanine aminotransferase
CR	Creatinine
SCC	Squamous cell carcinoma

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1 Introduction

The human immunodeficiency virus (HIV) epidemic is one of the world's most significant health problems. Sub-Saharan Africa has the highest prevalence globally with an estimated 5.7-6.7 million people in the region living with HIV.[1] South Africa is the epicenter of the epidemic. [2, 3]

HIV/ Acquired immunodeficiency syndrome (AIDS) affects many organ systems including the skin. At some time during their infection more than 90% of HIV infected individuals will have cutaneous manifestations of HIV. These HIV-related skin conditions are often atypical in presentation, may be severe and can be poorly or non-responsive to treatment when compared to HIV-uninfected individuals.[4-6] Some skin diseases or their 'atypical' appearance suggest the extent of underlying immunodeficiency i.e. findings on skin examination may provide useful clues to the patient's likely CD4 level. [7-9] (See table 1)

Disseminated and life-threatening disease in the HIV patient is often difficult to diagnose. The skin provides the clinician with a window from which to access diagnostic material via DNA-probes, culture and histology.[10] Skin diseases in the HIV infected can be mutilating, distressing and stigmatizing. HIV- infection is now an established disease that principally involves Africans with many countries having populations affected for over 20 years. More research is needed to improve the care and reduce the suffering of infected people on this continent.

Table 1: Correlation of CD4 + cell count with specific HIV - associated disorders, adapted from Bolognia textbook[11]

System	CD4 >500 cells/mm³	CD4 ≤500 cells/mm³	CD4 <250 cells/mm³	CD4 <50 cells/mm³
Dermatologic	Acute retroviral syndrome Seborrheic dermatitis Vaginal candidiasis Oral hairy leukoplakia	Herpes zoster Kaposi sarcoma Psoriasis, severe or refractory Eruptive atypical melanocytic nevi and melanoma Oropharyngeal candidiasis	Eosinophilic folliculitis Seborrheic dermatitis, refractory Herpes simplex viral infection, disseminated Mollusca, extensive Miliary/ extrapulmonary tuberculosis Cryptococcosis, disseminated Histoplasmosis, disseminated Botryomycosis Non Hodgkin lymphoma	Papular pruritic eruption Giant Mollusca Large, non-healing mucocutaneous HSV (e.g. perianal) Acquired ichthyosis Perianal ulcers due to CMV Aspergillosis Mycobacterium avium complex Major aphthae

1.2 The skin immune system and HIV infection

The skin immune system has two types of antigen presenting cells: the Langerhans cells and dermal dendritic cells. These work in a coordinated fashion upon stimulation by antigen.[6, 12] They migrate to peripheral lymph nodes to present antigen to the inactivated T cells. Activated T cells then undergo clonal expansion and migrate preferentially to skin where they exert their effector functions against viral, bacterial, fungal, parasitic and neoplastic invasion.[6, 12]

In HIV infection, the number and function of Langerhans cells are decreased. These dendritic cells plus CD4 T helper lymphocytes and monocytes are important targets in HIV. Dysfunction of these critical antigen presenting dendritic cells is believed to be the cause of immunodeficiency. Pope *et al* demonstrated that contact between HIV-1 incubated dendritic cells and CD4 T cells during antigen presentation aids in enormous HIV-1 replication, followed by injury to both the T cells and dendritic cells.[6,12] Impairment in the skin immune system as a consequence of the above causes the skin to be the target of infectious, non- infectious and neoplastic diseases.

1.3 WHO staging of HIV infection

Skin conditions assist in the staging of HIV/ AIDS and a number of these skin disorders are in the WHO staging of HIV. (See table 2)

1.4 Cutaneous manifestations of HIV

Cutaneous manifestations in HIV infected individuals can be broadly grouped into infectious-HIV related cutaneous disorders; noninfectious-HIV related cutaneous disorders and neoplastic HIV related cutaneous disorders (see table 3). There are many of these and only selected, most common disorders will be discussed in more detail.

Table 2: WHO staging of HIV infection, adapted from Mahe et al[13]

Clinical stage 1	Clinical stage 2
• Asymptomatic • Persistent generalized lymphadenopathy	• Moderate unexplained weight loss • Herpes zoster

	• Papular pruritic eruptions • Seborrheic dermatitis • Recurrent respiratory tract infections sinusitis, tonsillitis • Angular cheilitis • Recurrent oral ulceration • Fungal nail infections
Clinical stage 3	**Clinical stage 4**
• Unexplained weight loss (>10% of measured body weight) • Pulmonary tuberculosis • Persistent oral candidiasis • Unexplained chronic diarrhea for longer than 1 month • Unexplained persistent fever(above 37.6'C intermittent or constant • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis • Unexplained anemia (<8g/dl), neutropenia (<0.5 x10^9 per litre)	• HIV wasting syndrome • Kaposi's sarcoma • Esophageal candidiasis • Atypical disseminated leishmaniasis • Pneumocystis pneumonia • Extra pulmonary Cryptococcus • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital, or anorectal for more than 1 month's duration) • Extra pulmonary tuberculosis • Cytomegalovirus infections • Central nervous system toxoplasmosis • HIV encephalopathy • Disseminated non tuberculous mycobacterial infection

Table 3: Cutaneous manifestation of HIV infection, adapted from Jordaan et al[14]

Inflammatory	**Cancers**
Seborrheic dermatitis Psoriasis Reactive arthritis Pruritic papular eruption Eosinophilic folliculitis Xerosis	Kaposi sarcoma Lymphomas (B-Cell) Squamous cell carcinoma Malignant Melanoma Basal cell carcinoma
Viral infections	**Arthropod infections**
Herpes simplex virus Molluscum contagiosum Zoster Varicella Oral hairy leukoplakia Warts Cytomegalovirus infections Epstein Barr virus-related rash	Scabies (crusted/ Norwegian) Insect bites
Bacterial infections	**Fungal infections**
Impetigo Folliculitis Cellulitis Abscesses Ecthyma Mycobacteriosis Syphilis Bacillary angiomatosis Actinomycosis	Dermatophytosis Candidiasis Tinea versicolor Cryptococcosis Histoplasmosis Sporotrichosis Emmonsiosis
Miscellaneous	**Drug eruptions**
Erythema elevatum diutinum Atopic dermatitis Pseudolymphoma Pyoderma gangrenosum Urticaria, pruritus and prurigo Photosensitivity Precocious skin aging	
Metabolic changes	**Hair and nails**
Lipodystrophy malnutrition	Trichomegaly of eyelashes Alopecia secondary to scalp infections Alopecia areata Telogen effluvium
Vascular lesions	**Photosensitivity Reactions**
Vasculitis Livedo Thrombocytopenic purpura	Porphyria cutanea tarda Chronic actinic dermatitis

1.4.1 Infectious diseases

Herpes simplex virus

Viral infections serve as cofactors in disease progression of HIV especially herpes simplex virus (HSV) infections. In the setting of HIV positive patients, HSV presents as chronic, painful and non-healing ulcers which respond poorly to treatment. They appear on the junctions between skin and mucous membranes particularly perioral and peri anally. These ulcers must be differentiated from other causes of ulcers resulting from bacterial or fungal infections and cutaneous manifestations of lymphoma.[14, 15]

Varicella zoster virus

Herpes zoster infection in a young person should raise an issue of HIV testing. It is caused by human herpes virus (HHV) -3, is common in the early stages of HIV and it tends to be multidermatomal and recurrent. It presents as vesicles or blisters following a dermatome. Treatment is a combination of high dose systemic antivirals such as acyclovir (800mg 5 times a day for 7-10 days) or valacyclovir (1000mg 3 times a day for 7 days); analgesics and anti-inflammatories. Post herpetic neuralgia may occur as a complication in some patients if treatment is delayed.[14, 15]

Molluscum contagiosum

Molluscum contagiosum is caused by a poxvirus which is common in children and self-limiting. If it occurs in an adult and there are numerous, atypical lesions one must exclude an underlying immunodeficiency. Lesions are skin colored umbilicated papules with a predilection for the face and genitals and HIV individuals they tend to get giant lesions. In

HIV it is important to be differentiated from cutaneous cryptococcosis, basal cell carcinoma and keratoacanthomas by doing a skin punch biopsy and proper treatment be given thereof. In HIV positive patients restoration of the immune system is part of treatment together with the use of topical immunomodulators, such as 5% imiquimod cream; cryotherapy for resistant giant lesions.[4, 14, 15]

Human Papilloma virus

Viral warts are common manifestation of HIV and tend to occur in unusual locations with unusual severity and tend to be multiple and resistant to therapy but seldom serious. Genital warts if left untreated may progress to cervical carcinoma in females which can lead to greater morbidity or mortality if treatment is not instituted early.[4, 15]

Staphylococcus aureus

Staphylococcus aureus is the common bacterial pathogen affecting HIV positive patients. Disease manifestations range from bacterial folliculitis, impetigo, furunculosis and cellulitis. Methicillin- resistant *S.aureus* has high incidence in these patients causing soft tissue infections. Infections respond well to antibiotics they are sensitive to. The use of intranasal bactroban is of importance to temporary eradicating bacterial colonization which is common.[15]

Bacillary angiomatosis

Bacillary angiomatosis is caused by gram negative bacilli, *Bartonella*. It is associated with advanced immunosuppression. Lesions range from a few to a hundred papules, nodules or ulcers and have a vascular appearance and in HIV patients can have polymorphic clinical presentation. Diagnosis is made on histological features. There is vascular proliferation with numerous bacilli. Treatment is with a 2 month course of tetracyclines or macrolides. If left untreated systemic dissemination to lungs or liver can occur.[15]

Syphilis

Cutaneous signs of syphilis in HIV are usually atypical, extensive and mimic a number of other skin conditions. Skin punch biopsy is required to confirm the diagnosis. The disease progresses much more rapidly. In primary syphilis chancres are multiple, larger and deeper. Patients are prone to develop neurosyphilis.

Candidiasis

Mucosal candidiasis, particularly oral candidiasis was one of the initial conditions which were associated with HIV. It is due to overgrowth of normal resident flora. Oropharyngeal candida, the common form is an indicator to progression to AIDS. Burning and dysgeusia may be experienced. The esophageal candidiasis is an AIDS defining condition seen in those with very low CD4 counts. Recurrent vulvovaginal candidiasis is frequently seen in HIV positive women and may be first clinical sign of HIV infection. Diagnosis is usually clinical and demonstration of pseudo hyphae on a KOH preparation of lesional scrapings. Topical nystatin cream or clotrimazole cream, systemic ketoconazole, itraconazole and fluconazole are treatment of choice.[14]

Dermatophytoses

Superficial fungal infections are common in the seropositive patients. Dermatophytes infections infect the superficial dead layer of skin and keratinized hair and nails. In HIV they are usually atypical in presentation and often extensive. Tinea corporis, cruris and pedis are the frequent types seen in HIV. Infection of nails (onychomycosis) is also common. Distal subungual onychomycosis is seen in sero-negative patients but proximal superficial white subungual onychomycosis is the common type in HIV positive patients. [14] Dermatophytoses respond well to topical treatment even with underlying immunosuppression. Systemic therapy is reserved for extensive, chronic disease.

Systemic fungal infections

Cutaneous cryptococcosis and histoplasmosis occur as secondary disease in the skin from dissemination from the lungs and are seen with advanced immunodeficiency. These infections are polymorphous in their clinical presentation including papules, papulonodules, pustules, vesicles and verrucous plaques and can mimic a number of other skin conditions. Disseminated cryptococcosis may resemble molluscum contagiosum with dome shaped papules with central umbilication. Skin biopsy and tissue culture is always indicated in these patients .Intravenous Amphotericin B is the primary treatment of choice for fourteen days followed by oral antifungals like itraconazole, fluconazole, voriconazole. [10]

Scabies

Norwegian scabies or crusted scabies is seen in HIV patients and is highly contagious. Unlike ordinary scabies, crusted type is usually not itchy. Patients present with a generalized eruption of hyperkeratotic scaly plaques. It may resemble other scaly dermatoses seen in HIV like seborrheic dermatitis, psoriasis and drug reactions therefore difficult to diagnose. A skin punch biopsy confirms the diagnosis where there is a heavy infiltration of mites, eggs, or fecal material in the stratum corneum. Treatment of ordinary scabies is with topical benzyl benzoate but in HIV in severe cases use of oral ivermectin can be of benefit. [14, 15]

1.4.2 Inflammatory diseases

Seborrheic dermatitis

Seborrheic dermatitis is a common chronic skin disease. It is seen in sero negative infants at 3-6months of age and in 40-80% of sero positive patients depending on the population studied. The hypothesis is that it is a hypersensitivity to *Malassezia* yeast. In HIV, presentation is usually atypical, more severe and even erythroderma may occur. [16, 17] It affects the sebaceous gland bearing areas like the scalp, central face, central chest and skin folds. Lesions are erythematous with a greasy scale. Treatment is with topical antifungal shampoos and creams, which are directed against the fungus and topical corticosteroids, directed against the inflammation but with advanced HIV infection patients tend to be resistant to conventional treatment. [17]

Psoriasis

The prevalence of psoriasis is the same in HIV seropositive individuals as in general population. [18] In HIV the disease tends to be severe and often refractory to standard treatment. In patients with psoriasis before the diagnosis of HIV, they tend to have sudden worsening after infection with HIV.[18,19] All types of psoriasis are seen but guttate, inverse and erythrodermic occur with much frequency. One has to be more cautious when treating these patients because psoriasis treatment is immunosuppressing and these patients already have compromised immune system.

Papular pruritic eruption of HIV/ AIDS

Papular pruritic eruption (PPE) is one of the common HIV- related skin conditions seen in Africa occurring in patients with low CD4 counts. [20] It is believed to be secondary to hypersensitivity to insect bites; hence it is frequently seen in tropical areas. Clinically it presents as very pruritic, 0, 5-1cm papules, which may be excoriated from scratching. These papules are usually darker than the patient's uninvolved skin. They predominate on the extremities more than the trunk. The diagnosis is usually made clinically. Treatment is with antiretroviral therapy (ART) and potent topical steroids and topical capsaicin for pruritus. [20, 21]

Eosinophilic folliculitis

Eosinophilic folliculitis (EF) is an HIV-related skin disease not well understood. It is another extremely itchy condition occurring in HIV. It favors the face, neck and upper trunk and papules are erythematous and urticarial. It is said it almost never occurs below the nipple line. Post inflammatory hyperpigmentation is a cause of concern in darkly pigmented individuals following this disorder. Like PPE, it is seen in patients with low CD4 counts and it is a common cutaneous manifestation of immune reconstitution inflammatory syndrome (IRIS). [20]

Photosensitivity reactions

It is estimated that photosensitivity occurs in approximately 5.4% of HIV- positive patients. Africans are 6 times more likely to develop photosensitivity. HIV infection and use of ART itself also put them at risk of developing photosensitivity. Photosensitivity disorders seen in HIV patients are porphyria cutanea tarda, polymorphic light eruption, actinic prurigo, chronic actinic dermatitis, photosensitive granuloma annulare and lichenoid photo eruptions. [15] Lesions are photo distributed with a well demarcated border. Sun protection and use of topical steroids are usually prescribed.

1.4.3 Neoplastic HIV related cutaneous disorders

Kaposi Sarcoma

Kaposi sarcoma (KS) is one of the first HIV- associated neoplasms recognized and it is more prevalent in sub- Saharan Africa. [22-24] With the advent of ART there has been a decline in the incidence of KS. [25] There are 4 types of KS namely classic, African endemic, iatrogenic and epidemic AIDS related Kaposi sarcoma. The AIDS related KS is characterized by multiple purplish brown papules or macules (patch stage) or plaques and deep seated nodules (tumor stage) which favors the lower limbs and the oral mucosa. The HIV associated KS is associated with dissemination to the respiratory system and gastrointestinal tract. [24] Skin punch biopsy and PCR confirms the diagnosis. Treatment in HIV patients is by reconstitution of the immunity with ART, local therapies for a few lesions like radiation, photodynamic therapy, liquid nitrogen, intralesional interferon and systemic chemotherapy for disseminated disease. [24]

1.5 Approach to diagnosis

As mentioned earlier, cutaneous manifestations of HIV are atypical in the HIV population and they usually overlap and therefore they pose a diagnostic challenge. One must have a high index of suspicion when dealing with these individuals. The diagnosis is usually based on clinical presentation coupled with skin biopsies, skin scrapings, tissue cultures and serologic studies.

HIV testing must be offered to all high risk groups e.g. men who have sex with men, intravenous drug users, commercial sex workers, those with sexually transmitted infections or pregnant women. Atypical presentation and severe diseases e.g. multidermatomal herpes zoster infections in a young individual, chronic non healing HSV infection, generalized xerosis or pruritus are also an indication for HIV testing.

1.6 Treatment

Treatment of HIV positive patients requires a multi-disciplinary approach and it is important to co-manage these patients with infectious disease physicians.

1.6.1 Antiretroviral therapy

Since the advent of ART the incidence of opportunistic infections and cutaneous malignancies has declined dramatically. [25, 26]

The implementation of the universal test and treat (UTT) strategy for HIV positive patients was announced by the Minister of Health South Africa in his budget speech on the 10th of May 2016. This implementation is based on the WHO evidence based guidelines of UTT. All symptomatic and asymptomatic patients who test positive for HIV regardless of the CD4 count should be initiated on therapy. [27] The first line regimen consists of two nucleoside reverse transcriptase inhibitors (NRTIs) (typically tenofovir and emtricitabine) and one non-nucleoside reverse transcriptase inhibitors (NNRTI) (usually efivarenz).

1.6.2 Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is a well-recognized phenomenon which occurs in approximately 10- 27% of patients starting ART. [28] Approximately 50-78% of cases involve the skin. [29, 30]

There are two types of IRIS, “paradoxical” and “unmasking”. Paradoxical occurs when an opportunistic infection which was diagnosed pre-ART paradoxically worsens following ART initiation and unmasking when a clinically unapparent disease pre-ART, is triggered by initiation of ART, this must be accompanied by rapid restoration of pathogen specific immune response. [28] With the advent of ART, the incidence of dermatologic disorders associated with HIV infection declined, however IRIS manifest with a variety of skin conditions both infective and non-infective. The commonly reported skin manifestations are herpes zoster infection, HSV and Kaposi sarcoma. [29]

In conclusion, important research questions may be answered by research in the field of dermatology and HIV infection:

1. The effect of HIV treatment viz. the ARTs and that of drugs used in the management of opportunistic infections and malignancy, on the skin has not been well characterized in the Southern African population. Specifically the contribution of immune reconstitution following the introduction of ART, i.e. IRIS, to the development of skin disease, has had limited research attention in African literature on HIV/AIDS. [28, 30] A small study done at King Edward hospital, in KwaZulu Natal in 2006, described the spectrum of skin diseases in HIV positive patients, but this was before ART was available. [31]
2. Antiretroviral treatment failure and the skin. Do patients who previously had skin disease before ART re-present with skin disease at the time of failure of therapy and the development of resistance? Is the skin an 'early warning sign' of the onset of treatment failure?
3. Does the recognition of the early cutaneous manifestations of HIV infection e.g. the acute HIV Infection syndrome, provide an opportunity to diagnose HIV before the development of more severe immunodeficiency? Can the early recognition of HIV infection result in earlier entry into HIV care? Can Africa's dermatologists contribute to the recognition and containment of HIV infection in our communities?

Since the early 1990's, the HIV-epidemic has been recognized as a serious health problem in South Africa. Its origin and evolution in West and Central Africa in the early years of the last century are well described. [32] Despite the accumulation of large numbers of infected people on the continent and specifically in South Africa, there has been little systematic attempt to document the uniquely African manifestation of this infection. This is particularly true with regard to the skin, its infection by the HIV itself and infection with other pathogens, and its response to drugs used to manage the condition.

1.7 Study aims and objectives

1.7.1 Aims

The Helen Joseph Hospital has for many years supported a twice weekly dermatology clinic. This clinic cares for 4160 patients per year, many of whom are HIV-positive.
The aim of this study is to document the nature of skin diseases in the HIV-infected patient cohort at this hospital and the role of ART.

1.7.2 Objectives

1. To define and determine the frequency of disease(s) manifesting in the skin of subjects infected with HIV infection.
2. To establish whether a relationship exists between the skin conditions and demographic characteristics such as age, sex, basic laboratory including hemoglobin (Hb), alanine aminotransferase (ALT), creatinine (Cr) and CD4 counts and the use of antiretrovirals.

3. To provide an accurate description of each subject's skin condition, together with accompanying clinical findings and whether a specific cause was confirmed, and the clinical and/or laboratory basis for the diagnosis.

1.8 Research design

The paragraphs below outline the design of this study.

1.8.1 Methodology

Methodology used in this study is detailed below with a focus on study design, population, sampling method, inclusion and exclusion criteria, the site of the study and measurements.

1.8.1.1 Study design*:*

This was a retrospective and descriptive study of patients who were HIV-positive and were referred to the Dermatology Clinic of the Helen Joseph Hospital from 1/1/2014-31/12/2014.

1.8.1.2 Study population*:*

The out-patient Dermatology clinic records of all newly referred HIV positive patients were reviewed. Data of both those who were on ART and those not yet on ART were recorded.

1.8.1.3 Study sampling:

The sample consisted of HIV positive subjects who were enrolled in the clinic during the study period 1/1/2014- 31/12/2014. Those records that met the study inclusion and exclusion criteria were entered into the study database. All personal data was anonymized prior to entry into the study database.

1.8.1.4 Inclusion criteria

1. Male and female adults, >18 years of age, newly referred to the Dermatology clinic.
2. HIV-positive status had been confirmed on antibody/ antigen (Rapid or Elisa) tests or viral RNA (viral load) measurement
3. A CD4 cell count was available within 3-6 months before, at the time of, or 3-6 months after the initial clinic visit
4. A clinical diagnosis of the skin condition was verified i.e. the patient had been examined by a senior physician/consultant in the department, and/or confirmatory laboratory results e.g. skin histology, are available
5. Where additional laboratory results of relevance to the diagnosis or management of the patients were available these were included in the study-dataset

1.8.1.5 Exclusion criteria

HIV test results were unavailable and the HIV status of the subject cannot be confirmed.

1.8.1.6 Site of study

Helen Joseph Hospital situated in Auckland Park, Johannesburg, South Africa. This is 700- bed public sector hospital managed by local government. This is a quaternary specialist facility serving the sick of Johannesburg.

1.8.1.7 Measurements

A data collection sheet is attached with all the variables that were recorded from the files

1.9 Data processing and analysis

Descriptive statistics including mean and standard deviations, and medians, where required was used for numerical variables. Percentages were used for categorical data. Comparisons between groups were done using unpaired t-test or Mann-Whitney for numerical data and Fishers exact test for comparing categorical data.

1.10 Limitations

Inadequate or poor quality data was captured from the files as it was a retrospective study. Inherent biases were anticipated in retrospective research. Nevertheless, a study of this nature is expected to provide valuable material for subsequent prospective studies of skin disease in this group.

1.11 Ethics

This research proposal was submitted to the Human Research Ethics Committee of the University of the Witwatersrand for approval. Data for this research was only used for the purpose of this study and all detailed information was confidential. Consent was obtained from the CEO of the hospital and Head of the Division of Dermatology.

1.12 Funding

This study was self-funded.

Research Cost

Item	Cost
Stationary	R 500.00
Photocopying	R 100.00
Printing & Binding	R 500.00
Transport	R 100.00
Total	R 1200.00

1.13 Timing

Research schedule

Activity	**Dec - Jan 2016**	**Feb 2016**	**Mar - May 2016**	**Oct 2016**	**Nov-Jan 2016**	**Jan -Mar 2017**
Research protocol						
Protocol Assessment & Ethics application						
Data collection						
Data analysis						
Writing up						

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CHAPTER 2: Submissible article

Title:

Clinical Spectrum of Dermatological Disorders found in HIV-positive Patients at the Helen Joseph Hospital, South Africa

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Abstract

Background

The human immunodeficiency virus (HIV) epidemic is one of the world's most significant health problems. Sub- Saharan Africa has the highest prevalence globally with an estimated 5.7-6.7 million people in the region living with HIV (WHO, 2012). South Africa is the epicenter of the epidemic. HIV/ AIDS affect many organ systems including the skin. At some time during their infection more than 90% of HIV infected individuals will have cutaneous manifestations of HIV. These HIV- related skin conditions are often atypical in presentation, may be severe and can be poorly or non-responsive to treatment when compared to HIV-uninfected individuals. Limited studies have been conducted which describe the whole spectrum of cutaneous manifestations in HIV infected population and none has been done in Johannesburg.

Objectives

To describe the frequency and the spectrum of skin diseases in HIV positive patients and to correlate the clinical picture with CD4 counts and the use of ART.

Methods

This retrospective study is taken from the files of 81 patients who attended the dermatology outpatient department from January 2014 to December 2014. Random sampling was done and all patients who met the inclusion criteria were taken. Both those on ART and not yet on ART formed part of the study. Skin punch biopsies were taken in those patients where clinical diagnosis was difficult to make.

Results

Eighty-one (81) patients were included in the present study. A total of 25 different skin disorders were documented. Inflammatory skin disorders constituted the largest percentage of skin disorders followed by malignancies (Kaposi sarcoma). The most frequently diagnosed skin diseases were Kaposi sarcoma, seborrheic dermatitis, papular pruritic eruption of HIV/AIDS, dermatophyte infections and drug reactions. The majority (72.8%) of the sample was on ART. Autoimmune skin diseases were rare. The frequency of skin conditions was increased in patients with CD4 counts less than 200 cells/mm^3. Fifty-nine patients (72.8%) were on ART when they developed the skin diseases and twenty-two (27.2%) patients were not yet on therapy.

Conclusion

Skin diseases are common in patients with HIV and their frequency increase with low CD4 counts. This is the first study according to the author’s knowledge done in Johannesburg describing the spectrum of skin diseases found in patients with HIV infection.

2.1 Introduction

Human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS) affect many organ systems including the skin. It is estimated that more than 90% of HIV infected individuals will manifest a skin disease during the course of their illness. [1-3] The skin diseases are seen in all stages of HIV and they are often atypical in presentation, may be severe and can be poorly responsive to treatment when compared to HIV negative individuals.[1-3]

Skin conditions assist in the staging of HIV/ AIDS as certain diseases correlate with the number of CD4+ T lymphocytes i.e. Kaposi sarcoma (KS) occurs with advanced immunodeficiency state. With severe immunosuppression skin diseases occur more frequently and are severe. [4-6]

The skin immune system is affected in HIV infection. The number and function of antigen presenting cells which are Langerhans cells and dendritic cells is decreased and together with CD4 T helper cells these cells are targets in HIV. Dysfunction of the system is believed to be the cause of immunodeficiency. [3,7]

Skin conditions due to HIV infection can be categorized into infectious, inflammatory, neoplastic and miscellaneous. These conditions are often mutilating, distressing and stigmatizing and early detection and treatment thereof will help to reduce morbidity associated with them.[8]

Despite the accumulation of large numbers of infected people on the African continent and specifically South Africa, there has been little done to document the uniquely African manifestations of this infection. This is particularly true with regard to the skin, its infection by the virus (HIV) itself and infection with other pathogens, and its response to drugs used to manage the condition.

2.2 Aims

To document the spectrum of the skin diseases of the HIV- positive patients seen at Helen Joseph hospital, a tertiary hospital, correlate clinical picture with the CD4 counts and to assess the frequency of skin conditions in patients on ART and those not on ART.

2.3 Materials and Methods

Study population

A total of approximately 4000 patients were seen at the clinic in the year 2014. Only 96 files had HIV status of patients written and 81 patients only were enrolled who met the inclusion criteria. These were adult patients above 18 years of age who had their HIV positive test results confirmed on antibody/ antigen tests and whom their skin disease had been verified by senior registrar or a consultant in the dermatology department. Data from both those who were on ART and those not yet on treatment was recorded. Patients who were on anti-tuberculous (TB) treatment and bactrim were also included.

Data collection

After the HIV status of the patient had been confirmed, CD4 counts at the time of presentation were used. Where additional laboratory tests e.g. tissue cultures or results of relevance to the diagnosis or management of patients were required, these were also included.

Assays

The analyses of blood serum samples, skin punch biopsies, tissue cultures and skin scrapings were performed by the South African National Health Laboratory Services (NHLS). Adults normal reference range for hemoglobin (Hb), alanine aminotransferase (ALT's) and creatinine (Cr) were defined by the NHLS as follows, a normal Hb for males was 14.0- 18.0g/dL and for females, a normal Hb was considered to be 12.0- 16.0g/dL; the normal range for ALT was 7-35 U/L and for a CR, the normal range was 49- 90mL/min. Skin scrapings for suspected superficial fungal infections were treated with 10% potassium hydroxide (KOH) and underwent microscopic examination.

Statistical analysis

Descriptive statistics on general characteristics/ demographics of the patients such as age, gender and ethnic group were collated. Numerical variables such as age, Hb, ALT and Cr were described using mean and standard deviations. Associations between pairs of categorical variables were determined using the Fischer's exact test.

To test for association with continuous variables like age and the blood test levels, the one- way ANOVA test was used. Statistical significance was ascertained at the 5% level, thus a p-value of less than 0.05 was significant.

2.4. Results

Demographic characteristics

A total of 81 patients were enrolled in the study. The age of the study group ranged from 19 to 65 years with the mean (±SD) age at presentation being 39.26(10.1) years. There was no statistically significant difference on the impact of age on the diagnosis of skin diseases (p=0.595). There were predominantly more black patients.

Table 1: Baseline demographics

Ethnicity, number of patients (n)	**n (%)**
Blacks	66 (81.5)
Mixed race	15 (18.5)
Gender	**n (%)**
Females	44 (54.3)
Males	37 (45.7)
CD4 count (cells/mm^3)	**n (%)**
0-100	25 (30.9)
101-200	23 (28.4)
201-350	17 (21.0)
≥ 350	16 (19.8)
Duration of patients' rash	**n (%)**
1-3 months	25 (30.9)

4-6 months	17 (21.0)
7-9 months	14 (17.3)
10-12 months	(2.5)
≥12 months	23 (28.4)
Patients on ART	**n (%)**
Yes	59 (72.8)
No	22 (27.2)

n= number of patients

Table 2: Baseline blood results

***Hemoglobin (g/dL)**	**n=49**
Males: ≤ 14.0 14.0 - 18.0	 7 14
Females: ≤12.0 12.0 - 16.0	 14 14
***Alanine aminotransferase (U/L)**	**n=44**
7 - 35	33
≥ 35	11
***Creatinine (μmol/L)**	**n=51**
49 - 90	43
≥90	8

n= number of patients with results available

Cutaneous findings

A total of 25 different cutaneous disorders were documented, the frequency distribution is shown in table 3. These were categorized into groups namely infections, inflammatory, neoplasms, drug reactions and autoimmune. The inflammatory disorders accounted for the largest percentage (46.5%) of the disorders seen. This group of disorders consisted of seborrheic dermatitis (SD), papular pruritic eruption (PPE) of HIV, nodular prurigo, eczema, acne vulgaris, vasculitis, reactive arthritis, peri oral dermatitis, and hidradenitis suppurativa and post inflammatory hyperpigmentation. This was followed by neoplasms (23.7%), infections (19.5%) and adverse drug reactions (10.8%).

The most common skin diseases diagnosed were KS seen in twenty (21.5%) patients, followed by SD with seventeen (18.3%) patients, drug reactions (10.8%) and PPE of HIV (8.6%). The least diagnosed skin disorders were vitiligo (1.1) and alopecia areata (1.1) which are both auto immune skin disorders. The patient with alopecia areata developed the skin disease before the diagnosis of HIV and the vitiligo patient was already on ART with a high CD4 cell count. This confirms what is already described in literature that autoimmune diseases are rare in immunocompromised patients because of defective cell mediated immunity.

Kaposi sarcoma:

Of the twenty KS patients, fourteen were on ART. Of these fourteen patients on ART, eleven had CD4 counts less than 200 cell/mm^3 and five developed KS lesions within a year of starting ART. Of the twenty KS patients, seventeen had lesions on the lower limbs.

Twelve had lymphedema of the legs. One patient was confirmed to have disseminated disease to the lungs. Lesions consisted of violaceous papules, plaques, nodules and ulcerated tumors in two patients.

Seborrheic dermatitis:

Seventeen patients had SD. Two patients had secondary bacterial infection on their lesions. Two were erythrodermic and four had lesions concentrated on sun exposed areas. Twelve were on ART and five were not yet on treatment. Of the twelve who were on treatment, seven had CD4 counts less than 200 cell/mm³. One patient developed SD within the first three months of starting ART. Lesions were erythematous scaly and greasy papules and plaques. Post inflammatory hyperpigmentation was found on long standing lesions.

Table 3: Frequency of skin conditions and the number of patients on ART and the ART naïve group

Diseases= 25	**N=81 (%)**	**On ART (%)**	**Not on ART (%)**
Kaposi sarcoma	20 (21.5)	14 (70)	6 (30)
Seborrheic dermatitis	17 (18.3)	12 (70.5)	5 (29.4)
Pruritic papular eruption of HIV	8 (8.6)	6 (75)	2 (25)
Dermatophyte infections	5 (5.4)	5 (100)	
Human papilloma virus(warts)	4 (4.3)	4 (100)	
Nodular prurigo	4 (4.3)	2 (50)	2 (50)
Eczematous dermatoses	4 (4.3)	4 (100)	

Lichenoid drug reactions	4 (4.3)	3 (75)	1 (25)
Steven Johnson's Syndrome	3 (3.2)	1 (33.3)	2 (66.6)
Epidermodysplasia verruciformis	3 (3.2)	2 (66.6)	1 (33.3)
Opportunistic fungal infections	2 (2.2)	1 (50)	1 (50)
Molluscum contagiosum	2 (2.2)	2 (100)	
Post inflammatory hyperpigmentation	2 (2.2)	2 (100)	
Scar	2 (2.2)	1 (50)	1 (50)
Staphylococcus infections	1 (1.1)	1 (100)	
Vasculitis	1 (1.1)	1 (100)	
Hidradenitis suppurativa	1 (1.1)	1 (100)	
Reactive arthritis	1 (1.1)	1 (100)	
TB verrucosa cutis	1 (1.1)	1 (100)	
Urticaria with angioedema	1 (1.1)	1 (100)	
Alopecia areata	1 (1.1)		1 (100)
Acne vulgaris	1 (1.1)	1 (100)	
Vitiligo	1 (1.1)	1 (100)	
Peri oral dermatitis	1 (1.1)	1 (100)	
Fixed drug reaction	1 (1.1)	1 (100)	
Erythema multiforme	1 (1.1)	1 (100)	
Toxic epidermal necrolysis	1 (1.1)	1 (100)	

ART: antiretroviral therapy; n= number of patients

Drug reactions

Five males and three females had a drug reaction. The proportion of males with drug reaction was not significantly different to the proportion of females with drug reaction ($p=0.459$).

Six patients with CD4 counts of less than 200 cells/ mm^3 had a drug reaction and two patients with CD4 counts of more than 200 cells/ mm^3 had a drug reaction. Of the eight patients with drugs reactions, six patients were on ART and two patients were not on ART.

Four patients had lichenoid drug eruptions (LDE) and two were on poly pharmacy. One was on ART's, azathioprine, trepiline and prednisone while the other one was on ART and anti TB treatment. Lesions were slaty macules or patches mostly on sun exposed areas and on the trunk

Three had Steven Johnson's syndrome (SJS). All three patients with SJS had a blistering eruption involving two mucous membranes namely the eyes and lips, few with erosions on the genital areas. Involvement by the eruption was up to 10% of body surface area. One SJS was due to anti tuberculosis (TB) medication which was started a month prior, another one was due to herbal medication and this patient was not on ART or TB medication or bactrim and the third patient was on ART and also taking brufen.

There was one fixed drug eruption. Patient was on ART only. Lesions were on the face and they consisted of well circumscribed slaty macules on the face.

One patient had toxic epidermal necrolysis (TEN). This patient was on ART for six months and on bactrim for a week. The reaction was assumed to be most likely due to the use of bactrim. He had more than 30% of body surface area involved with blisters, targetoid lesions and two mucous membranes were involved. One patient had erythema multiforme. Patient was on ART for a week. Lesions were targetoid and concentrated on the extremities.

Pruritic papular eruption of HIV:

Eight patients were found to have PPE.The clinical features of PPE are shown in table 4. Lesions started as erythematous itchy discrete papules which later were hyperpigmented and excoriated due to severe pruritus.

Table 4 PPE features

Distribution	**n=8**	**On ART**	**Not on ART**
Generalized	3	1	2
Exposed area	5	5	
Non exposed areas	0		
Healing	**n=5**	**On ART**	**Not on ART**
Hyperpigmentation	4	4	
Scars and hyperpigmentation	1	1	

ART: antiretroviral therapy

Epidermodysplasia verruciformis:

Of the eighty-one patients in the sample, three had epidermodysplasia verruciformis. Two of these had developed squamous cell carcinomas (SCC) on their sun exposed lesions.

All patients had flat- topped hyper- and hypopigmented papules, pityriasis versicolor- like and seborrheic keratosis-like lesions.

Patients on ART, bactrim or anti TB treatment

Fifty-nine patients (72.8%) of the sample were on ART when they developed the skin diseases and twenty-two (27.2%) patients were not yet on therapy. Three patients were also on bactrim and eight on anti TB treatment.

The study further outlined that in forty-two patients, skin lesions started after taking ART while thirty-nine patients were not on treatment when they developed the rash. Of the forty-two patients who were on treatment, ten of them developed skin lesions within the first 3 months on treatment with 17 of them having developed the rash within a year on treatment.

Dual pathology

Ten patients (12.3%) were found to have more than one skin disease manifesting at the same time. Nine had two skin disorders and one was found to have three skin disorders.

2.5 Discussion

We report a spectrum of skin disorders found in patients who are infected with HIV infection in Johannesburg, Helen Joseph hospital.

A total of 29 different skin conditions were noted among 81 patients studied. The most common skin conditions seen were KS, SD, PPE of HIV and drug eruptions. This pattern is similar to that seen in other African countries like Mali and Tanzania.[9,10] This pattern is also similar to a study which was conducted in KwaZulu Natal (KZN), South Africa.[11] In these studies herpes zoster (HZ) was common, which is a different finding from this study. This could be due to the small sample size of our study and the fact that HZ can be managed at primary health care clinics.

In this study there was a slight female predominance. A study which was done in KZN showed the similar results where more females presented to hospital than males.[11] Statistics in South Africa generally show that females report and use public health services more than their male counterparts;[12-14] this might be due to the fact that females take care of themselves better than males and that they seek medical attention earlier than males.

A significant number of patients who developed skin diseases had low CD4 counts. A total of 59.3 % of our patients had CD4 counts less than 200cells/mm^3. It is documented in literature that the incidence and severity of skin disorders increases as immune system function deteriorates. This is comparable to other studies which were conducted in India, Nigeria and Cameroon. [4-6]

KS was the most common skin manifestation, which was seen in 20 (21.5%) patients. In other African countries KS is among the top 5 skin diseases seen in HIV positive patients. [6,10,15] This is different from studies done in the USA and Asia. One study done in Asia reported no case of KS. This was attributed to the absence of HHV8 in the region.[16] In the current study, predominantly males were affected by KS which is similar to other western countries.[6] With the fast spread of HIV/AIDS, KS is currently the most prevalent tumor seen in males while it's prevalence within females is ranked second in many parts of Africa.[15] In a large case control study conducted in Johannesburg, South Africa consisting of 8487 patients, the authors documented the most common malignancies in a black population over a 9-year period (1995- 2004). In those with HIV infection, there was an increased risk of getting certain cancers: Kaposi's sarcoma increased by 50- fold, a 6- fold in non- Hodgkin's lymphoma[17] and 1.5- 2- fold in cervical, anogenital, squamous cell skin carcinoma and Hodgkin's lymphoma.

The classic SD distribution is on the scalp and face, the "seborrheic" areas. In HIV patients features can be beyond the typical SD areas and have diffuse pattern. Seventeen patients had SD and ten of these had a generalized distribution. This finding was similar to the series which was done in United States, Botswana and South Africa of twenty patients where all twenty patients had a diffuse HIV associated SD.[18] SD is reported to be the most common skin condition in patients who are HIV positive, seen in 85% of patients during their lifetime.[19] In our study population it accounted for 18.3% making it the second most common skin disease in the present study. SD is said to be the early manifestation of HIV.[19] However, our study failed to demonstrate this finding, ten of seventeen patients who had SD their CD4 counts were less than 200 cells/ mm^3. This might be due to late presentation of patients to dermatology clinic.

PPE is a commonly encountered dermatologic disorder found in patients with HIV infection. It is estimated to occur in 12- 46% of patients with the infection.[20,21] It occurs in patients with low CD4 cell counts. Interestingly, four of eight patients in our sample who had PPE their CD4 counts were above 350 cells/ mm^3 and they were on ART, this could be a manifestation of IRIS but were not classified as such because of missing parameters in files to diagnose IRIS. A Thai study of 20 HIV positive patients with PPE found that the majority of their patients had CD4 counts less than 50 cells/ mm^3 but it is not clear whether these patients were on ART or not.[20] In a study done in Uganda, 84.3% of biopsies confirmed an arthropod bite reaction in lesions of PPE which is a postulate as a cause of PPE. However, in our sample skin biopsies were not done, diagnoses were made on clinical appearance of lesions. Seven of eight of our patients were Africans. This is similar to a study done in Johannesburg, South Africa where all their patients were black patients. [21]

In this study, ten patients had more than one skin condition manifesting at the same time. The most commonly found combinations were seborrheic dermatitis, tinea corporis, Kaposi sarcoma and folliculitis. This differs from the study which was conducted in Nigeria by Akinboro *et al* where common combinations were oral candidiasis and PPE and/or xeroderma.[4] Eight of the ten patients with these dual pathologies had CD4 counts less than 200 cells/ mm^3. In a review done by Grayson *et al* in Johannesburg looking at the histology of skin biopsies of HIV infected patients, CMV was the most frequently encountered co-incidental pathogen but it precise pathological significance was not clear.[22]

Epidermodysplasia verruciformis is a rare inherited genodermatosis which is associated with increased susceptibility to beta- human papilloma virus (HPV) especially the oncogenic subtypes HPV-5 and HPV -8. There is loss of function mutations in EVER 1 and EVER 2 genes.[23] This classic form occurs early in childhood and is associated with squamous cell carcinomas. Few cases have been documented of EDV- like syndrome associated with acquired cell mediated immunodeficiency states like allograft recipients, systemic lupus erythematosus, hematological malignancies and HIV infection.[24-27] In this study, three patients had HIV associated EDV. On clinical examination they were found to have flat wart-like lesions on the face, neck, trunk and upper extremities in addition they also had pityriasis versicolor-like lesions and seborrheic keratosis-like lesions on the face, neck, trunk and upper extremities. On histology these showed large keratinocytes on the upper epidermis with blue- gray cytoplasm. These findings are consistent with those seen in the classic inherited form of EDV.[25,28] Interestingly, two of our patients had multiple squamous cell carcinomas on their scalps and foreheads. This is not frequently seen with the acquired form of EDV.[23-25,29] This underreporting may be due to rarity of EDV in the HIV population and not necessarily to difference in disease biology. The question still remains if the same genes EVER 1 and EVER 2 involved in the classic form of EDV are the same as those causing the acquired form.

Since the advent of ART, cutaneous manifestations of HIV have been reduced by 40% but the incidence of cutaneous adverse drug reactions (CADR) has increased in HIV positive population, reported 100 times more than in general population.[30,31] The incidence increases with increasing immunosuppression[32]. TEN and SJS are the most severe CADR seen in these patients.[33,34] The prevalence increases if there is co infection with TB.[32] In our sample ten patients (10.8%) had CADR. Seven patients had CD4 counts less than 200 cells/mm^3. One patient who had TEN was on both ART and bactrim. Three patients with SJS, one was due to ART, the other was on TB treatment and non- steroidal anti inflammatories (NSAIDS) and the last one was due to herbal medication most likely as she did not give history of other medication. The use of poly pharmacy in HIV patients put them at risk of developing CADR.[32]

Some of the limitations of the study were the fact that it was a retrospective study and there was data that was missing from patients' files and histology was not done in some patients. In addition, despite the numbers of patients in this study being small, this is the first description of skin diseases in HIV infected patients from Johannesburg. Furthermore, the description of each patient's clinical picture was difficult to ascertain because of the subjective assessment by other doctors.

Conclusion

Skin diseases are common in patients with HIV and they occur with increased frequency with advanced immunosuppression. Patients presented late to both ART and dermatology clinics when they already had advanced immunosuppression hence a majority had low CD4 cell counts. A rare genodermatosis was seen in three of patients and two with transformation into squamous cell carcinomas. Proper skin surveillance and long term follow up is important in HIV infected patients to early detect such complications. One must always bear in mind multiple pathologies when dealing with HIV positive patients. This is the first study according to the author’s knowledge done in Johannesburg describing the spectrum of skin diseases found in patients with HIV infection.

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CHAPTER 3: APPENDICES

3.1 Ethics clearance

R14/49 Dr Silindile Ayanda Sibisi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150224

NAME: (Principal Investigator)	Dr Silindile Ayanda Sibisi
DEPARTMENT:	Dermatology Helen Joseph Hospital
PROJECT TITLE:	Clinical Spectrum of Dermatological Disorders Found in HIV-Positive Patients at Helen Joseph Hospital
DATE CONSIDERED:	27/02/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr David Spencer and Prof D Modi
APPROVED BY:	Professor A Woodiwiss, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	11/12/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature   Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

3.2 Data Collection Sheet

DATA COLLECTION SHEET

Unique patient ID: ____________________ Date: ____________________

Demographic data

Age: [ ]

Gender: [ ] Male [ ] Female

Marital Status: [ ] Married [ ] Single [ ] Divorced [ ] Widowed

Nationality [ ]

Laboratory data at time of clinic attendance

Cd4	VL	WCC	PLT	UREA	CREAT	LFTs	Skin biopsy

Clinical characteristics

Date of diagnosis of HIV [ ]

Date of diagnosis of skin [ ]

Baseline CD4 counts [ ] Current CD4 count [ ]

Viral load baseline VL on ART ________________________________

ARV's [ ] Yes [ ] No

Other drugs: Bactrim ________________________________

Anti- TB ________________________________

Date of ARV initiation [ ]

What is the main complaint? ________________________________

Duration of rash/ skin complaint ________________________________

Indication of skin punch biopsy ____

Skin lesion started before ARV therapy ☐ Yes ☐ No

If Yes, time interval between ART initiation and development of rash/ skin complaint

____