Skin manifestations in HIV positive patients and it's relation to viral load and CD4 counts

This thesis is submitted to the dermatology department / Faculty of medicine / Benghazi university in partial fulfillment of requirement for the degree of Master (M.Sc) in dermatology and venereology.

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CERTIFICATION

This thesis entitled " Skin manifestations in HIV positive patients and it's relation to viral load and CD4 count " prepared by Dr.Nabil A.Eljehawi, under supervision of Prof. Dr. Gamal A. Duweb, has been approved for submission to the dermatology department / Faculty of medicine / Benghazi university / Benghazi - Libya, as partial fulfillment for the certification of Master in dermatology and venereology.

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I Sincerely dedicate this work to my parents, my family and Prof. Dr. Gamal A. Duweb

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1 . Summary

Introduction:

HIV/AIDS occurrence is a major health problem facing all countries in the world. Cutaneous manifestations are common findings in HIV infected patients. Certain characteristic skin changes can thus help clinicians to recognize previously undiagnosed HIV infection. In addition , skin disorders in patients with unknown HIV status, may lead to HIV testing . The mucocutaneous manifestations often influence general health status and indicate a worse prognosis of the disease, as well as a diagnostic factor in the monitoring of the immune status of the patients. Several studies have shown that association of skin disorders with HIV infection can serve as an indicator for advanced HIV infection, immunosuppression and decreased CD4 cell counts.

Aim of the study:

The aim of our study is to assess the cutaneous manifestations in HIV positive Libyan patients and their relationship to CD4 counts , viral load and treatment.

Materials and methods:

In this study , the cutaneous manifestations among 220 HIV positive patients were evaluated retrospectively in Benghazi center of infectious diseases and immunology (BCIDI) over 8 years (during the period from January 2003 to november 2010) . The patients age ranging from 7 to 46 years old. The study is conducted by reviewing the patient records and their visits by using the management information system (MIS) .

The patients were screened for dermatological findings and the relation to CD4 counts(cell/mm^3) and viral load were assessed by using flow cytometry/ Facs calibar and M2000 abbot PCR respectively at different visits and stages of the disease which were also obtained by reviewing the patient records. Statistical analysis of the data was carried out by using t- test , and Chi square tests.

Results:

Among 220 HIV positive patients , 119 (54.1%) were males and 101 (45.9%) were females. Of these , most patients ; (78.6%) were in the age group 10–19 years and majority of patients (86%) were residents of Benghazi city,whereas (14%) were resident in rural areas. The predominant mode of transmission was by parenteral abuse in 95% of patients, from child to mother (4.5%) and only one patient acquired infection via vertical (mother to child) transmission.

Positive family history was observed in 12% of patients.

Ninety percent of patients were coinfected with at least one viral agent while 62.7% were coinfected with more than one. Among those patients ; 80.9% were coinfected with cytomegalovirus , followed by hepatitis C virus (46.8%) , hepatitis B virus (22%) and uncommonly toxoplasmosis and rubella (10% and 3.6%) respectively.

Among the total number of visits to dermatologist , 93% had single disease , 6.1% had two diseases and only 0.7% had three diseases. Among the total number of skin diseases diagnosed during the visits; parasitic infestations were seen in 92 patients (21.0%), eczematous and related disorders in 78 patients (17.8%), viral infections in 71 patients (16.2%) , bacterial infections in 41 patients (9.3%) and fungal infections in 35 patients (7.9%) from all complaint. Dermatophyte infection was the most common fungal infection and recorded in 19 patients (4.3%), followed by candidal infection in 11 patients (2.5%) from all complaint. Warts represent 5.9% of viral infections followed by Herpes zoster (4.1%) from all complaint.

Among the 41 patients of recorded bacterial infections , 9 patients (2.1%) were impetigo followed by ecthyma in 8 patients (1.8%) and furuncle in 7 patients (1.6%) .

Eczematous disorders were seen in 11.5 % from all complaint and atopic dermatitis ,

photodermatitis and seborrheic dermatitis were the common disorders and presented in 16 (3.6%) , 9 (2.1%) and 8 (1.8%) respectively.

Insect bite and scabies were seen in 58 (13.2%) and 31 patients (7.1%) respectively .

The total number of cases of other skin dermatoses was 122 patients (27.8%) from all complaint including pitryiasis alba in 40 patients (9.1%), acne vulgaris and xerosis in 17 patients (3.9%)for each.

Based on the current status of antiretroviral therapy , it seems to have no significant difference on the proportion of skin disorders.

Concerning CD4 count at the visits , it does not show significant difference regarding proportions of the disorders and P value < 0.238 .

More infections including bacterial and fungal when CD4 count > 200 were observed and the viral infection is higher when CD4 count <200 as compared to other infections.

Conclusion:

HIV positive patients should be examined for skin disorders because early diagnosis and management of such problems will improve the quality of life in these patients.

2 . Introduction

Human immunodeficiency virus (HIV) infection has now been recorded in every region of the world. With high-quality disease surveillance, the end-stage clinical manifestations of infection characteristic of acquired immunodeficiency syndrome (AIDS) were first noticed in a rich industrialised country. However, two decades after it was first described, it is abundantly clear that the main brunt of the epidemic is falling on resource-poor countries particularly in sub-Saharan Africa.[1]

Since 1981, when the first reports about AIDS were published in the medical literature, skin and mucocutaneous diseases have played an important role in the clinical diagnosis of acquired immunodeficiency.

Opportunistic infections of the skin and oral cavity such as herpes simplex and candidiasis were noted to be clinical markers of acquired immunodeficiency. [2]

Candida albicans infection presenting as extensive oral thrush or recalcitrant monilial diaper dermatitis is the most common and often the first manifestation of paediatric HIV infection. Bacterial infections including severe forms of staphylococcal impetigo, ecthyma and furuncles are also common.[3] Extensive molluscum contagiosum, Herpes simplex infection and plane warts are also common with lesions which are more widely distributed and very difficult to treat.

Non infective/inflammatory dermatoses like seborrhoeic eczema and Kaposi's sarcoma, which are common in adults in whom they become more widespread and refractory to treatment as CD4+ T-cell count declines, are exceptional in children. Pruritic Papular Eruption of HIV/AIDS (PPE) is common in both adults and children with marked depletion of CD4+ T-lymphocytes.[4]

Among HIV-infected individuals, skin diseases cause significant morbidity and may be frequently initial signs of immunosuppression. Skin manifestations have been shown to be valuable clinical indicator of HIV infection and associations have been established between some skin conditions and CD4 cell counts in HIV-infected individuals. The normal absolute CD4 count in adolescents and adults ranges from 500 to 1500 cells per mm^3 of blood. In general, the CD4 (CD4 % or absolute count) progressively decreases as HIV disease advances.[5, 6] Low CD4 cell count is associated with a moderately higher risk for disease progression among HIV positive patients. Skin conditions may indicate progression of HIV disease and they can be disabling, disfiguring, or even life-threatening. The mucocutaneous manifestations often influence general health status and indicate a worse prognosis of the disease, as well as a diagnostic factor in the monitoring of the immune status of the patients.[7]

Recognising the HIV-related skin conditions may enable initial HIV diagnosis and also provide clinical confidence in the predicted degree of immunosuppression where CD4 counts are not readily available. Whereas some cutaneous conditions such as oral candidiasis, extensive molluscum contagiosum, eosinophilic pustular folliculitis, cryptococcosis or Kaposi's sarcoma are highly suggestive of HIV disease by their mere presence, other conditions common in the general population are distinguished in HIV infection by their atypical presentation, severity, frequency of recurrence or recalcitrant nature.[8]

The seroconversion eruption classically presents as a transient, generalised measles-like eruption on the trunk and extremities of the body but may be associated with vesicles and oral ulcers.

Systemic features include fever, lethargy, myalgias and lymphadenopathy. This condition may go unnoticed by the patient.

HIV-related skin change represents a continuum along which patients may present.

After seroconversion, skin diseases may follow along general population demographics with no signs of infection during early asymptomatic HIV disease.

In the next stage of HIV, skin presentations represent disease progression with opportunistic infections or acquired immunodeficiency syndrome (AIDS)-defining illnesses due to falling immunity.

Since the advent of antiretroviral therapy, HIV skin disease is also seen in the clinical context of immune reconstitution inflammatory syndrome, with a spectrum of systemic or local inflammatory, infective, autoimmune or malignant disease with rising cell counts.[9,10]

Seborrhoeic dermatitis is a common condition, affecting as much as 85% of patients with HIV.[11] It can present at any CD4 cell count, but with deteriorating counts it is often extensive, more severe and has a reduced response to treatment.

Eosinophilic folliculitis presents as intensely pruritic 2-3 mm pruritic, erythematous, oedematous, urticarial papules centred around follicles and may have central vesicles or pustules. The distribution is over the forehead, neck, shoulders, trunk and upper arms. Secondary changes resulting from scratching are common, and include excoriations with secondary staphylococcal infection, prurigo nodularis, lichen simplex chronicus and post–inflammatory pigmentary changes. Clinically, it is most commonly seen in those not on antiretroviral therapy with advanced HIV with CD4 cell counts below 300 cells/μL.[9, 12]

Pruritis is one of the most common symptoms in patients with HIV and has multiple causes including skin infections, infestations, insect bites, papulosquamous disorders, xerosis and drug reactions .

Drug eruptions are common and can present in a variety of contexts both on and off antiretroviral therapy. Drug eruptions are the most common cause of erythroderma in patients with HIV. Commonly measles-like drug eruptions can occur in as many as 65% of patients on sulfamethoxazole for *Pneumocystis* pneumonia treatment and prophylaxis.

Erythematous macules and papules can become generalised, persisting even after therapy cessation. Sulfonamides also cause urticaria, erythema multiforme, Steven Johnson's syndrome, and potentially life-threatening skin shedding called toxic epidermal necrolysis.

Other frequently used medications that can cause toxic epidermal necrolysis in undiagnosed HIV include penicillin antibiotics or fluconazole.

Antiretroviral drugs such as nevirapine can cause mild to severe skin rashes, including toxic epidermal necrolysis, but rashes associated with other antiretroviral drugs are usually not severe.[13,14]

3 . Review of literature

3 . 1 . History :

AIDS was first reported June 5, 1981, when the U.S. Centers for Disease Control (CDC) recorded a cluster of *Pneumocystis carinii* pneumonia in five homosexual men in Los Angeles.[15] In the beginning, the CDC did not have an official name for the disease, often referring to it by way of the diseases that were associated with it, for example, lymphadenopathy, the disease after which the discoverers of HIV originally named the virus.[16,17] They also used *Kaposi's Sarcoma and Opportunistic Infections*, the name by which a task force had been set up in 1981.[18] In the general press, the term *GRID* (Gay-related immune deficiency) had been coined.[19] The CDC, in search of a name, and looking at the infected communities coined “the 4H disease,” as it seemed to single out Haitians, homosexuals, hemophiliacs, and heroin users.[20] The term GRID became misleading and *AIDS* was introduced at a meeting in July 1982.[21] By September 1982 the CDC started using the name AIDS, and properly defined the illness.[22]

Genetic research indicates that HIV originated in west-central Africa during the late nineteenth or early twentieth century.[23,24] AIDS was first recognized by the U.S. Centers for Disease Control and Prevention in 1981 and its cause, HIV, identified in the early 1980s.[25]

3 . 2 . Definition :

Acquired immune deficiency syndrome or acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV).[26,27,28]

3 . 3 . Classification :

HIV is a member of the genus *Lentivirus*, part of the family of Retroviridae.[29] Lentiviruses have many common morphologies and biological properties. There are two species of HIV known to exist: HIV-1 and HIV-2 (Table -1) . HIV-1 is the virus that was initially discovered and termed LAV. It is more virulent, more infective,[30] and is the cause of the majority of HIV infections globally.

3 . 4 . Epidemiology:

The AIDS pandemic can also be seen as several epidemics of separate subtypes; the major factors in its spread are sexual transmission and vertical transmission from mother to child at birth and through breast milk.[31] Despite recent, improved access to antiretroviral treatment and care in many regions of the world, the AIDS pandemic claimed an estimated 2.1 million (range 1.9–2.4 million) lives in 2007 of which an estimated 330,000 were children under 15 years.[32] Globally, an estimated 33.2 million people lived with HIV in 2007, including 2.5 million children. An estimated 2.5 million (range 1.8–4.1 million) people were newly infected in 2007, including 420,000 children.[32]

Sub-Saharan Africa remains by far the worst affected region. In 2007 it contained an estimated 68% of all people living with AIDS and 76% of all AIDS deaths, with 1.7 million new infections bringing the number of people living with HIV to 22.5 million, and with 11.4 million AIDS orphans living in the region. Unlike other regions, most people living with HIV in sub-Saharan Africa in 2007 (61%) were women. Adult prevalence in 2007 was an estimated 5.0%, and AIDS continued to be the single largest cause of mortality in this region.[32] South Africa has the largest population of HIV patients in the world, followed by Nigeria and India.[33] South & South East Asia are second worst affected; in 2007 this region contained an estimated 18% of all people living with AIDS, and an estimated 300,000 deaths from AIDS.[32] India has an estimated 2.5 million

infections and an estimated adult prevalence of 0.36%.[32] Life expectancy has fallen dramatically in the worst-affected countries; for example, in 2006 it was estimated that it had dropped from 65 to 35 years in Botswana.[31] In the United States, young African-American women are also at unusually high risk for HIV infection. Approximately 1.1 million persons are living with HIV/AIDS in the United States, and more than 56,000 new infections occur every single year.[34] Most people infected with HIV will progress to AIDS within 10 years of HIV infection.[35,36] Treatment with anti-retrovirals increases the life expectancy of people infected with HIV. Even after HIV has progressed to diagnosable AIDS, the average survival time with antiretroviral therapy was estimated to be more than 5 years as of 2005.[37] Without antiretroviral therapy, someone who has AIDS typically dies within a year.[38]

3 . 5 . Pathophysiology:

The pathophysiology of AIDS is complex, as is the case with all syndromes.[39] Ultimately, HIV causes AIDS by depleting $CD4^+$ T helper lymphocytes which are essential to the immune response and without them, the body cannot fight infections or kill cancerous cells. [40]

During the acute phase, HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for $CD4^+$ T cell depletion, although apoptosis may also be a factor. During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in $CD4^+$ T cell numbers.

Although the symptoms of immune deficiency characteristic of AIDS do not appear for years after a person is infected, the bulk of $CD4^+$ T cell loss occurs during the first weeks of infection, especially in the intestinal mucosa, which harbors the majority of the lympho-cytes found in the body.[41]

The reason for the preferential loss of mucosal $CD4^+$ T cells is that a majority of mucosal $CD4^+$ T cells express the CCR5 {Chemokine (C-C motif) receptor 5 } coreceptor, whereas a small fraction of $CD4^+$ T cells in the blood stream do so.[42]

Continuous HIV replication results in a state of generalized immune activation persisting throughout the chronic phase.[43] Immune activation, which is reflected by the increased activation state of immune cells and release of proinflammatory cytokines, results from the activity of several HIV gene products and the immune response to ongoing HIV replication. [44]

A major cause of $CD4^+$ T cell loss appears to result from their heightened susceptibility to apoptosis when the immune system remains activated. Although new T cells are continuously produced by the thymus to replace the ones lost, the regenerative capacity of the thymus is slowly destroyed by direct infection of its thymocytes by HIV. Eventually, the minimal number of $CD4^+$ T cells necessary to maintain a sufficient immune response is lost, leading to AIDS.

The virus, entering through which ever route, acts primarily on the following cells;[45] CD_4+ T-Helper cells, macrophages , monocytes ,B-lymphocytes,certain endothelial cells, microglia , astrocytes, oligodendrocytes and indirectly on neurones (through cytokines and gp-120) .

The virus has cytopathic effects but how it does it is still not quite clear. It can remain inactive in these cells for long periods, though. This effect is hypothesized to be due to the CD_4-gp120 interaction.[45]

3 . 6 . Transmission of HIV:

3 . 6 . 1 . Sexual transmission:

Sexual transmission occurs with the contact between sexual secretions of one person with the rectal, genital or oral mucous membranes of another. Unprotected sexual acts are riskier for the receptive partner than for the insertive partner, and the risk for transmitting HIV through unprotected anal intercourse is greater than the risk from vaginal intercourse or oral sex. However, oral sex is not entirely safe, as HIV can be transmitted through both insertive and receptive oral sex.[46,47]– Sexual assault greatly increases the risk of HIV transmission as condoms are rarely employed and physical trauma to the vagina or rectum occurs frequently, facilitating the transmission of HIV.[48] Other sexually transmitted infections (STI) increase the risk of HIV transmission and infection.[49] However, each 10-fold increase in the level of HIV in the blood is associated with an 81% increased rate of HIV transmission.[49,50] Women are more susceptible to HIV-1 infection due to hormonal changes, vaginal microbial ecology and physiology, and a higher prevalence of sexually transmitted diseases.[51,52] People who have been infected with one strain of HIV can still be infected later on in their lives by other, more virulent strains.

3 . 6 . 2 . Exposure to blood-borne pathogens:

This transmission route is particularly relevant to intravenous drug users, hemophiliacs and recipients of blood transfusions and blood products. Sharing and reusing syringes contaminated with HIV-infected blood represents a major risk for infection with HIV.

Needle sharing is the cause of one third of all new HIV-infections in North America, China, and Eastern Europe. The risk of being infected with HIV from a single prick with a needle that has been used on an HIV-infected person is thought to be about 1 in 150.

Post-exposure prophylaxis with anti-HIV drugs can further reduce this risk.[53]

This route can also affect people who give and receive tattoos and piercings.

The WHO estimates that approximately 2.5% of all HIV infections in sub-Saharan Africa are transmitted through unsafe healthcare injections.[54] The risk of transmitting HIV to blood transfusion recipients is extremely low in developed countries where improved donor selection and HIV screening is performed. However, according to the WHO, 5 to 10% of the world's HIV infections come from transfusion of infected blood and blood products.[55]

3 . 6 . 3 . Perinatal transmission:

The transmission of the virus from the mother to the child can occur *in utero* during the last weeks of pregnancy and at childbirth. In the absence of treatment, the transmission rate between a mother and her child during pregnancy, labor and delivery is 25%.

However, when the mother takes antiretroviral therapy and gives birth by caesarean section, the rate of transmission is just 1%.[56] The risk of infection is influenced by the viral load of the mother at birth, with the higher the viral load, the higher the risk. Breastfeeding also increases the risk of transmission by about 4 %.[57]

3 . 7 . Clinical features:

Infection with HIV-1 is associated with a progressive decrease of the $CD4^+$ T cell count and an increase in viral load. The stage of infection can be determined by measuring the patient's $CD4^+$ T cell count, and the level of HIV in the blood.

HIV infection has basically four stages: incubation period, acute infection, latency stage and AIDS. The initial incubation period upon infection is asymptomatic and usually lasts between two and four weeks.

3 . 7 . 1 . Acute HIV infection :

The first stage of infection, the primary, or acute infection, is a period of rapid viral replication that immediately follows the individual's exposure to HIV leading to an abundance of virus in the peripheral blood with levels of HIV commonly approaching

several million viruses per mL.[58] This response is accompanied by a marked drop in the numbers of circulating $CD4^+$ T cells. This acute viremia is associated in virtually all patients with the activation of $CD8^+$ T cells, which kill HIV-infected cells, and subsequently with antibody production, or seroconversion. During this period (usually 2–4 weeks post-exposure) most individuals (80 to 90%) develop an influenza or mononucleosis-like illness called acute HIV infection, the most common symptoms of which may include fever, lymphadenopathy, pharyngitis, rash, myalgia, malaise, mouth and esophagal sores, and may also include, but less commonly, headache, nausea and vomiting, enlarged liver/spleen, weight loss, thrush, and neurological symptoms. Infected individuals may experience all, some, or none of these symptoms.[59]

3 . 7 . 2 . Latency stage :

A strong immune defense reduces the number of viral particles in the blood stream, marking the start of the infection's *clinical latency* stage. Clinical latency can vary between two weeks and 20 years. During this early phase of infection, HIV is active within lymphoid organs, where large amounts of virus become trapped in the follicular dendritic cells (FDC) network.[60] The surrounding tissues that are rich in $CD4^+$ T cells may also become infected, and viral particles accumulate both in infected cells and as free virus. Individuals who are in this phase are still infectious. During this time, $CD4^+$ $CD45RO^+$ T cells carry most of the proviral load.[61]

3 . 7 . 3 . AIDS :

When $CD4^+$ T cell numbers decline below a critical level of 200 cells per µL, cell-mediated immunity is lost, and infections with a variety of opportunistic microbes appear. The first symptoms often include moderate and unexplained weight loss, recurring respiratory tract infections (such as sinusitis,bronchitis,otitis media,pharyngitis), prostatitis, skin rashes, and oral ulcerations. Typically, resistance is lost early on to oral Candida species and to *Mycobacterium tuberculosis*, which leads to an increased susceptibility to

oral candidiasis(thrush) and tuberculosis. Later, reactivation of latent herpes viruses may cause worsening recurrences of herpes simplex eruptions, shingles, Epstein-Barr virus-induced B-cell lymphomas, or Kaposi's sarcoma. Pneumonia caused by the fungus *Pneumocystis jirovecii* is common and often fatal. In the final stages of AIDS, infection with cytomegalovirus (another herpes virus) or Mycobacterium avium complex is more prominent. Not all patients with AIDS get all these infections or tumors, and there are other tumors and infections that are less prominent but still significant.

3 . 7 . 4 . Pulmonary infections:

Pneumocystis pneumonia (originally known as *Pneumocystis carinii* pneumonia, PCP) is relatively rare in healthy, immunocompetent people, but common among HIV-infected individuals. It is caused by *Pneumocystis jirovecii*.

In developing countries, it is still one of the first indications of AIDS in untested individuals, although it does not generally occur unless the CD4 count is less than 200 cells per µL of blood.[62]

Tuberculosis with HIV co-infection (TB/HIV) is a major world health problem according to the World Health Organization: in 2007, 456,000 deaths among incident TB cases were HIV-positive, a third of all TB deaths and nearly a quarter of the estimated 2 million HIV deaths in that year.[63] In advanced HIV infection, TB often presents atypically with extrapulmonary (systemic) disease a common feature.

3 . 7 . 5 . Gastrointestinal infections:

Esophagitis is an inflammation of the lining of the lower end of the esophagus . In HIV infected individuals, this is normally due to fungal (candidiasis) or viral (herpes simplex-1 or cytomegalovirus) infections. In rare cases, it could be due to mycobacteria.[64]

Unexplained chronic diarrhea in HIV infection is due to many possible causes, including common bacterial (*Salmonella*, *Shigella*, *Listeria* or *Campylobacter*) and parasitic

infections; and uncommon opportunistic infections such as cryptosporidiosis, microsporidiosis.[65]

In some cases, diarrhea may be a side effect of several drugs used to treat HIV, or it may simply accompany HIV infection, particularly during primary HIV infection.[66]

3 . 7 . 6 . Other infections:

AIDS patients often develop opportunistic infections that present with non-specific symptoms, especially low-grade fevers and weight loss. These include opportunistic infection with *Mycobacterium avium-intracellulare* and cytomegalovirus (CMV). CMV can cause colitis, as described above, and CMV retinitis can cause blindness.

Penicilliosis due to *Penicillium marneffei* is now the third most common opportunistic infection (after extrapulmonary tuberculosis and cryptococcosis) in HIV-positive individuals within the endemic area of Southeast Asia.[67]

An infection that often goes unrecognized in AIDS patients is Parvovirus B19. Its main consequence is anemia, which is difficult to distinguish from the effects of antiretroviral drugs used to treat AIDS itself.[68]

3 . 7 . 7 . Neurological and psychiatric involvement :

HIV infection may lead to a variety of neuropsychiatric sequelae, either by infection of the nervous system, or as a direct consequence of the illness itself.

Toxoplasmosis is a disease caused by *Toxoplasma gondii*; it usually infects the brain, causing toxoplasma encephalitis.[69] Cryptococcal meningitis is caused by *Cryptococcus neoformans*. It can cause fevers, headache, fatigue, nausea, vomiting, seizures ,confusion, and can be lethal.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease, in which the gradual destruction of the myelin sheath covering the axons of nerve cells impairs the transmission of nerve impulses. It is caused by a virus called JC virus which occurs in 70%

of the population in latent form. It progresses rapidly, usually causing death within months of diagnosis.[70]

AIDS dementia complex (ADC) is a metabolic encephalopathy induced by HIV infection and fueled by immune activation of HIV infected brain macrophages and microglia.

Prevalence is 10–20% in Western countries[71] but only 1–2% of HIV infections in India.[72,73] AIDS related mania is sometimes seen in patients with advanced HIV illness; it presents with more irritability and cognitive impairment and less euphoria .

3 . 7 . 8 . Tumors and malignancies:

Patients with HIV infection have substantially increased incidence of several cancers. This is primarily due to co-infection with an oncogenic DNA virus, especially Epstein-Barr virus (EBV), Human herpes virus-8 (HHV-8), and human papillomavirus (HPV).[74,75]

Kaposi's sarcoma (KS) is the most common tumor in HIV-infected patients. The appearance of this tumor in young homosexual men in 1981 was one of the first signals of the AIDS epidemic. caused by a gammaherpes virus HHV-8 , it often appears as purplish nodules on the skin, but can affect other organs, especially the mouth, gastrointestinal tract, and lungs. High-grade B cell lymphomas such as Burkitt's lymphoma, Burkitt's-like lymphoma, diffuse large B-cell lymphoma (DLBCL), and primary central nervous system lymphoma present more often in HIV-infected patients. Epstein-Barr virus (EBV) or HHV-8 cause many of these lymphomas. [76]

Invasive cervical cancer in HIV-infected women is also considered AIDS-defining. It is caused by human papillomavirus (HPV).[77]

Other tumors, notably Hodgkin's disease, anal and rectal carcinomas, hepatocellular carcinomas, head and neck cancers, and lung cancer.

In areas where HAART is extensively used to treat AIDS, the incidence of many AIDS-related malignancies has decreased.[78]

3 . 8 . HIV-associated skin diseases:

3 . 8 . 1 . Acute HIV exanthema:

In 40-90 % of all patients infected with HIV-1 an acute, febrile, mononucleosis-like disease with constitutional symptoms and an exanthema occurs. This nonspecific eruption starts 1-3 weeks after HIV transmission, and several weeks before HIV seroconversion.[79]

The macular exanthem favors the upper trunk and is characterized as fairly non-pruritic with erythematous macules from 0.5 to 1 cm in diameter.

Morbilliform or rubella-like eruptions and palmoplantar hyperkeratotic eczema occur less frequently. Histopathology reveals a nonspecific perivascular and interstitial infiltrate in the upper and mid dermis.[80]

Oral aphthous ulcers, frequently in combination with shallow genital ulcers (bipolar aphthosis) are another important clinical sign.[81]

3 . 8 . 2 . Aphthous ulcers and other oral lesions:

At least three different kinds of aphthous ulcers occur in the oral cavity of HIV-infected patients. The most frequent diagnosis is recurrent aphthous stomatitis (canker sores) (1) with single or few painful lesions 3-10 mm in size usually localized in the vestibule of the mouth. Single or multiple large aphthae (2) which are >1cm in diameter and usually persist for several weeks are less common. Bipolar aphthosis (3) , involving the oral and genital mucosal membranes, is an important clinical symptom of acute HIV infection or Behcet's disease. [82] The incidence of oral disease has decreased since HAART was introduced.[83]

3 . 8 . 3 . Bullous Impetigo:

Bullous impetigo is most common in hot, humid weather, presenting as very superficial blisters or erosions, most commonly seen in the groin or axilla. Because the blisters are flaccid, they are short-lived; often only erosions or yellow crusts are present. These lesions closely mimic cutaneous candidiasis.[84]

3 . 8 . 4 . Ecthyma:

Ecthyma is an eroded or superficially ulcerated lesion with an adherent crust. Under this crust is often a plane of purulent material teeming with staphylococci. Removal of this crust is necessary to treat the lesion topically.

3 . 8 . 5 . Folliculitis:

Pustular, papular or edematous-papular follicular lesions, involving the proximal limbs and the upper trunk. Possible causes include *Staphylococus, Malassezia furfur, Demodex folliculorum*, and drugs such as indinavir. Today, it is well established that HAART naive patients with pruritic eosinophilic folliculitis significantly improve after the initiation of antiretroviral therapy.[85]

3 . 8 . 6 . Bacillary angiomatosis:

A treatable opportunistic infection, was initially reported as atypical subcutaneous infection in patients with advanced HIV disease caused by *Bartonella*.[86]

Bacillary angiomatosis initially was considered primarily a disorder of the skin, but systemic involvement is common. Visceral disease may include osseous lesions,[87] hepatic and splenic involvement,[88] lymph node disease, pulmonary lesions,[89] brain lesions,[90] and widespread fatal systemic involvement.

The most characteristic cutaneous lesions of bacillary angiomatosis resemble pyogenic granulomas ; fleshy, friable, protuberant papules-to-nodules that tend to bleed very easily. In addition, deep cellulitic plaques and subcutaneous nodules may occur. Lesions number from a few to hundreds. Diagnosis is confirmed by identifying the causative organism in affected tissue using silver stains or electron microscopy. Systemic findings such as fever, night sweats, weight loss, and anemia are common in patients with bacillary angiomatosis.

Reports describe mucosal lesions of the conjunctiva and upper respiratory tract.[89] Visceral lesions may be as or more common than cutaneous lesions.

3 . 8 . 7 . Cutaneous Mycobacterial Infection:

Reports describe increased frequency of infections with *Mycobacterium avium*-intracellulare and *Mycobacterium tuberculosis* in patients with HIV disease. These infections may be disseminated, unusual, and severe.[91,92] Cutaneous lesions caused by these organisms, however, are unusual. They commonly present as chronic sinuses over involved lymph nodes (scrofula), chronic ulcerations, or hemorrhagic macules.[93]

In most cases, acid-fast bacilli (AFB) in skin lesions indicate disseminated mycobacterial disease, usually from *M. avium*-intracellulare.[94] *M. haemophilum* rarely causes mycobacterial infection in immunosuppressed persons. Typically, it presents with cutaneous abscesses or ulcerations and tenosynovitis or arthritis.

Rarely, *M. kansasii* can cause cutaneous lesions in HIV-infected persons. The histology may be that of a spindle cell proliferation resembling KS. Unless special stains for mycobacteria are ordered, a misdiagnosis may result.[95]

3 . 8 . 8 . Genital warts (condylomata acuminata):

Genital warts are sexually transmitted hyperkeratotic and verrucous papules of the anogenital region, caused by a variety of human papilloma viruses (HPV 6, 11, 16, 18, etc.) . HIV-infected patients have a high prevalence of these lesions (17 %), and genital warts are directly related to the number of sexual partners. Genital warts, located in the perianal or intra-anal region are characteristic of receptive anal intercourse. Patients who have anogenital warts, should be offered HIV testing, especially if they have other HIV risk factors. Anogenital warts (condylomata acuminata) may be a nonspecific and insensitive marker for HIV infection. HPV-6 and HPV-11 (not associated with malignant potential) have been identified as the types most frequently found.[96] It is now accepted, that genitoanal lesions due to oncogenic HPV types, especially HPV 16 and 18, are substantial risk factors for malignant cervical, penile, and anal carcinomas .

In contrast to the beneficial effects of HAART on the incidence and the clinical course of Kaposi's sarcoma and NHL, there is no clear impact on cervical and anal carcinoma.[97] Screening should include clinical inspection, acetowhite-stain, colposcopy, proctoscopy, cytology (Pap smear) and, if necessary, histopathology . Due to orogenital sexual contacts HPV 16 and other oncogenic HPV are also found in the oral cavity.[98] HAART can lead to regression of warts,[99,100] but some patients have been seen whose warts persist or return after many years remission and this seems to be related to low CD4 counts.[101]

3 . 8 . 9 . Superficial Fungal Infections:

Superficial yeast and fungal infections can be broken down into the following three groups: thrush; intertriginous infections; and nail, paronychial, and foot infections.

3 . 8 . 9 . 1 . Thrush:

The most common form of yeast infection in HIV-infected persons is thrush. Angular cheilitis ; fissuring, maceration, and erythema of the corners of the mouth may accompany thrush. Oral candidosis has classically been associated with immunosuppressive states and was one of the first features to be recognized in the early days of the HIV epidemic before the syndrome was clearly defined and the causative agent identified.[2] Oesophageal candidosis is an AIDS-defining diagnosis. It is commoner in homosexual seropositive patients than intravenous drug users.[102] Practically all people with HIV infection will have *Candida* as a pathogen at some stage in their disease.[103]

3 . 8 . 9 . 2 . Intertriginous Infections:

Either *Candida* or Tinea may cause intertriginous infection and may involve the groin, axillary vault, or inframammary areas. In these areas, candidiasis presents as a vivid red, slightly eroded eruption in the depths of the folds. The surface is wrinkled and a white membrane may coat the eroded surface. A hallmark of this rash is satellite pustules extending out centrifugally from the eroded areas. In males, the scrotum is often involved. Patient complaints of a burning pain may be as numerous as those related to pruritus.

Tinea in the groin is usually pruritic. The scrotum is spared. The depth of the folds may be clear, and a well - demarcated, annular patch expands down the upper thigh. In more extensive cases, the lesions may extend through the pubic hair onto the lower abdomen and buttocks. Rarely, Tinea of the groin may extend to cover large areas of the body.(104)

Both *Candida* and Tinea are diagnosed by potassium hydroxide examination of scales taken from the active border or a satellite pustule.

3 . 8 . 9 . 3 . Candida Infection of the Nails:

Candida almost always affects the tissue around the fingernails, frequently presenting as a paronychia. Infection tends to be chronic, in which case the cuticle is lost and the nail plate may become ridged or dystrophic. Onycholysis (separation of the nail plate from the nail bed) may also occur. Chronic frequent exposure to water is a significant predisposing factor in candidal nail infection.

3 . 8 . 9 . 4 . Tinea of the nails, feet, and hands:

Onychomycosis is very common in HIV and AIDS.*Trichophyton rubrum* is the commonest pathogen.(105) Infections of the skin, hair or nails with dermatophytes (in Western Europe predominantly *Trichophyton, Microsporum* and *Epidermophyton species*). Tinea has a high prevalence in the general population. There is no significant difference between HIV negative and HIV-infected adults. The prevalence is dependent upon climate, profession, clothing, and participation in team sports. In homosexual men, the prevalence is 29 to 37%. (106) Tinea of the nail, in contrast to Candida, involves primarily the nail plate, favors the toenails over the fingernails, and does not cause acute paronychia. Nails become opaque and thickened, and may split or crumble. An associated infection of the soles or toe webs is common, manifested by chronic maceration, scaling, blistering, and/or thickening of the skin. Occasionally, the palms are involved in a similar manner.

Tinea is especially likely if two feet and one hand are affected . Improvement of onychomycosis with HAART in the absence of specific antifungal treatment has been observed.[107]

3 . 8 . 10 . Deep (Systemic) Fungal Infections :

Systemic infections reported in patients with symptomatic HIV disease include: cryptococcosis,histoplasmosis,sporotrichosis,aspergillosis,candidiasis, coccidioidomycosis, actinomycosis, and phaeohyphomycosis.[108] Only the first four present significant dermatologic problems.

3 . 8 . 10 . 1 . *Cryptococcosis*:

Cryptococcosis is common in patients with advanced HIV disease and usually presents as meningitis. Cutaneous lesions may precede or occur simultaneously with central nervous system (CNS) disease. Approximately 6% of patients with HIV disease and cryptococcosis have skin lesions. Lesions appear anywhere on the body but are most common on the head and neck; they typically present as pearly 2 to 5 mm translucent papules that resemble molluscum contagiosum.[109] Diagnosis is established by skin biopsy and culture. Cryptococcosis in the skin is an indication of disseminated infection, so appropriate work-up, especially of the CNS, is mandatory.

3 . 8 . 10 .*2* . *Histoplasmosis*:

Disseminated histoplasmosis occurred in more than 5% of patients with advanced HIV disease in one series from Houston, Texas.[110] Most cases probably represent reactivation of previous histoplasmosis infection rather than dissemination of newly acquired infections. Skin involvement occurs in about 10% of patients with advanced HIV disease with disseminated histoplasmosis.[110]

The cutaneous lesions are not specific and present as erythematous macules, papules, maculopapular dermatitic lesions, pustules, acneiform lesions, ulcerations, and plaques.

Histologic analysis of the skin may demonstrate granulomas; organisms are easily seen

with special stains (e.g., methenamine silver). Bone marrow biopsy and culture are positive in 69% of cases, and blood culture is positive in 27% of cases.[110] About 10% of patients with disseminated histoplasmosis present with sepsis, disseminated intravascular coagulopathy, and pulmonary, CNS, and renal failure. This syndrome is usually fatal.

3 . 8 . 10 . 3 . *Sporotrichosis*:

In non-HIV-infected persons, sporotrichosis most commonly presents as a disease of the skin and draining lymphatics. Rarely, sporotrichosis may disseminate. Disseminated sporotrichosis associated with HIV infection apparently begins as an asymptomatic pulmonary infection that spreads hematogenously to the skin and joints. Skin biopsies and cultures establish the diagnosis. Multiple widespread cutaneous ulcers and subcutaneous nodules are present.[111,112]

3 . 8 . 10 . 4 . *Aspergillus* :

Cutaneous *Aspergillus* can occur as primary or secondary infection. The latter is from hematogenous spread or from direct invasion of underlying structures. Primary cutaneous aspergillosis is associated with local skin injury (from tape, intravenous catheter sites) and neutropenia. Lesions can appear as erythematous indurations with overlying pustules, hemorrhagic ulcers, or molluscum contagiosum-like lesions.[113]

3 . 8 . 11 . Herpes simplex virus infections:

Herpetic infections of the skin and mucous membranes are frequent opportunistic infections in HIV-infected patients. In advanced HIV infection; painful, deep and large ulcerations of the anogenital region, but also of the face and other parts of the body (e.g. herpetic whitlow) will appear. Herpes lesions ease HIV transmission between sexual partners by breaking the epithelial barriers, stimulating HIV reproduction via pro-inflammatory cytokines, and enhancing expression of cellular HIV receptors (CD4, etc.) on the surfaces of immunocompetent cells.[114, 115]

3 . 8 . 12 . Herpes Zoster:

Patients with Previous Varicella :

Varicella zoster virus (VZV) infection is commonly seen early in the course of HIV infection, particularly in healthy appearing individuals, before the onset of other symptoms.[116-120] Because most HIV-infected persons have had varicella previously, the initial manifestation of VZV infection is usually herpes zoster. During the course of HIV disease, herpes zoster often precedes thrush and oral hairy leukoplakia by about 1 year,[118] making it an important early finding and raising suspicion of HIV infection in persons at risk .

Unlike zoster in individuals without HIV infection, this dermatomal eruption may be particularly bullous, hemorrhagic, necrotic, and painful in HIV-infected persons. The duration of blisters and crusts is usually 2 or 3 weeks. The approximate duration of significant pain is also 2 or 3 weeks. Necrotic lesions may last for up to 6 weeks and heal with severe scarring. This dermatomal scarring is characteristic of HIV-infected patients and should be sought when evaluating at-risk individuals. In severe cases, and occasionally in severe cases in non-HIV-infected persons, excruciating and disabling pain may last for many months . Recurrences have been reported in up to 25% of African HIV-infected persons with herpes zoster.[119] This number is about 5% higher than that seen in San Francisco.[121] As immune suppression advances, recurrent episodes may increase in severity . Dissemination of VZV in HIV infection is fortunately uncommon.[122] The clinical manifestations of disseminated VZV infection include typical widespread Tzanck-positive blisters with or without an associated dermatomal eruption. In addition, chronic disseminated VZV may present as widespread ecthymatous ulcers or hyperkeratotic verrucous lesions.[123-125] Children with HIV infection may frequently develop primary, recurrent and persistent VZV infection.[126]

Patients Without Previous Varicella Zoster Virus Infections :

On initial exposure to VZV, a disseminated blistering eruption called varicella (chickenpox) usually occurs. This presentation is followed by lifelong immunity, but dormant virus can later reactivate dermatomally, causing herpes zoster. In HIV-infected children and adults, however, varicella may be severe, cause visceral disease, and be fatal.[127,128] The predisposition for visceral disease seems greater in children than in adults with HIV disease. Recurrences or persistence of varicella can occur despite acyclovir therapy.[124]

3 . 8 . 13 . Molluscum contagiosum:

In HIV-infected patients, the clinical manifestations can differ significantly from those seen in the normal host. Spontaneous healing is rare; most patients have high numbers of lesions, typically occurring in the face and neck region, which is otherwise a rare location. The presence of multiple mollusca on the face, is a typical disease marker, indicating advanced cell-mediated immunodeficiency with CD4+ T-cell counts <100/µl.[106] The growth of mollusca in the immunocompromised host is not always exophytic, sometimes endophytic lesions occur.

3 . 8 . 14 . Oral hairy leukoplakia (OHL):

Is a clinical manifestation of Epstein-Barr virus infection, which is almost exclusively found in patients with untreated advanced HIV disease. Non-cytolytic viral replication in the glossal epithelium, especially in the lateral parts of the tongue, leads to asymptomatic white verrucous plaques that do not rub off. OHL is diagnosed on clinical findings; initially parallel white or grayish hyperkeratotic rows arranged vertically on the lateral aspects of the tongue are characteristic. Unilateral lesions are seen , but bilateral occurrence of plaques is more typical. If the diagnosis is in doubt, a biopsy or cytology can confirm the diagnosis. The diseases respond well to HAART, which has led to a significant decrease (80-90%) of these oral diseases.[129]

3 .8.15.Immune reconstitution inflammatory syndrome (IRIS)related skin reactions:

HAART recovers the TH-1 immune response and the tuberculin test reactivity. In association with this immune reconstitution, clinical manifestations of herpes zoster, mucocutaneous herpes simplex infections, mycobacterial infections, eosinophilic folliculitis, foreign-body granulomas, cutaneous sarcoidosis and aggressive Kaposi‘s sarcoma were reported.(130) These infectious, as well as some non-infectious inflammatory skin diseases and tumors, occur within a few days to 3 months after the initiation of HAART.

3 . 8 . 16 . Kaposi's Sarcoma:

KS is a neoplasm of endothelial cells involving the skin and, at times, other internal organs. KS is common among HIV-infected persons, but there is not an equal incidence in all risk groups. Most KS patients are homosexual men. In one series, 46% of homosexual men with advanced HIV disease had KS at the time of their initial diagnosis. The incidence in heterosexual injection drug users is only 3.8%.(131) The prevalence of KS has declined over the past 10 years among patients with advanced HIV disease in San Francisco. After a peak incidence of 65% in 1982, only 20% of patients with advanced HIV disease developed KS in 1987.(132) In homosexual men in Vancouver, Canada, the strongest predictor for the development of KS was an elevated number of sexual contacts in high-risk areas (San Francisco, Los Angeles, and New York).(133) Several homosexual men have been identified who developed KS but who are uninfected with HIV by all current testing methods.(134) Herpes virus 8 (HHV-8) has been associated with KS . KS may affect any portion of the cutaneous surface. KS may affect mucosal surfaces and internal organs with or without involving the skin. Visceral involvement occurs in 72% of patients with advanced HIV disease and KS, most often affecting the gastrointestinal tract (50%), lymph nodes (50%), and lungs (37%).(135) The natural history of HIV-associated KS is not uniform, but the prognosis is poor. The average survival of patients is 18 months.(135) Most

individuals have generalized, slowly progressive disease; others have stable KS. Even more rarely, the disease may resolve spontaneously.[136] Poor prognostic findings include generalized disease and coexistent opportunistic infections; the latter are the most common cause of death.[135]

3 . 8 . 17 . Cutaneous lymphomas:

Malignant B and T-cell lymphomas are rare in HIV infected patients.[137] Cutaneous B-cell lymphomas usually grow as red to violaceous nodules, that are easily mistaken for Kaposi's sarcoma. They can also look like persistent hematoma or nonspecific asymptomatic papules. A biopsy should be performed on any clinically unclear tumor of the skin. Cutaneous T-cell lymphomas are rare malignancies in HIV-infected patients. The prevalence among 2149 HIV patients in Frankfurt/M. was 0.06 %. The clinical course starts with nonspecific eczematous patches (stage I), which are usually not diagnosed as cutaneous lymphoma, even after several biopsies because of the paucity of findings such as cellular atypia. Biggar et al (2007) calculated a relative risk for cutaneous T-cell lymphomas in HIV-infected patients of 15.0 in comparison to the general population.

3 . 8 . 18 . Pruritus:

Chronic, often unremitting pruritus is one of the most frequent clinical symptoms of HIV infection. One in three patients is affected. Etiology remains unclear in most patients, and therefore only symptomatic treatment can be offered which may be unsatisfying.[138] Pruritus in HIV-infected patients can be a complication of infectious diseases. Viral, bacterial, and fungal infections (e.g. *Malassezia furfur* folliculitis) and scabies can cause severe itching.

Also, dry eczematous skin (xerosis), papulosquamous skin diseases, systemic lymphomas, renal insufficiency and hepatic disease are causative conditions. Finally, many antiretroviral and other drugs given to the HIV- infected patient can cause pruritus (with or

without rash). It has been suggested that a viral load of more than 55 000 copies/ml are associated with pruritus.[139]

3 . 8 . 19 . Papular dermatoses:

Patients can present either with monomorphic skin colored to red papules (size 2 - 5 mm) or with combined eruptions consisting of papules and pustules (sterile eosinophilic pustulosis Ofuji). There is no special predilection for any site. The etiology of papular eruptions is heterogeneous.[140] These papules can be due to a *hypersensitivity reaction* to drugs, microbiological agents (viruses, bacteria, fungi), parasites, or saprophytes (*Sarcoptes scabiei*, *Demodex folliculorum*, Malassezia and others). In the case of sterile eosinophilic pustulosis (Ofuji), or papular dermatosis of unknown origin, therapy is symptomatic.

3 . 8 . 20 . Ingrown nails:

Patients on HAART are the most recent group of patients to regularly develop ingrown nails. These are ascribed to retinoid-like side effects of several antiretrovirals, especially indinavir, but also lamivudine and nelfinavir. Usually, the great toenails are involved, but all other toenails and fingernails can be affected. The therapy of choice , is to substitute indinavir or lamivudine with other antiretrovirals. This has led to complete remission in several patients.[141]

3 . 8 . 21 . Psoriasis vulgaris:

The incidence of psoriasis in HIV infected persons has been reported to be between 2.5 % and 4.9 % . Being a T-cell mediated disease, the pathomechanisms of severe and recalcitrant psoriasis in HIV infected patients with a substantial decrease in CD4 cell counts, are not well understood.[142] The use of antiretrovirals improves psoriasis.

Typical psoriatic plaques can be eruptive, guttate, or chronic and stationary. Atypical findings include inverse localization on the palms or soles and in the genital region and axillae, exudative, pustular, or erythrodermic manifestations. In general, the severity of

psoriasis parallels the impairment of the immune system. Besides infection, drugs have to be considered as possible triggers. In the final stages of HIV infection, psoriasis can be generalized and extremely resistant to therapy. Alternatively, the disease may disappear completely.

3 . 8 . 22 . Reiter's syndrome:

Reiter's syndrome is regarded as a variant of psoriasis in patients who carry HLA B27. This rare chronic-relapsing disease mainly affects young men, the incidence being higher in HIV-infected men than in the general population (0.6 to 6 %).[143,144] The classical triad consists of: urethritis, conjunctivitis and arthritis . The triad is found in about 30 % of patients. Furthermore, constitutional symptoms (attacks of fever, malaise, leukocytosis, elevated ESR) and skin lesions can be found. The skin lesions are characterized by erythema with sterile pustules on the palms and soles, and later, hyperkeratotic, scaling, exudative lesions known as keratoderma blenorrhagicum.

3 . 8 . 23 . Eosinophilic Folliculitis of HIV Disease :

A culture-negative folliculitis commonly reveals eosinophils on biopsy.[145] This disorder typically occurs in HIV-infected persons with helper T cell counts below 200. The eruption waxes and wanes. Intensely pruritic, edematous, urticarial papules and pustules appear in crops on the trunk or face or both. Cultures and histologic examination for infectious agents are negative, but a relative peripheral eosinophilia may be present.

3 . 8 . 24 . Atopic Dermatitis :

Atopic dermatitis may appear in both children and adults infected with HIV. In one series, 50% of infants with advanced HIV disease had atopic dermatitis.[146] Hemophilic children infected by blood transfusion may have flare-ups of previously quiescent atopic dermatitis.[147] Adults with a previous history of atopic disease may also note recurrence of atopy in advanced HIV disease.[148] They may develop atopic dermatitis when previously they had only respiratory atopic symptoms.

3 . 8 . 25 . Drug Reactions :

TMP-SMZ is used frequently in managing PCP. The incidence of adverse reactions to the drug is very high; in one study, 62% of HIV-infected patients with PCP could not complete their course of therapy because of adverse reactions.[149] Most reactions occur in the second week of therapy and are typical maculopapular/morbilliform reactions.Cutaneous eruptions occurred in 48% of treated patients. Other drug-induced hypersensitivity reactions in HIV-infected patients are urticarial reactions, exfoliative erythroderma, fixed-drug eruption, erythema multiforme, and toxic epidermal necrolysis. These reactions are most often due to antibiotics, especially TMP-SMZ and the penicillins.[150] Eruptions due to acyclovir, ketoconazole , amphotericin B, Zidovudine (AZT), Didanosine (DDI) , Zalcitabine (DDC), Stavudine (D4T) , Lamivudine (3TC) , and the protease inhibitors are uncommon.

3 . 8 . 26 . Insect Bite Reactions :

Urticarial pruritic papules are a common morphologic lesion in HIV-infected patients. This lesion is clinically specific but etiologically nonspecific. In occasional patients, this lesion is associated with insect bites and is called papular urticaria. In HIV-infected patients in San Francisco, except for scabies mites, fleas most commonly cause papular urticaria. In the southern United States, mosquitoes may be the primary offender.[151,152]

3 . 8 . 27 . Scabies:

In the case of severe cellular immunodeficiency, crusted scabies or Norwegian scabies can occur. Besides HIV-patients, persons with general physical or mental debilitation are affected. Over weeks to months, eczematous lesions covered with asbestos- like crusts extend over large areas and the plaques can be mistaken for psoriasis.

Norwegian/crusted scabies is highly contagious and its diagnosis should arouse suspicion of underlying HIV infection. Crusted scabies in HIV infection may be localized to the soles.[153] Crusted scabies carries many more mites than regular scabies . up to 10,000

mites/g scales. The history of unremitting and intractable itching is suggestive of scabies. The diagnosis is made by the clinical picture and proven by the demonstration of the mites, their ova, or fecal droppings in the scales by light microscopy of KOH treated scales. On histology, the female mite can be visualized in the stratum corneum.

3 . 8 . 28 . Seborrheic dermatitis:

The incidence in the general population is estimated to be 3.5 % of all young men. The liphophilic yeast Malassezia furfur is believed to be of pathogenetic relevance. Here the specific subtype appears to be more important than the density of colonization. In HIV infection 20-60 % are affected depending on the immune status. Seborrheic dermatitis appearing de novo or exacerbation of mild seborrheic dermatitis in a known HIV-positive patient could indicate seroconversion from a latency state to a symptomatic state. Seborrhoeic dermatitis is more common in seropositive homosexual men than seronegative homosexuals, and among infected patients it is commoner and has an earlier onset in homosexuals and bisexuals compared with intravenous drug users.[154]

Areas rich in sebaceous glands, such as the scalp, forehead, eyebrows, nasolabial folds, over the sternum, between the shoulder blades, external ear canal, and retroauricular area, develop yellowish, oily scales and crusts on mildly erythematous to very red plaques. The lesions may be pruritic.[155]

3 . 8 . 29 . Syphilis:

There is epidemiological synergy between HIV and other STIs.[156] Syphilis increases the risk of HIV acquisition and onward transmission. Infection with HIV may alter the natural history of syphilis. In most patients with early HIV infection, the clinical features, serological test results and response to treatment are similar to those in non-HIV-infected persons. With advancing immunosuppression, all of these may be significantly altered. Lues maligna, neurological and ocular involvement have been reported more commonly.[157-160] *Syphilis* may present differently in HIV infection.[161]

In primary syphilis, painful anal or oral chancres occur. Persistent chancres can still be found when the exanthems of secondary syphilis and symptoms such as generalized lymphadenopathy appear. In secondary syphilis, syphilids can ulcerate and develop thick crusts (rupia syphilitica or rupial syphilid), which are accompanied by high fever and severe illness. This unusual and otherwise rare course of syphilis, which is termed malignant syphilis, is found in 7 % of all syphilis associated with HIV infection. In addition, early neurosyphilis and a very short latent period before the onset of tertiary symptoms of syphilis are described. Neurosyphilis is partly due to a reduced blood-brain barrier, and a failure of benzathine penicillin G to prevent neurosyphilis in these patients is reported. The interpretation of syphilis serologies, especially in patients with repeated infections and severe immunodeficiency, can be complicated by false negative results and persistent antibodies. Therefore, it is advisable to verify *T. pallidum* infection in any clinical manifestation suspected to be syphilis by direct proof (dark-field microscopy, direct fluorescent antibody testing of exudates, or biopsy specimens).

Syphilis therapy, as recommended by the CDC, WHO, and the German STD Society (DSTDG) is identical for HIV-infected and non-HIV-infected patients.

HIVinfected patients should be evaluated clinically and serologically for failure of treatment at 3, 6, 9, 12, and 24 months after therapy.

3 . 8 . 30 . Xerosis/Dry skin:

Dry skin is a very frequent complication of any kind of immunodeficiency.

In the pre-HAART-era, dry skin was diagnosed in one of three HIV infected patients .

The prevalence of dry skin in HIV-infected patients decreased after the introduction of HAART, but is sometimes seen in patients on indinavir.[138,162] Some years ago, it had shown that the lipid film of the skin surface has a different composition in HIV-infected patients, but is not diminished in quantity.

3 . 8 . 31 . Photosensitivity :

Reports rarely describe photosensitivity in HIV-infected persons.[163] The photosensitivity is usually due to the shorter ultraviolet spectrum (UVB). Frequently prescribed photosensitizing medications (nonsteroidal anti-inflammatory drugs and TMP-SMZ) used in HIV-infected patients may play a role in their photosensitivity.

3 . 8 . 32 . Porphyria cutanea tarda (PCT) :

Porphyria cutanea tarda (PCT) has been described in many HIV-infected persons, suggesting an association between the two.[164-166] Many patients who are genetically susceptible to PCT develop the disease only after exposure to hepatotoxic agents that interfere with uroporphyrinogen decarboxylase. Hepatitis C has been associated with PCT.[167] Why patients capable of developing PCT do so after HIV infection is unknown, but in many cases, patients have been exposed to one or more of the above mentioned precipitating factors.

3 . 8 . 33 . Pruritic Papular Eruptions :

Pruritic papules are common in HIV infection[168] and are due to various causes. Reports describe *S. aureus* folliculitis, eosinophilic folliculitis, demodicidosis mites,[169] insect bite reactions, and granulomas with no identifiable infectious agent (e.g., granuloma annulare)[170] as causes of itching in the setting of HIV. Evaluation requires a skin biopsy. Most patients with pruritic papular eruptions have folliculitis. The approach is to search for staphylococcal infection by abrading and culturing an unruptured pustule (if present), followed by empiric treatment for staphylococcus with a semisynthetic penicillin (e.g., dicloxacillin) or a first-generation cephalosporin for 1 to 2 weeks.

3 . 9 . Skin and mucocutaneous disease related to antiretroviral drugs :

3 . 9 . 1 . Nucleoside analog reverse transcriptase inhibitors (NRTIs)

AZT, zidovudine, RetrovirTM: Drug eruptions occur in (6%) mostly macular, rarely severe reactions such as erythema multiforme and Stevens-Johnson syndrome, melanonychia striata medicamentosa, pigmentation , lichenoid eruptions of mucosal membranes, vasculitis, urticaria, pruritus, hyperhidrosis (5-19 %) and tongue ulcers.

ddI, didanosine, VidexTM: Drug eruptions and itching (4%), erythema multiforme, oral dryness (30 %), and papuloerythrodermia Ofuji.

d4T, stavudine, ZeritTM: Drug eruptions with fever.

3TC, lamivudine, EpivirTM: Exanthems, vasculitis, light sensitivity, linear nail hyperpigmentation, hair loss, paronychia, ingrown toenails.

FTC, emtricitabine, EmtrivaTM: Exanthems, especially in combination with ddI and efavirenz (10 %), cause unidentified.

ABC, abacavir, ZiagenTM: Maculopapular exanthems, hypersensitivity syndrome (5 %) after 9 (3-42) days, frequently associated with respiratory problems, nausea, and vomiting, increase in liver transaminases. Any suspicion of hypersensitivity syndrome forces immediate cessation of treatment.[171] Abacavir reexposure is contraindicated (severe, sometimes lethal reactions).

Tenofovir, VireadTM: rare exanthemas.

3 . 9 . 2 . Non-nucleoside analog reverse transcriptase inhibitors (NNRTIs)

Nevirapine, ViramuneTM: frequent drug eruptions (33 %), severe reactions 6 % (mostly within the first 6 weeks of treatment), Stevens-Johnson syndrome 0.5 %, and few cases of toxic epidermal necrolysis. Less frequent drug reactions (22 %), when therapy is initiated with low doses, and very low rate, and when HLA-Cw 8 positive patients are excluded from nevirapine therapy.[172] Cetirizine, as aprophylactic, is not effective.[173] Treatment must be stopped in 3-5 %. Reasons are severe skin reactions, exanthemas with fever,

conjunctivitis, pain of the limbs, meningitis, eosinophilia (DRESS syndrome = Drug rash with eosinophilia and systemic symptoms;[174,175] , occasionally diffuse loss of hair. Exanthems are 7x more frequent, and therapy has to be stopped 3.5 x more often in women compared to men.[176] Patients, especially women older than forty, with residual cell mediated immune functions (CD4 cells > 250/µl), are particularly at risk.

Delavirdine, RescriptorTM: Maculopapular or erythematous rashes, with or without pruritus in up to 50 %, starting 2-3 weeks after initiation of treatment and involving especially the trunk and upper arms. Mild exanthems without other complications can regress spontaneously without a need to discontinue treatment.

Efavirenz, SustivaTM: Frequent macular or urticarial exanthems (11 %). Light exanthems can regress spontaneously without discontinuation of treatment. In case of complications, it is necessary to stop treatment. Fat wasting.

3 . 9 . 3 . Protease inhibitors (PI)

Saquinavir, InviraseTM: Aphthous oral lesions (6 %), cheilitis, exanthems- (4 %), rarely Stevens-Johnson syndrome, bullous eruptions, papular pruritic folliculitis.

Ritonavir, NorvirTM: exanthems (0.9-2.6 %), papular pruritic folliculitis (8 %), perioral paresthesia (25 %).

Indinavir, CrixivanTM: In many patients a sicca syndrome with very dry skin, dry mouth and eyes is observed. In addition, exanthems are frequently papular and intensely itching, involving the lateral parts of the upper arms, the upper trunk and the lateral neck in particular, can occur. Differential diagnosis: papular pruritic eruption (folliculitis). Paronychia (pyogenic granuloma-like) and ingrown toenails, light diffuse loss of hair (12 %), severe and generalized loss of terminal and vellus hair in 1- 2 %. Hematoma and hemarthrosis in hemophiliacs. Lipodystrophy (.Crixi-belly., buffalo hump, facial lipotrophy, etc.), metabolic syndrome and asymptomatic hyperbilirubinemia.

Nelfinavir, ViraceptTM: Exanthems (infrequent), paronychia (single cases).

Amprenavir, AgeneraseTM: Exanthems (3%, mostly starting during the 2nd week of treatment, [177]), perioral paresthesia.

Atazanavir, ReyatazTM: Exanthems [(178)], hyperbilirubinemia, in some cases with jaundice and scleral icterus.

Lopinavir/r, KaletraTM: Exanthemas (infrequent). Lipodystrophy.

3 . 9 . 4 . Entry-Inhibitors

T-20, Enfuvirtide, FuzeonTM: Erythems and indurations at the injection sites (96%, almost obligatory), exanthems <1% .[(179)]

3 . 10 . Diagnosis :

The diagnosis of AIDS in a person infected with HIV is based on the presence of certain signs or symptoms. Since June 5, 1981, many definitions have been developed for epidemiological surveillance such as the Bangui definition and the 1994 expanded World Health Organization AIDS case definition. However, clinical staging of patients was not an intended use for these systems as they are neither sensitive, nor specific. In developing countries, the World Health Organization staging system for HIV infection and disease, using clinical and laboratory data, is used and in developed countries, the Centers for Disease Control (CDC) Classification System is used.

3 . 10 . 1. WHO disease staging system:

In 1990, the World Health Organization (WHO) grouped these infections and conditions together by introducing a staging system for patients infected with HIV-1.[(180)] An update took place in September 2005. Most of these conditions are opportunistic infections that are easily treatable in healthy people. (Table 2) shows the proposed WHO staging system for patients infected with HIV-1.[(195)]

Stage I: HIV infection is asymptomatic and not categorized as AIDS

Stage II: includes minor mucocutaneous manifestations and recurrent upper respiratory tract infections

Stage III: includes unexplained chronic diarrhea for longer than a month, severe bacterial infections and pulmonary tuberculosis

Stage IV: includes toxoplasmosis of the brain, candidiasis of the esophagus, trachea, bronchi or lungs and Kaposi's sarcoma; these diseases are indicators of AIDS.

3 . 10 . 2. CDC classification system:

There are two main definitions for AIDS, both produced by the Centers for Disease Control and Prevention (CDC). The older definition is to referring to AIDS using the diseases that were associated with it, for example, lymphadenopathy, the disease after which the discoverers of HIV originally named the virus.[16,17] In 1993, the CDC expanded their definition of AIDS to include all HIV positive people with a $CD4^+$ T cell count below 200 per µL of blood or 14% of all lymphocytes.[181] The majority of new AIDS cases in developed countries use either this definition or the pre-1993 CDC definition. The AIDS diagnosis still stands even if, after treatment, the $CD4^+$ T cell count rises to above 200 per µL of blood or other AIDS-defining illnesses are cured.

3 . 10 . 3. HIV test:

Many people are unaware that they are infected with HIV.[182] Less than 1% of the sexually active urban population in Africa has been tested, and this proportion is even lower in rural populations. Furthermore, only 0.5% of pregnant women attending urban health facilities are counseled, tested or receive their test results. Again, this proportion is even lower in rural health facilities.[182] Therefore, donor blood and blood products used in medicine and medical research are screened for HIV.

HIV tests are usually performed on venous blood. Many laboratories use *fourth generation* screening tests which detect anti-HIV antibody (IgG and IgM) and the HIV p24 antigen.

The detection of HIV antibody or antigen in a patient previously known to be negative is evidence of HIV infection. Individuals whose first specimen indicates evidence of HIV infection will have a repeat test on a second blood sample to confirm the results.

The window period (the time between initial infection and the development of detectable antibodies against the infection) can vary since it can take 3–6 months to seroconvert and to test positive. Detection of the virus using polymerase chain reaction (PCR) during the window period is possible, and evidence suggests that an infection may often be detected earlier than when using a fourth generation EIA screening test.

Positive results obtained by PCR are confirmed by antibody tests.[183] Routinely used HIV tests for infection in neonates and infants (ie, patients younger than 2 years),[184] born to HIV-positive mothers, have no value because of the presence of maternal antibody to HIV in the child's blood. HIV infection can only be diagnosed by PCR, testing for HIV pro-viral DNA in the children's lymphocytes.[185]

3 . 11 . HIV treatment:

Antiretroviral treatment of HIV began in the mid-1980s with the nucleoside analogue zidovudine (azidothymidine) and the demonstration that this was better than placebo in the treatment of symptomatic disease. However, the treatment of HIV infection was revolutionized in developed countries as a result of the introduction of HAART. This has reduced short-term mortality and markedly increased quality of life by preventing opportunistic diseases.[186] HAART has developed as a result of controlled trials showing that dual nucleoside analogue therapy improves survival compared with zidovudine monotherapy,[187] and that three-drug therapy consisting of two nucleoside analogues and a protease inhibitor is superior to two drugs.[188]

The dramatic improvements in survival with the use of HAART coincided with the development of two potent classes of drugs. Following incorporation of viral DNA into the host genome, viral progeny are produced as a result of the transcription of this DNA,which

accompanies cell activation. This produces polyproteins, which to be effective have to be digested by a virally coded protease. A variety of inhibitors of this protease are now available to clinicians and all are extremely potent.

The other potent class of compounds are the nonnucleoside reverse transcriptase inhibitors (NNRTIs). As described previously, the virus encodes for a unique enzyme, reverse transcriptase, that is responsible for converting viral RNA into a DNA copy, which is then incorporated in the host genome. The originally introduced therapies for HIV were all nucleoside analogues, which act as chain terminators of the growing DNA chain.

Reverse transcriptase can also be inhibited very potently by a variety of chemicals that act in a pocket of the reverse transcriptase closely adjacent to the catalytic site. The potency of these drugs was only appreciated when they were given to individuals who had not previously received treatment, accompanied by nucleoside analogues.[189]

This combination inhibits viral replication sufficiently completely to prevent selection of viral mutants with resistance to the NNRTI class.[190]

The original hypothesis for optimum treatment of HIV infection was 'hit hard and hit early' [191], i.e. to use potent regimens and to use them early in the disease course with the hope of completely eradicating evidence of infection within a definite period. Unfortunately, as understanding of the pathogenesis of HIV infection has improved, this hypothesis has turned out to be unrealistic, perhaps most importantly because HIV is also incorporated into long-lived cells which generally divide very occasionally.[192] It is only during the process of cellular replication that anti-HIV drugs are active, and therefore the early hopes of eradication within a 3–4 year period have not been realized, and it is likely that present treatment will be required lifelong to continually suppress viral replication. Early treatment was also advocated because it was assumed that HIV caused irreversible deletions in the immune repertoire and so if treatment was started late, patients would remain susceptible to opportunistic infections. Fortunately this has been shown not to be

the case. Even individuals treated in late disease show considerable reconstitution of the immune repertoire.[193,194]

Those drugs in current usage are listed by class in (Tables 3-5). The principal non dermatological side effects are included.

Table- 3 Listed the *nucleoside analogue reverse transcriptase inhibitors. (After Moyle & Gazzard [196]; Ward et al. [197].)*

Table- 4 Listed the *non - nucleoside reverse transcriptase inhibitors. (After Moyle & Gazzard [198].)*

Table -5 Listed the *protease inhibitors. (After Moyle & Gazzard [199].)*

4 . Aim of the study

About 39–46 million people in the world are currently living with HIV/AIDS and HIV infection constitutes a main health problem worldwide. skin disease is one health problem among HIV positive patients presenting with a variety of dermatologic manifestations .

Studies on different domains of internal medicine have been trying to look for correlation between CD4 cell counts & systemic changes.

The aim of this study is

1- To assess epidemiologically and clinically cutaneous manifestations in HIV positive Libyan patients.

2- To study the patterns of the cutaneous manifestations and their relationship to CD4 counts , viral load and treatment received.

5 . Materials and methods

In a retrospective study , 220 HIV positive Libyan patients registered and attending dermatology clinic for one or more occasions with different skin lesions in Benghazi center of infectious diseases and immunology (BCIDI) over 8 years (during the period from January 2003 to november 2010). The patients age ranging from 7 to 46 years old.

The study is conducted by reviewing the patient records and their visits and the data were collected by using the management information system (MIS) . The patients were screened for dermatological findings by thorough history which include age , sex , residency , family history and date of HIV diagnosis .

Details including the number of visits to dermatologist , clinical findings, diagnosis , treatment , either the patient is on antiretroviral therapy or not , and the presence of other viral coinfection e.g hepatitis C virus , hepatitis B virus , cytomegalovirus , toxoplasmosis and rubella all are documented .

CD4 counts (cell/mm^3) is assessed by using flow cytometry / Facs calibar (gold standard for CD4 T lymphocyte measurements) .

HIV viral load is assessed by M2000 abbot PCR . Both are obtained from medical records at different visits and stages of the disease.

The data were collected and fulfilled according to a previously perpared proforma. (Fig 1)

Statistical analysis of the data were carried out using SPSS (version 12) software and analyzed by using t - test , and Chi square tests (Fisher exact test or likelihood ratio when Chi square test was not applicable).

6 . Results:

Among 220 HIV positive patients included in this study , 119 patients (54.1%) were males and 101 patients (45.9%) were females .The age ranges between 7 and 46 years (mean 16.5 years). 189 patients (86%) were resident in Benghazi , whereas 31 patients (14%) were resident in the rural areas .

Family history of HIV was positive in 12% of cases (5% were parents , 4.1% were sons or daughters ,1.8% were siblings and only 0.9% were more than one member).

Ninety percent of cases were diagnosed between 1998 – 2000 while the remaining cases were diagnosed in the later years. (Table 6)

The age of onset of HIV were seen between the age of 0-5 years in 66.3% of cases (146 patients) , 18.6% between the age of 6-10 years and the remaining cases were seen in the older ages. (Table 7)

The most affected age group was 10 to 19 years which constitutes 78.6% of patients (173 patients) , the next affected group constitutes 15.5% (34 patients) seen in the age group 20-29 years while the older age groups were affected less frequently. (Table 8)

The predominant mode of transmission of HIV in our patients was by parenteral abuse which was seen in 209 patients (95%), from child to mother (4.5%) in which cracks in the nipple of lactating mother and presence of oral erosions or ulcers of the child may facilitate the transmission of HIV by blood through breast feeding. (Table 9)

Ninety percent of patients were coinfected with at least one viral infection and about 62.7% of them were coinfected with more than one viral agent. (Fig 2)

The most prevalent infection was cytomegalovirus and observed in 80.9% , followed by hepatitis C virus (46.8%) , hepatitis B virus (22%) and uncommonly by toxoplasmosis (10%) and rubella in only 3.6% .

The number of visits to dermatologist during this period was 408 (1.86 per single patient) and the total number of complaints was 439 (2 per single patient).

Among the total number of visits to dermatologist , 93% had single disease , 6.1% had two diseases and only 0.7% had three diseases.

Among the total number of skin diseases diagnosed during the visits; parasitic infestations were seen in 92 patients (21.0%), eczematous and related disorders in 78 patients (17.8%), viral infections in 71 patients (16.2%) , bacterial infections in 41 patients (9.3%) and fungal infections in 35 patients (7.9%) from all complaint. (Table 10)

Dematophyte infection was the most common fungal infection and recorded in 19 patients (4.3%), followed by candidal infection in 11 patients (2.5%) from all complaint. (Fig 3)

Warts represent 5.9% of viral infections followed by Herpes zoster (4.1%). (Fig 4)

Among the 41 patients of recorded bacterial infections , 9 patients (2.1%) were impetigo followed by ecthyma in 8 patients (1.8%) and furuncle in 7 patients (1.6%). (Fig 5)

Eczematous disorders constitute 11.5 % from all complaint and atopic dermatitis , photo-dermatitis and seborrheic dermatitis were the common disorders seen and presented in 16 (3.6%) , 9 (2.1%) and 8 (1.8%) respectively. (Fig 6)

Insect bite and scabies were seen in 58 and 31 patients (13.2% &7.1%) respectively.(Fig 7)

The total number of cases of other skin dermatoses was 122 patients (27.8%) including pitryiasis alba in 40 patients and acne vulgaris and xerosis in 17 patients each. (Table 11)

Out of the total visits 369 , CD4 count 500-999 cells /mm^3 was recorded in 42.8% while 200-499 cells /mm^3 was recorded in 34.7%. (Fig 8)

According to the visits , despite of the higher number of cases of non infectious and infectious disorders in male gender , the data was statistically not significant and P value was < 0.772 .(Table 12)

Also the distribution of different infections including viral , bacterial and fungal was not statistically significant. (Table 13)

In relation to absence or presence of one or more coinfection with HIV , there was no significant differences in non infectious , infectious disorders and the distribution of different infection and P value was <0.573 and <0.53 respectively. (Table 14,15)

Based on the current status of antiretroviral therapy , it seems to have no significant difference on the proportion of skin disorders. (Table 16)

Concerning CD4 count at the visits , it does not show significant difference regarding proportions of the disorders and P value < 0.238 . (Table 17)

More infections including bacterial and fungal when CD4 count > 200 were observed and the viral infection is higher when CD4 count <200 as compared to other infections. (Fig 9)

Analysis of viral load by PCR at the recorded visits , showed infectious disease disorders were higher among patients with low viral load P value < 0.038 . (Table 18 , Fig 10)

Table (6) distribution of cases in study sample according to the year of diagnosis

Year of diagnosis	Frequency	Percent	Cumulative Percent
1998	147	66.8	66.8
1999	43	19.5	86.4
2000	10	4.5	90.9
2001	5	2.3	93.2
2002	2	.9	94.1
2003	6	2.7	96.8
2004	2	.9	97.7
2005	2	.9	98.6
2007	1	.5	99.1
2009	2	.9	100.0
Total	220	100.0	-

Table(7) Distribution of Patients according to the age of onset of HIV

Age / years	No	%
0-5	146	66.3
6-10	41	18.6
11-15	19	8.6
16-20	1	0.5
21-25	2	1
26-30	8	3.5
31-35	3	1.5

Table(8) Distribution of Patients according to age group

Age group / years	No	%
0-9	1	0.5
10-19	173	78.6
20-29	34	15.5
30-39	6	2.7
40-49	6	2.7

Table(9) Distribution of Patients according to the mode of transmission of HIV

Mode of transmission	No	%
Parenteral	209	95
From child to mother	10	4.5
Vertical transmission from mother to child	1	0.5

Fig (2) distribution of cases in study sample according to number of coinfections

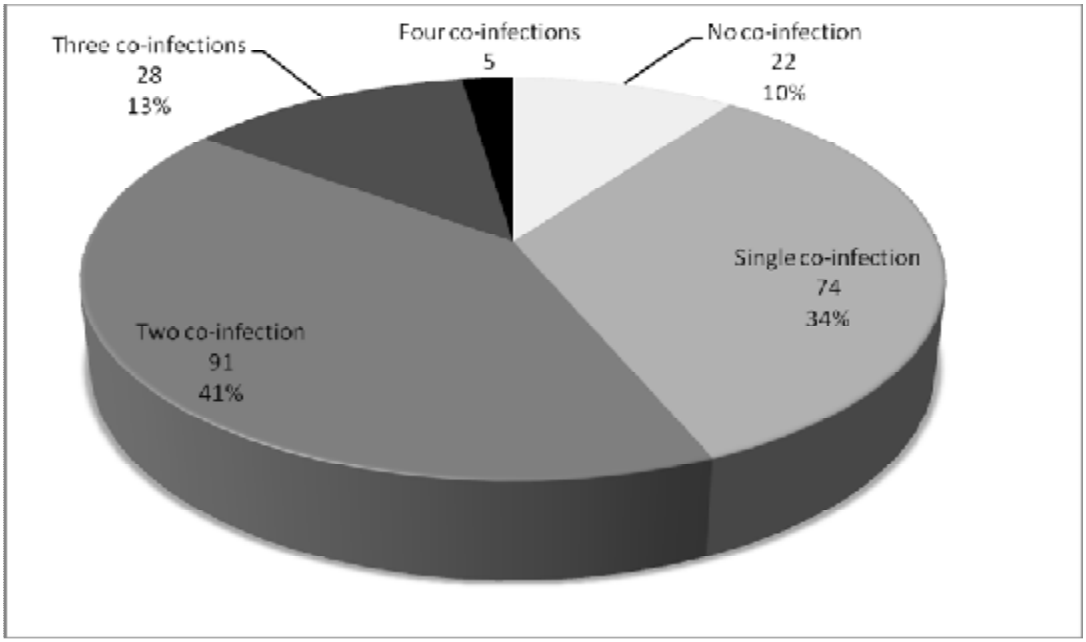

Table (10) Common skin disorders in the complaints of study sample

Skin disorder	As single skin disorder	With another skin disorder	All observations	% from all complaints
Parasitic infestations	86	6	92	21.0%
Eczema and related disorders	68	10	78	17.8%
Viral infections	60	11	71	16.2%
Bacterial infections	40	1	41	9.3%
Fungal infections	30	5	35	7.9%
Total	284	33	317	72.2%

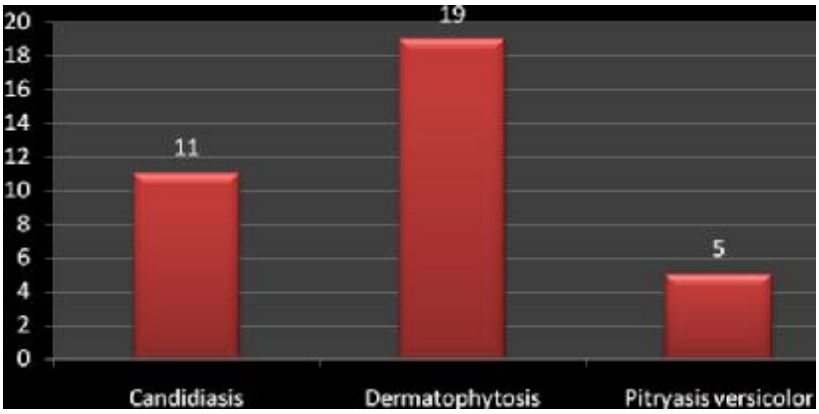

Figure (3) Fungal infections in the complaints of study sample

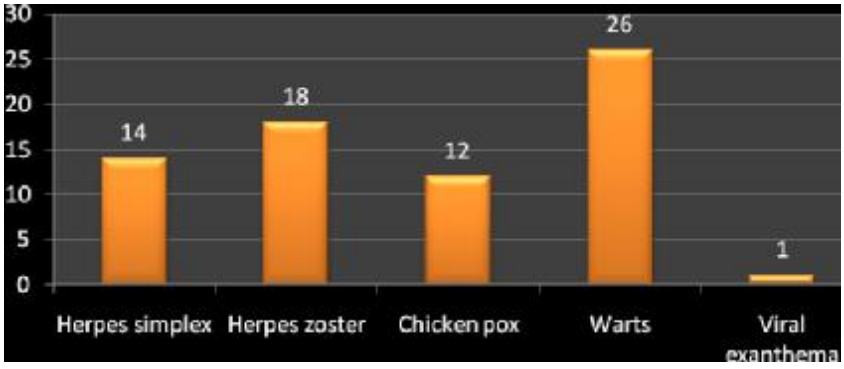

Figure (4) Viral infections in the complaints of study sample

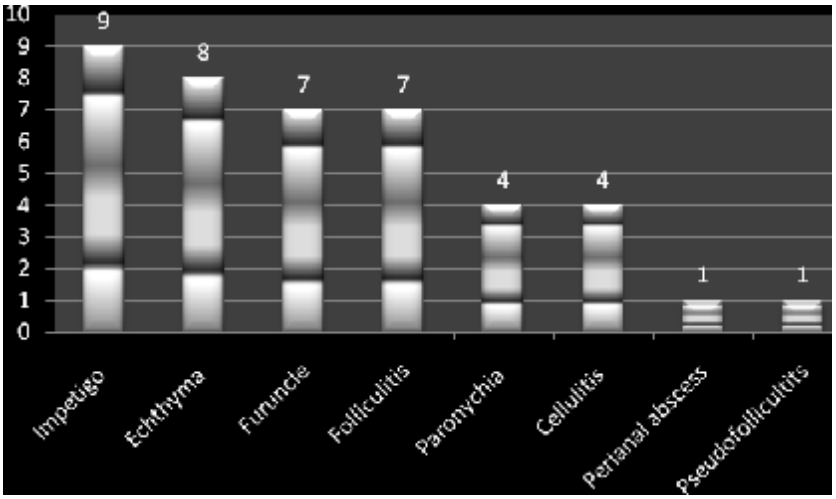

Figure (5) Bacterial infections in the complaints of study sample

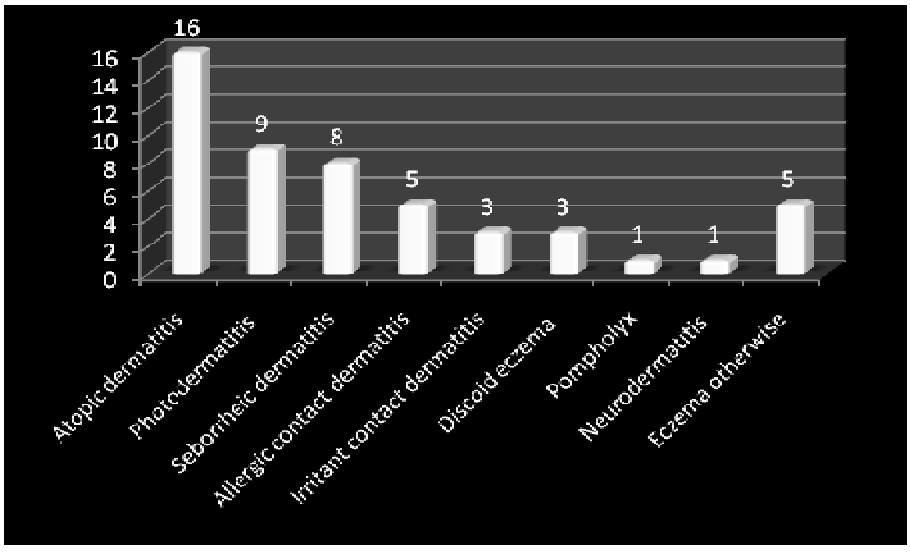

Figure (6):Eczematous dermatosis in the complaints of study sample

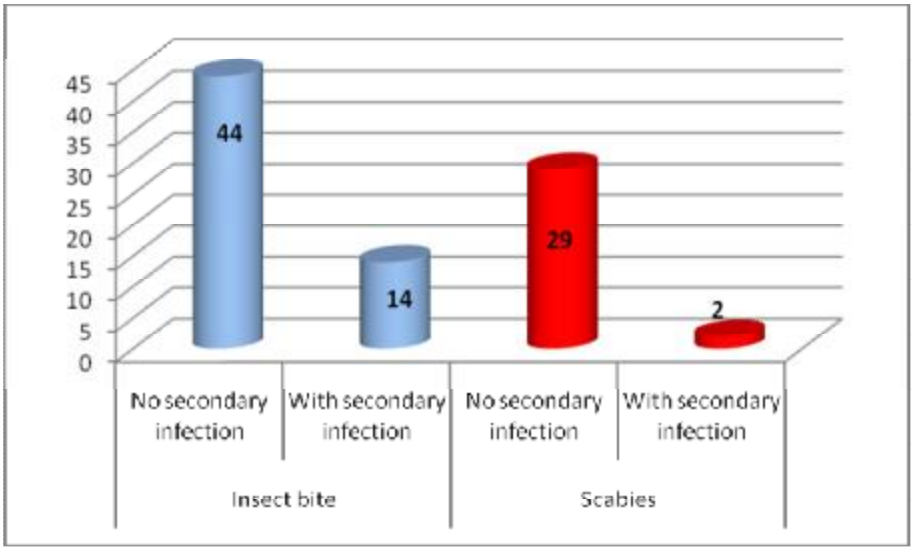

Figure (7): Arthropod infestations in the complaints of study sample

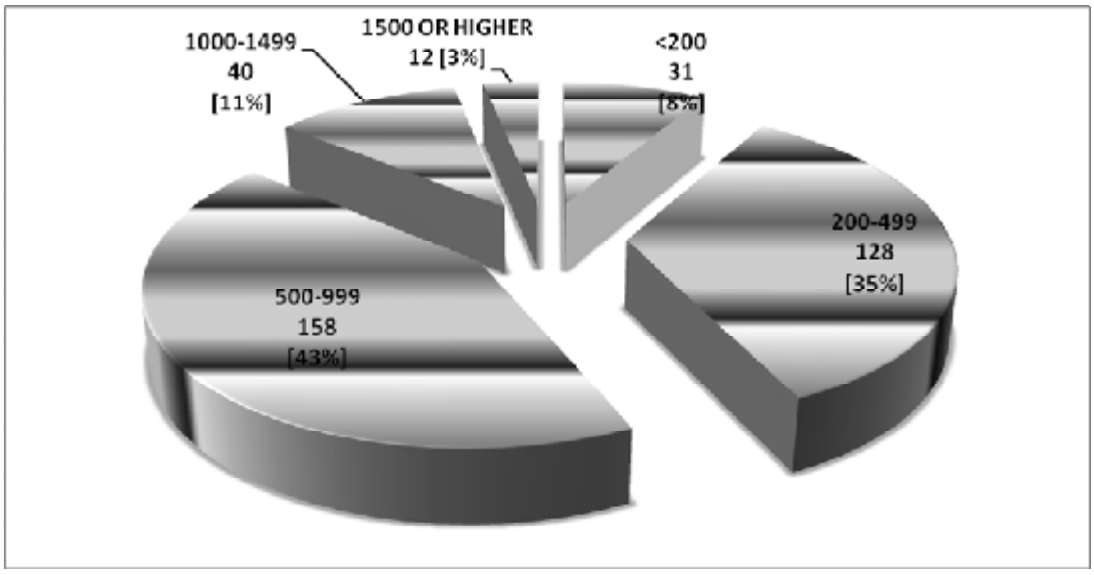

Figure (8): Frequency and percentage of visits in different categories of CD4 count

Table (11): Other skin disorders in the complaints of study sample

Skin disorder	As single skin disorder	With another skin disorder	All observations	% from all complaints
Acne vulgaris	15	2	17	3.9%
Xerosis	11	6	17	3.9%
Aphthous ulcer	7	1	8	1.8%
Angular stomatits	5	2	7	1.6%
Cheilitis	4	1	5	1.15%
Dandruff	5	0	5	1.15%
Alopecia	4	0	4	0.9%
Psoriasis vulgaris	4	0	4	0.9%
Keratosis pillaris	4	2	6	1.4%
Pitryasis rosea	2	0	2	0.5%
Pitryasis ameatacea	1	1	2	0.5%
Acneiform eruption	1	0	1	0.2%
Callosities	1	0	1	0.2%
Chilblains	1	0	1	0.2%
Ichthyosis vulgaris	1	0	1	0.2%
Necrobiosis lipoidica diabeticorum	1	0	1	0.2%
Pitryasis alba	29	11	40	9.1%
Total	96	26	122	27.8%

Table (12): Gender of the patient according to the category of skin disorder in the visits with single disorder diagnosed at visit

Gender of the patient	Major category of skin disorder		Total
	Non-infectious disorders	Infectious disorders	
Male	144 (66.7%)	72 (33.3%)	216 (100.0%)
Female	107 (65.2%)	57 (34.8%)	164 (100.0%)
Total	251 (66.1%)	129 (33.9%)	380 (100.0%)

Table (13): Patient gender according to the category of infectious skin disorder in visits with single infectious disorder

Gender of the patient	Subcategory of infectious skin disorder			Total
	Bacterial infection	Fungal infection	Viral infection	
Male	26 (36.1%)	17 (23.6%)	29 (40.3%)	72 (100.0%)
Female	14 (24.6%)	13 (22.8%)	30 (52.6%)	57 (100.0%)
Total	40 (31.0%)	30 (23.3%)	59 (45.7%)	129 (100.0%)

Table (14): Number of coinfections according to the category of skin disorder in the visits with single disorder

Number of coinfections	Major category of skin disorder		Total
	Non-infectious disorders	Infectious disorders	
No co-infection	32 (74.4%)	11 (25.6%)	43 (100.0%)
Single co-infection	77 (62.6%)	46 (37.4%)	123 (100.0%)
Two co-infection	101 (64.7%)	55 (35.3%)	156 (100.0%)
Three co-infections	34 (69.4%)	15 (30.6%)	49 (100.0%)
Four co-infections	7 (77.8%)	2 (22.2%)	9 (100.0%)
Total	251 (66.1%)	129 (33.9%)	380 (100.0%)

Table (15): Presence of coinfections according to the category of infectious skin disorder in visits with single infectious disorder

Coinfection	Subcategory of infectious skin disorder			Total
	Bacterial infection	Fungal infection	Viral infection	
No co-infection	2 (18.2%)	3 (27.3%)	6 (54.5%)	11 (100.0%)
Single co-infection	16 (34.8%)	8 (17.4%)	22 (47.8%)	46 (100.0%)
Two co-infection	15 (27.3%)	17 (30.9%)	23 (41.8%)	55 (100.0%)
Three co-infections or more	7 (41.2%)	2 (11.8%)	8 (47.0%)	17 (100.0%)
Total	40 (31.0%)	30 (23.3%)	59 (45.7%)	129 (100.0%)

Table (16): Antiretroviral therapy status according to category of skin disorders in the visits with single disorder

Antiretroviral therapy	Major category of skin disorder		Total
	Non-infectious disorders	Infectious disorders	
Not taken	40 (63.5%)	23 (36.5%)	63 (100.0%)
On treatment	164 (66.9%)	81 (33.1%)	245 (100.0%)
Off treatment	47 (65.3%)	25 (34.7%)	72 (100.0%)
Total	251 (66.1%)	129 (33.9%)	380 (100.0%)

Table (17): CD4 categories according to category of skin disorders in the visits with single disorder

Category of CD4 count	Major category of skin disorder		Total
	Non-infectious disorders	Infectious disorders	
Less than 200	19 (61.3%)	12 (38.7%)	31 (100.0%)
200 – 499	75 (62.5%)	45 (37.5%)	120 (100.0%)
500 – 999	102 (70.3%)	43 (29.7%)	145 (100.0%)
1000 – 1499	26 (68.4%)	12 (31.6%)	38 (100.0%)
1500 and higher	8 (72.7%)	3 (27.3%)	11 (100.0%)
Total	230 (66.7%)	115 (33.3%)	345 (100.0%)

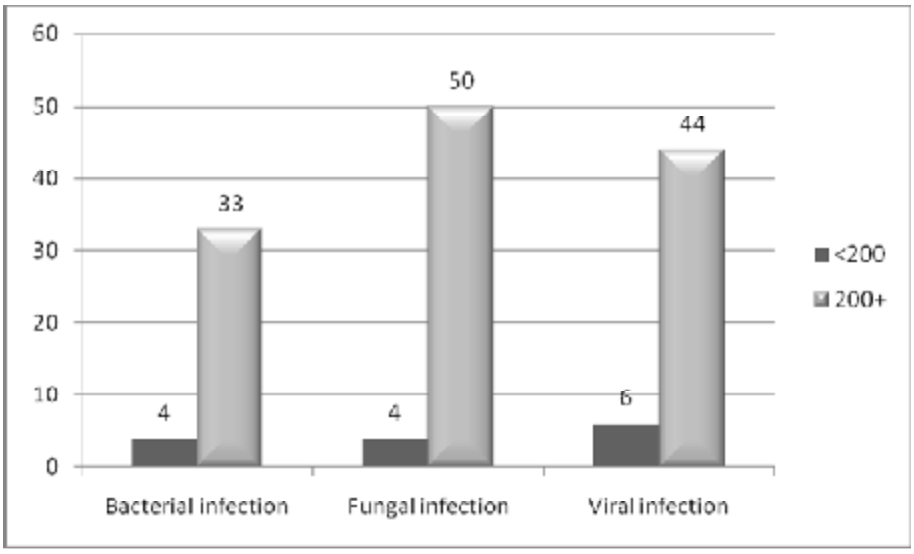

Figure (9): CD4 categories according to category of skin disorders in the visits with single infectious disorder

Table (18): Viral load by PCR categories according to category of skin disorders in the visits with single disorder

Category of viral load by PCR	Major category of skin disorder		Total
	Non-infectious disorders	Infectious disorders	
<400	18 (47.4%)	20 (52.6%)	38 (100.0%)
400 – 1499	73 (74.5%)	25 (25.5%)	98 (100.0%)
1500 – 9999	30 (68.2%)	14 (31.8%)	44 (100.0%)
10000 – 59999	57 (67.9%)	27 (32.1%)	84 (100.0%)
60000 and more	47 (60.3%)	31 (39.7%)	78 (100.0%)
Total	225 (65.8%)	117 (34.2%)	342 (100.0%)

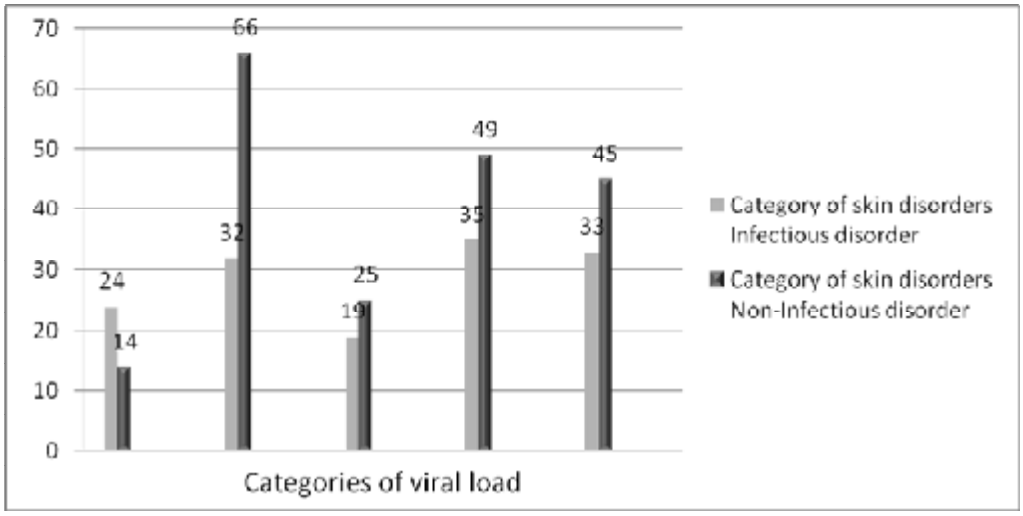

Figure (10): Viral load by PCR categories according to category of skin disorders in the visits with single disorder

7 . Discussion

Cutaneous manifestations of human immunodeficiency virus (HIV) disease may result from HIV infection itself or from opportunistic disorders secondary to the decline in Immunocompetence from the disease. Cutaneous disorders may be the initial signs of HIV-related immunosuppression. Recognizing HIV-related skin changes may lead to the diagnosis of HIV infection in the early stages, allowing initiation of appropriate antiretroviral therapy.

A variety of neoplastic, infectious, and noninfectious diseases can produce cutaneous manifestations throughout the course of HIV disease. These manifestations may occur more frequently than in persons without HIV infection and may be less responsive to usual treatment modalities.[200]

There is evidence in literature pertaining to the fact that prevalence and pattern of skin diseases vary from region to region,[201,202,203] for instance the prevalence rates of dermatologic problems in Tanzania,[204] Cameron,[5] Thailand[203] and Zambia[205] were 41.7%, 68.8%, 95%, 98.3% respectively. This could be explained by differences in status of self health care, climatic and environmental conditions.

In our study , at least one skin lesion was detected in 93% of the patients and this is consistent to other studies including Pitche et al (82.5%) , Sanadaj city in Iran (94.3%) , Jeffrey et al in 86% of their patients [203,206,207] whereas a south western France study showed that it is relatively lower (65.3%).[208]

Results of the present study showed that 119 patients (54.1 %) were males and 101 patients (45.9 %) were females which is relatively similar to another study in the tertiary care hospital in atribal (Bastar) region of Chhattisgarh in India where they found among 137 patients , 83(60.58%) were males and 54 (39.41%) were females .[209]

In our patients the age ranges between 7 and 46 years (mean 16.5 years) and the most affected age group was 10 to 19 yrs that constitutes 78.6% of our patients which is not correlated to Bravo et al.(2006)[210] who found out that the most affected age was the sexually active age group 30 to 39 yrs-51%. Also the age of onset of HIV in our patients were seen between the age of 0-5 years in 66.3% of cases (146 patients) , 18.6% between the age of 6-10 years and the remaining fewer cases were seen in the older ages . This may be explained by the fact that the predominant mode of transmission of HIV in our patients was by parenteral abuse (95%) while they were admitted to children hospital in 1998 , the remainders were either mothers who got the infection from their children or through vertical transmission from mother to child (4.5% & 0.5% respectively) ; unlike the results of other study,[208] where it has been reported that the modes of transmission was 35.3% homosexual, 27.8% intravenous drug use , and 24.4% heterosexual .

Among our data 189 patients (86%) were resident in Benghazi and only 31 patients (14%) were resident in the rural areas and they were referred to children hospital , whereas the results of the study in abastar region Chhattisgarh in india where the majority (90%) of the patients were belonged to rural areas and belonged to lower socioeconomic status and poor nutritional status which itself can accelerate the progression of HIV.[209] This could be explained that the majority of hospital admission and follow up were from Benghazi where they got the infection inside the hospital.

Family history of HIV was positive in 12% of cases (5% were parents , 4.1% were sons or daughters ,1.8% were siblings and only 0.9% were more than one member) .

Ninety percent of cases were diagnosed between 1998 – 2000 while the remaining cases were diagnosed in the later years .

Among the total number of skin diseases diagnosed during the visits; parasitic infestations were seen in 92 patients (21.0%), eczematous and related disorders in 78 patients (17.8%), viral infections in 71 patients (16.2%) , bacterial infections in 41 patients (9.3%) and fungal infections in 35 patients (7.9%) from all complaint.

Similar to Eichmann's study , eczema was common in our patients.[213]

Viral, bacterial and fungal infections were common in our study which is consistent with other studies where fungal, viral, bacterial infections and neoplasm were the most common findings.[211,212]

In comparison to other studies ; oral candidiasis was observed in only 2.5% of our patients which is very low as compared to other studies in which oral candidiasis forms 34.3% and 54.17% in Sivayathorn and Wiwanitkit reports respectively.[214,215]

Dermatophytosis was observed in 4.3% from all complaints and this is not consistent to a study in USA which forms 34% of cases.[205]

Widespread or recalcitrant warts may be observed on the oral mucosa, the face, the perianal region, and the female genital tract in patients infected with HIV. The perianal and cervical lesions may be difficult to treat.

Large plantar warts caused by human papillomoavirus–66 (HPV-66) and an epidermodysplasia verruciformis like eruption, which is believed to be associated with HPV infection, have also been reported in patients infected with HIV.[216]

A 42-month prospective study by Smith et al in 912 HIV-1–infected patients found that condylomata acuminata and verrucae are observed early, and their frequency does not increase as the disease progresses, whereas the incidence of HSV infections, and oral hairy leukoplakia increases as the disease advances.[217, 218]

According to Leibovitz et al, chronic VZV infections associated with HIV-1 infection begin as vesicles and progress into necrotic, nonhealing ulcers. Chronic VZV infection may mimic basal cell carcinoma.[219,220,221]

Regarding viral infections in the present study ; warts was the most common and constitutes 37% of all viral infections (5.9% from all complaint). This was different from the study carried out at the Phramongkutkloa hospital skin clinic , Bangkok which shows herpes zoster as the most common viral infection (48.2%) of all viral infections and no cases of warts were reported.[222]

In our study; herpes zoster was observed in only 4.1% from all complaints which is very much lower than Sivayathorn[214] report in which herpes zoster constitute 16.3% of cases .

Also herpes simplex was observed in only 3.2% from all complaints and is not consistent with the same study report [214] in which herpes simplex constitutes 14.9% of cases .

Oral hairy leukoplakia was the second common finding caused by viral infection as reported by Chiewchannvit and Wongmaneerojn[223] which is different from the study of Kullavanijaya and Bisalbutra[224] who reported a low incidence of oral hairy leukoplakia , while in our study ; there is no reported case of oral hairy leukoplakia.

Bacterial infections was observed in 9.3% from all patients which is considered low as compared to Bhandary et al.(1997) reports which constitutes 25% of cases.[225]

Patients with HIV have been found to have increased rates of cutaneous colonization by staphylococcus aureus, and in patients with advanced disease, sepsis and deep tissue infection can be common. Methicillin-resistant S aureus (MRSA) soft-tissue infection is an increasing problem.[226]

Scabies was seen in about 7.1 % of our patient presentation which is considered high as compared to reports from Kumarasamy et al.(2000) which showed only 0.5% of their patients were infected by scabies.[227]

Seborrheic dermatitis may be the initial cutaneous manifestation of HIV disease.

According to Mathes et al, seborrheic dermatitis like eruptions are observed in 83% of patients with AIDS in which the eruption is characterized by widespread inflammatory and hyperkeratotic lesions and may progress to erythroderma in some patients.[228]

Although our and another study reported low frequency of seborrheic dermatitis and recorded in 1.8% and 4.7% respectively[222], other international data reported higher percentage of seborrheic dermatitis including 21% and 46.6% respectively.[214,215]

In our study; psoriasis was observed in 0.9% from all complaints and this is not consistent to Sivayathorn[214]study which is reported in 6.5% of cases .

Generalized dry skin syndrome is frequently observed in patients with HIV infection. Xerosis may be the initial clinical manifestations of AIDS and is often causes pruritis.

In our study; xerosis was observed in 3.9% from all complaints and this is consistent to a retrospective study carried out among 286 patients at Kingston hospital out-patient clinic , Jamaica ; which constitutes 3% of cases[229] while it is very low if compared with other studies in which xerosis forms 52.5% and 73.3% respectively.[209,215]

Vin-Christian et al found that photosensitivity in HIV-infected patients appears to be a manifestation of advanced disease.[230] Most of the patients in that study were sensitive to ultraviolet B (UV-B) light; however, the patients who were most severely affected were sensitive to both UV-B and UV-A light.[230] In our study ; photosensitivity was observed in 2.1% from all complaint .

Diffuse alopecia or alopecia areata may be associated with HIV disease and may be inflammatory and permanent. The apoptotic follicular stem cell population in higher proportion may represent a hair cycle disturbance in patients with diffuse alopecia related to HIV-1 infection.[231]

Only few cases of alopecia were recorded and represent 0.9% of our patients which is not consistent with the reports from Wiwanitkit that constitutes 6.67% of cases.[215]

Acquired ichthyosis may begin on the lower extremities and disseminate in advanced HIV disease. Acquired ichthyosis may be a marker of concomitant infection with HIV-1 and human lymphotropic virus II in persons who use intravenous drugs and have profound helper T-cell depletion.[232]

In our study ; ichthyosis vulgaris was observed in 0.2% of our patients which is close to the study carried out at Kingston hospital out-patient clinic , Jamaica in which ichthyosis vulgaris forms 1% of cases .[229]

In our study ; acne vulgaris was observed in 3.9% from all complaint while it constitutes 7% of cases in the study carried out at Kingston hospital , Jamaica.[229]

In a prospective study, Crum-Cianflone et al found that 6% of HIV-infected persons developed a cutaneous malignancy over a mean follow-up period of 7.5 years.[233]

Regarding malignant skin changes, Kaposi sarcoma was the first reported malignancy associated with HIV infection and the world wide prevalence of KS in patients with AIDS may approach 34% , in United states ; however , the prevalence of KS patients with HIV disease is less than 5% .

In the present study ; no single case of Kaposi sarcoma or other skin malignancy was reported which is quite different as compared to other studies which may be attributed to the fact that 78.6% of our patients were within the age group 10 – 19 years which is not the age of onset of Kaposi sarcoma , in addition only 17.3% of our patients are not on antiretroviral therapy (ART) while 82.7% of patients are either on ART or was on ART and most of our patients are regular on follow up the HIV clinic and the other special clinics where they are getting special care by the staff and the data are registered at the management information system (MIS) which is routinely used .

Several studies have shown that association of skin disorders with HIV infection can serve as an indicator for advanced HIV infection, immunosuppression and decreased CD4 cell counts.[201,204,205,211,212]

In our study CD4 cell count was < 200 with viral infections compared to other infections but in some studies mean CD4 cell count in patients with viral disorders were higher than that of our study.[5,203]

In general, our study showed no strong correlation between CD4 cell counts and skin disorders which could be due to that majority of our patients had higher values of CD4 count . However we concluded that skin disorders can be seen with higher CD4 cell counts in HIV patients.

Concerning CD4 cell counts among 28 patients in a retrospective study carried out at the Phramongkutkloa hospital skin clinic , Bangkok , there was no statistically significant association between incidence of skin diseases and the level of CD4 counts[222] ; this finding was in agreement with that reported by Coopman et al.(1993)[234] which is consistent to our study.

Analysis of viral load by PCR at the recorded visits , showed infectious disease disorders were higher among patients with low viral load .

The use of antiretroviral therapy was high (82.7%) in our study population and this is consistent with Spira et al study who reported an 88.2% use of ARTs in their study population.[208]

Based on the current status of antiretroviral therapy , it seems to have no significant difference on the proportion of skin disorders .

Ninety percent of patients were coinfected with at least one viral infection and about 62.7% of them were coinfected with more than one viral agent.

The most prevalent infection was cytomegalovirus and observed in 80.9% , followed by hepatitis C virus (46.8%) , hepatitis B virus (22%) and uncommonly by toxoplasmosis (10%) and rubella in only 3.6% .

8 . Conclusions

1. Mucocutaneous changes are frequent and may be the initial manifestations of HIV diseases . At least one skin disease was detected in 93% of our patients.

2. The most affected age group was 10-19 years and reported in 78% of our patients and in majority (66%) , the age of onset was recorded at the age ≤ 5years.

3. The predominant mode of transmission was by parenteral abuse which presented in 95% of patients.

4. The common dermatoses recorded were parasitic infestations, viral infections, eczema, bacterial and fungal infections respectively.

5. In general , our study showed no significant correlation between CD4 cell count and reported skin disorders and CD4 cell count was lower (< 200) in viral infections as compared to other infections.

6. Analysis of viral load showed that infectious disorders were higher among patients with low viral load.

7. There is no significant correlation between Antiretroviral therapy and reported skin disorders.

8. Regarding malignant skin changes , there is no single case of Kaposi sarcoma or other malignancy was reported .

9. Recommendations

1. Dermatologic disorders constitute a major health problem in HIV patients and may be the initial manifestations , therefore dermatologists and other medical specialities should be aware of diagnosing HIV disease.

2. A better cooperation between dermatology departments and clinics with HIV centers and clinics over all the country.

3. Efficient and regular STDs training courses including HIV disease for medical students, postgraduate students in dermatology , community medicine , pediatrics , infectious diseases and others.

4. Community educational programs about the disease mode of transmission and preventive control measures , in cooperation with community departments , HIV centers and libyan CDC.

5. Further advanced studies and researches about HIV and skin diseases at different HIV centers and clinics at different places in Libya are required. In ddition providing HIV centers and clinics with recent and advanced diagnostic and therapeutic equipments and medications.

ملخص البحث

المقدمة :-

شكل ظهور مرض العوز المناعي المكتسب " الايدز " مشكلة صحية كبيرة واجهت كل دول العالم وساعدت التغيرات الجلدية الشائعة المصاحبة للمرض في تشخيص مرض الايدز في حالات لم تكن مشخصة في السابق عن طريق إجراء اختبار الايدز إضافة أن الإعراض الجلدية المصاحبة للمرض غالباً ما تعبر عن الحالة الصحية العامة وتندر بعلامات سيئة للمرض و تعطى عوامل تشخيصية في تحديد الحالة المناعية للمرض . كما أن العديد من الدراسات بينت العلاقة بين مرض الايدز والإعراض الجلدية المصاحبة والتي تعتبر دلالة على تقدم المرض وهبوط المناعة ونقص تعداد خلايا سى دى 4 (CD4).

مبررات وأهداف البحث:-

1- التقييم السريري والوبائي للإعراض الجلدية لمرض العوز المناعي المكتسب في ليبيا .
2- دارسة النمط والتغيرات الجلدية للمرض و علاقتها بتعداد خلايا س دي4 (CD 4) وحمولة الفيروس والعلاج المعطي .

طريقة البحث :-

شملت الدراسة الحالية 220 مريض حاملين لفيروس نقص المناعة المكتسبة (الايدز) والذين كانوا يترددون على عيادة الجلدية بمركز الإمراض السارية والمناعة – بنغازي . وبعضهم كان نزيلاً بقسم الباطنة أو الأطفال بالمركز على مدى 8 سنوات (في الفترة من يناير 2003 إلى نوفمبر 2010) .

تراوحت أعمار المرض بين 7- 46 سنة .

أجريت الدارسة بمراجعة سجلات وملفات المرضى من خلال زياراتهم المسجلة على المنظومة الخاصة بالمركز.

تمت عملية مسح شامل للإمراض الجلدية المصاحبة وعلاقتها بالحالة المناعية للمرض وإجراء التحليل الاحصائي للبيانات .

النتائج :-

تكونت مجموعة المرضى من 220 حالة منهم 119 (54.1 %) ذكور و 101 (45.9 %) إناث .
معظمهم (78.6%) في المرحلة العمرية من 10-19 سنة .
معظم المرضى (86%) من مدينة بنغازي والباقي (14%) من خارج بنغازي.
كانت طريقة انتقال العدوى الرئيسية هو الحقن المتعمد (95%) من الحالات أثناء تواجد المرضى أو ترددهم على مستشفى الأطفال ببنغازي بينما شكل انتقال المرض من الاطفال للأمهات (4.5%) ويوجد مريض واحد فقط أصيب بالمرض عن طريق والدته المصابة خلال فترة الحمل والولادة.
كان التاريخ العائلي للعدوى إيجابي في 12 % من الحالات,شكلت الإصابات الفيروسية المصاحبة 90% من الحالات على الاقل بفيروس واحد فقط بينها 62.7% مصابة بأكثرمن فيروس مصاحب ,80.9% إصابة مصاحبة بفيروس سيتوميجالو فيروس , 46.8% إصابة مصاحبة بفيروس الكبد الوبائي ج , 22% إصابة مصاحبة بفيروس الكبد الوبائي ب .
شكل مرض الاكزيما والإمراض المتعلقة بها 17.8 % من مجموعة الإمراض الجلدية في هذه الدراسة بينما بلغت الأخماج الفيروسية نسبة 16.2% والاخماج البكتيرية نسبة 9.3% والاخماج الفطرية 7.9% .
شكلت الحساسية المفرطة للدغة بعض الحشرات 13.2 % ومرض الجرب المعدي 7.1 % من الحالات .
بقية الإمراض الجلدية الأخرى شكلت 27.8% من مجموعة الحالات منها النخالة البيضاء بنسبة 9.1% , مرض حب الشباب وجفاف الجلد بنسبة 3.9% لكل منها , تفرحات الفم 1.8% , التهابات زوايا الفم 1.6%, تشققات الشفاه 1.1% , القشرة 1.1% , الثعلبة 0.9%, الصدفية 0.9% ,التقرن الشعري 1.4% والنخالة الوردية بنسبة 0.5% .

التوصيات :-

ينصح بالفحص الدوري لمرضي العوز المناعي المكتسب والتشخيص والعلاج المبكر لاي مرض جلدي والتي ستساهم في تحسين نمط الحياة لهولاء المرضي .

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APPENDIX

Figure (1) : Patient Proforma

Patient Name …….. File No:……Sex……

Date of birth :…….. Date of HIV Diagnosis ……..

Family history……..Residency……

Co infection: HBV HCV CMV Other .

ART yes ( ) No( ).

* If yes :…… ,……..,……

Start on :……stop on :……..

Cause of stop R, ……..……..…….

*……..,……,……..

Start on :……. Stop on:……..

Cause of stop R,…….

1- Date **- Dx.**

Muco cutaneous lesions : - Site

- Severity

-Type of lesion

C D4 count CD4 % CD8 count CD8 %

Viral load

WBC Hb

Neutrophils lymphocytes monocytes platelets

Treatment received

2- Date **- Dx**

Muco cutaneous lesions : - Site

- Severity

-Type of lesion

C D4 count CD4 % CD8 count CD8 %

Viral load

WBC Hb

Neutrophils lymphocytes monocytes platelets

Treatment received

---

3 - Date **- Dx**

Muco cutaneous lesions : - Site

- Severity

-Type of lesion

C D4 count CD4 % CD8 count CD8 %

Viral load

WBC Hb

Neutrophils lymphocytes monocytes platelets

Treatment received

---

4 - Date - **Dx**

Muco cutaneous lesions : - Site

- Severity

-Type of lesion

C D4 count CD4 % CD8 count CD8 %

Viral load

WBC Hb

Neutrophils lymphocytes monocytes platelets

Treatment received

5- Date - **Dx.**

Muco cutaneous lesions : - Site

- Severity

-Type of lesion

C D4 count CD4 % CD8 count CD8 %

Viral load

WBC Hb

Neutrophils lymphocytes monocytes platelets

Treatment received

(Table -1) Comparison of HIV species

Species	Virulence	Infectivity	Prevalence	Inferred origin
HIV-1	High	High	Global	Common Chimpanzee
HIV-2	Lower	Low	West Africa	Sooty Mangabey

(Table-2) Proposed WHO staging system for patients infected with HIV-1[195]

Stage 1:

- Asymptomatic
- Persistent generalised lymphadenopathy

Stage 2:

- Weight loss between 5% and 10% of body weight
- Minor mucocutaneous manifestations (seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular stomatitis)
- Herpes zoster within the past five years
- Recurrent upper respiratory tract infections (for example, bacterial sinusitis)

And/or

- Performance scale 2: symptomatic, normal activity

Stage 3:

- Weight loss >10% body weight
- Unexplained chronic diarrhoea for longer than one month
- Unexplained prolonged fever (intermittent or constant) for longer than one month
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis within last year
- Severe bacterial infections (for example, pneumonia, pyomyositis)

And/or

- Performance scale 3: bedridden for less than 50% of the day during the last month

Clinical stage 4 (AIDS):

- HIV wasting syndrome*
- *Pneumocystis carinii* pneumonia
- Toxoplasmosis of the brain
- Cryptosporidiosis with diarrhoea for more than one month
- *Cryptococcus*, extrapulmonary
- Cytomegalovirus infection of an organ other than liver, spleen, or lymph nodes
- Herpes simplex virus infection ; mucocutaneous for more than 1 month or visceral of any duration
- Progressive multifocal leukoencephalopathy
- Any disseminated endemic mycosis
- Candidiasis of the oesophagus, trachea, bronchi, or lungs
- Atypical mycobacteriosis, disseminated
- Non-typhoidal salmonella septicaemia
- Extrapulmonary tuberculosis
- Lymphoma
- Kaposi's sarcoma
- HIV encephalopathy

And/or

Performance scale 4: bedridden for more than 50% of the day during last month

*Defined by the Centers for Disease Control and Prevention as weight loss of greater than 10% body weight, plus either unexplained chronic diarrhoea (greater than 1 month) or chronic weakness and unexplained prolonged fever (greater than 1 month).

*Defined by the Centers for Disease Control and Prevention as clinical findings of disabling cognitive dysfunction and/or motor dysfunction, interfering with activities of daily living, progressing over weeks to months in the absence of a concurrent illness or condition other than infection with HIV that could explain the findings.

(Table- 3) ***Nucleoside analogue reverse transcriptase inhibitors. (After Moyle & Gazzard [196]; Ward et al. [197].)***

Drug	**Side effects**
Zidovudine (AZT/ZDV)	Nausea, bone marrow suppression, myopathy
Zalcitabine (ddC)	Peripheral neuropathy
Didanosine (ddI)	Nausea, bloating, diarrhoea, pancreatitis, peripheral neuropathy, gynaecomastia, gout
Stavudine (d4T)	Peripheral neuropathy, gynaecomastia
Lamivudine (3TC)	Nausea, bone marrow suppression, peripheral neuropathy
Abacavir, tenofovir (nucleotide)	Nausea, diarrhoea

(Table- 4) ***Non-nucleoside reverse transcriptase inhibitors. (After Moyle & Gazzard [198].)***

Drug	**Side effects**
Nevirapine	Clinical and biochemical hepatitis
Delavirdine	Biochemical hepatitis
Efavirenz	Insomnia, nightmares

(Table -5) ***Protease inhibitors. (After Moyle & Gazzard*** [199]***.)***

Drug	**Side effects**
Amprenavir	Nausea, diarrhoea,
Indinavir	Nausea, nephrolithiasis, haematuria, hyperbilirubinaemia, porphyria, hyperaesthesia
Nelfinavir	Diarrhoea
Ritonavir	Nausea, vomiting, dysgeusia, biochemical hepatitis, hyperaesthesia
Saquinavir, Lopinavir	Nausea, diarrhoea

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