

Skin in HIV

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Introduction to HIV Basics

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INTRODUCTION

The Acquired Immuno Deficiency Syndrome (AIDS) was first recognized in 1981 in the United States, when several cases of Pneumocystis carinii Pneumonia (PCP), and Kaposi's sarcoma were reported in homosexual men in New York and California. The variety of unusual infections and other conditions declared a new form of cellular immunodeficiency [1].

Soon after, the syndrome was reported in injecting drug users, hemophiliacs and recipients of blood transfusion. Early epidemiological data suggested that, the cause was a sexually transmissible blood borne infective agent. During 1983, in France, Dr Luc Montagnier isolated a new retrovirus from a patient with persistent generalized lymphadenopathy. Initially he referred it as Lymphadenopathy associated virus (LAV). In 1984, in United States, Robert Gallo discovered multiplication of this retrovirus in human T lymphocytes and he named the virus, HTLV-III [2].

International committee for nomenclature of viruses understood that, the virus discovered by Dr Luc Montagnier and described by Robert Gallo are one and same. Hence the committee renamed the name of virus as Human Immunodeficiency Virus (HIV) in 1986.

At the time of its discovery, HIV was already widespread, the earliest infections probably having occurred before the 1950s [1]. The recognition of heterosexual intercourse as the most common means of HIV transmission worldwide followed the investigation of epidemics in Africa and the Caribbean. Infected mothers could pass the virus on to their fetus or neonate, establishing vertical transmission as another route of HIV infection.

In 1986 a second retrovirus causing AIDS, HIV-2 was identified by Dr Luc Montagnier in Senegal town, West Africa. It is largely confined to this region, while HIV-1 is the cause of the World Pandemic of AIDS [1].

Table 1.1: Milestones in the history of HIV and AIDS

Pre 1970s	HIV-1 transmitted to humans in Africa, probably from chimpanzee source
1970s	Unrecognized global spread of HIV
1981	Epidemic Pneumocystis pneumonia and Kaposi's sarcoma reported in New York, Los Angeles, and San Francisco
1983	New human retrovirus isolated from a patient in France by Dr Luc Montagnier
1984	Retrovirus confirmed as cause of AIDS, CD4 shown to be its binding receptor. Screening for HIV antibodies in donated blood introduced in industrialized countries. Robert Gallo described replicating cycle of HIV CD4+T Lymphocyte.
1985	ELISA was developed to diagnose HIV infection. ICMR Task Force recommended Government of India to do sero surveillance in India at all The International Airports and also international travelers.
1986	HTLV-III/HIV renamed human immunodeficiency virus (HIV) by the International Committee for Taxonomy of Viruses. Effective prevention of Pneumocystis pneumonia by co-trimoxazole and other drugs. HIV-2 isolated from West African patients.
1986	April – CSW was found HIV +ve in Chennai. May – CSW was found HIV +ve in Bombay.
1987	Zidovudine improves survival in AIDS. Government of India launched National AIDS Control Programme in India. (NACP)
1988	World AIDS Day first declared by World Health Organization (WHO) on December 1 st .
1990	Antigenic variation warns that development of HIV vaccines will not be easy.
1992	NACP was upgraded by GOI to National AIDS Control Organization.
1993	Concorde trial demonstrates that survival benefit from Zidovudine monotherapy is not sustained.
1994	Zidovudine shown to reduce vertical transmission of HIV by two-thirds. HHV-8 discovered as the cause of Kaposi sarcoma.
1995	High HIV and immune cell turnover demonstrated during asymptomatic phase of HIV infection. Dual combination of nucleosides shown to be superior to monotherapy.
1996	Prognostic value of HIV RNA estimation (viral load) demonstrated. Protease inhibitors in triple regimens show marked reduction in progression to AIDS and death over the short to medium term. Chemokines co-receptors for HIV demonstrated, mutant receptors confer resistance to HIV infection in some exposed uninfected subjects.
1997	Non-nucleoside reverse transcriptase inhibitors introduced.
1998	Epidemiological studies show major reduction in death rates in patients with AIDS on triple therapy. Vertical transmission of HIV shown to be reduced by elective caesarean section.
2001	Inexpensive antiretroviral treatment available in resource poor countries.
2003	President Bush announces PEPFAR –the President Emergency Plan for AIDS Relief. PEPFAR is a five year \$ 15 billion initiative to address HIV/AIDS, Tuberculosis and Malaria in hard hit countries. School AIDS Education Programme was introduced in India. UTA – University Talk AIDS project was introduced by UGC.
2009	President Obama launches the Global Health Initiative (GHI), a six year effort to develop a comprehensive approach to addressing global health in low and middle income countries, with PEPFAR as a core component.
2010	26 ART drugs approved by US FDA.
2014	37 ART drugs approved by US FDA. Approval of fixed dosage combination tablets. Emtricitabine 200 mg and Tenofovir disoproxil fumarate 300 mg, co-packed with Nevirapine 200 mg tablets.

HIV may be regarded as zoonoses. HIV-1 is derived from a simian immunodeficiency virus in the chimpanzee – *Pan Troglodyte's* troglodytes. HIV-2 is derived from the sooty mangabey monkey – *Cercocebus atys* [Figure 1.1].



Figure 1.1: African green monkey (*Chlorocebus Aethiops*) Accessed from: <http://www.forestryimages.org> [7].

HIV TYPES

Based on molecular and antigenic differences, two types of HIV have been recognized. The subtypes have varying geographical distribution and susceptibility to drugs.

Flow chart

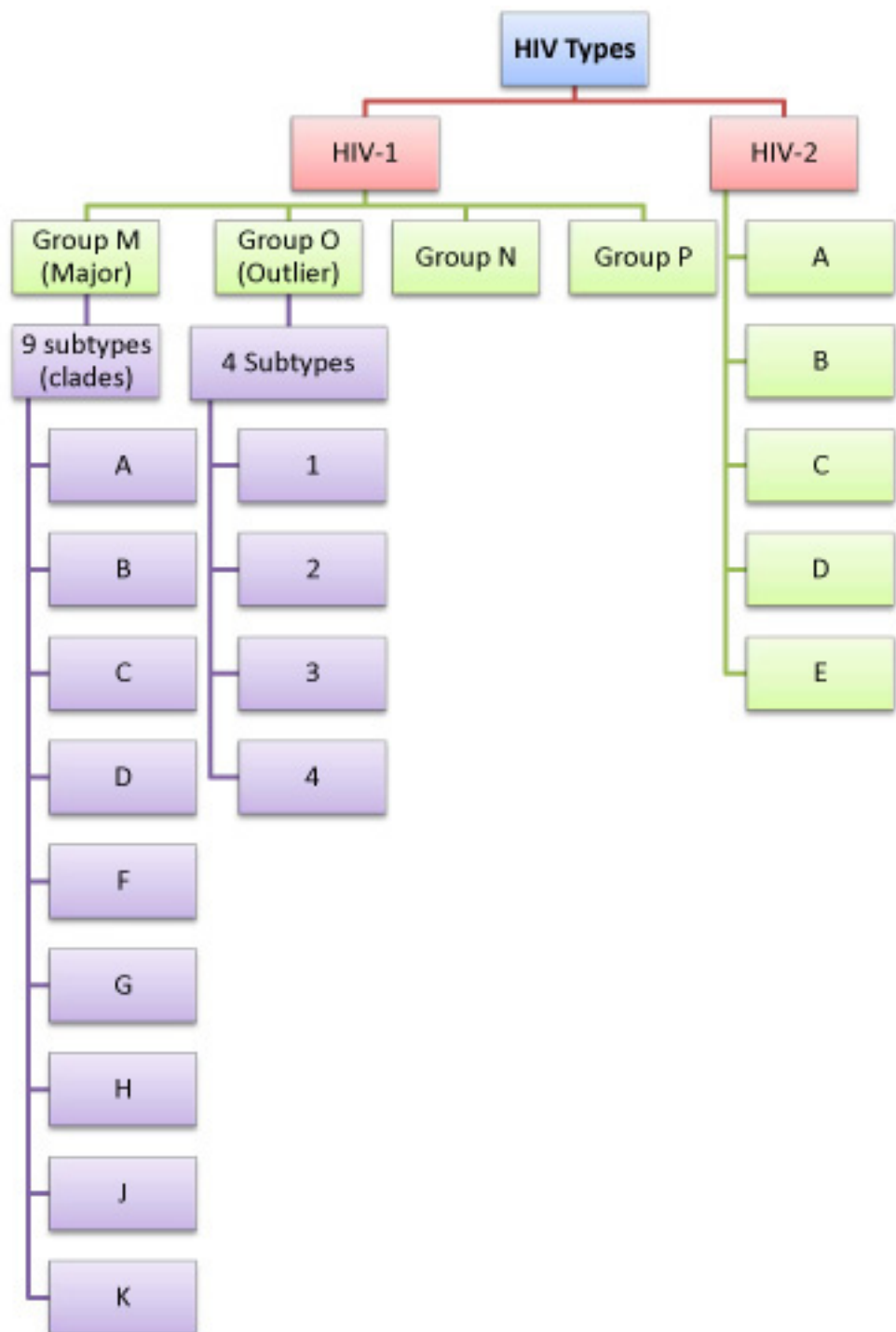
The HIV-1 subtype M and clades A and D are found in central Africa, B in North America and Europe, C in India and E in Thailand.¹ HIV-1 causes severe disease. HIV-1 is susceptible to all antiretroviral drugs. HIV-2 mainly found in West Africa, causes mild disease and is not susceptible to non-nucleoside reverse transcriptase drugs.

MORPHOLOGY OF HIV

HIV is a spherical shaped, enveloped virus, measuring about 90-120 nm in size. (Figure 1.2)

Electron microscopy shows that the HIV virion is icosahedral structure containing several external spikes formed by the two major envelope proteins, the external gp120 and the transmembrane gp41.

The virion buds from the surface of the infected cell and incorporates a variety of host



Flow chart 1.1: HIV Types

proteins, including major histocompatibility complex (MHC) class I and class II antigens, into its lipid bilayer [3].

The core contains two identical copies of the single strand RNA genome. The genome is diploid, composed of two identical single-stranded, positive sense RNA copies. The RNA molecules are

8-10 kb long and are complexed with reverse transcriptase and tRNA. Other viral proteins, such as integrase and protease are also components of the virion particle [3].

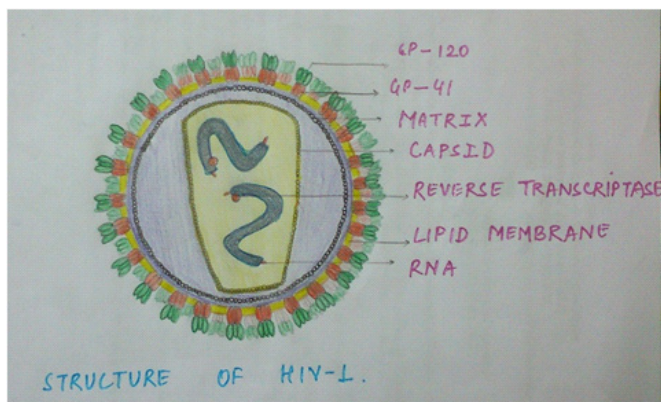


Figure 1.2: Structure of HIV-1, including the gp 120 envelop, gp 41 transmembrane components of the envelop, genomic RNA, enzyme reverse transcriptase, p 18(17) inner membrane (matrix), and p 24 core protein (capsid) [3].

REPLICATION OF HIV

The replication cycle of retroviruses proceeds in two phases. In the first phase, the virus enters the cytoplasm after binding to a specific cell surface receptor, gp 120 and co-receptor of CD4+T lymphocytes. The viral genome RNA and reverse transcriptase enters the CD4+T cell cytoplasm (Figure 1.3).

The reverse transcriptase enzyme converts viral RNA to viral DNA. Initially it is single stranded DNA and later it changes to double-stranded DNA. The viral DNA now called provirus. Provirus moves into the nucleus and integrates into the host cell genome with the help of viral integrase enzyme. This proviral integration is permanent.

The second phase includes the synthesis and processing of viral genomes, mRNAs and proteins using the host cell machinery, often under the influence of viral gene products. Virions are assembled and released from the cell by budding from the membrane. Host cell membrane proteins are frequently incorporated into the envelop of the virus [3]. Budding viruses damage the CD4+T lymphocytes and they are killed. T4 cells decrease in numbers. Viral infected cells also do not function normally. Infected T4 cells do not appear to release normal amounts of interleukin-2, gamma interferon and other lymphokines [4]. Cell mediated immune response is damped because of this.

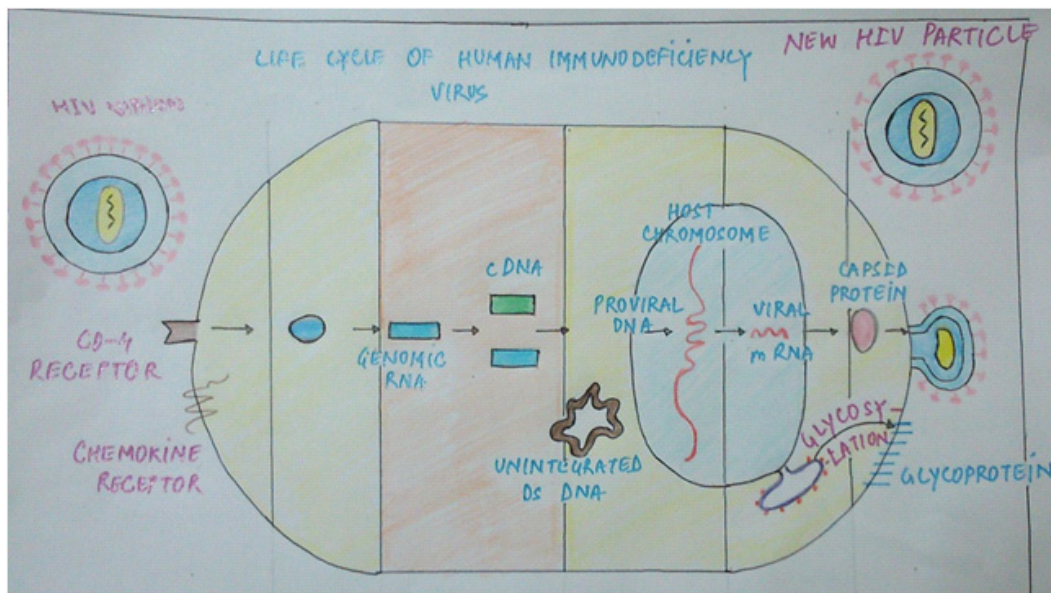


Figure 1.3: Lifecycle of HIV 1

HIV 1 binds to CD4 and one of the chemokine co-receptors expressed on the surface of target cells such as T helper lymphocytes or dendritic cells. A conformational change in the transmembrane gp41 then facilitates fusion of the virion with the cell membrane. The virion enters the cell, uncoats, and undergoes the process of reverse transcription, by which viral RNA is transcribed into complementary DNA (c DNA). After reverse transcription, double stranded DNA is formed, migrates to the cell nucleus, and is integrated into the host genomic DNA as a provirus. The virus can then be transcribed back into messenger RNA (mRNA), and the resultant proteins and genomic RNA are assembled near the cell surface and packed into a new virion, which buds from the cell membrane. Post budding maturation of the virion is facilitated by viral protease [5].

HIV INFECTION AND IMMUNITY

The primary pathogenic mechanism in HIV infection is the damage caused to the CD4+ T Lymphocyte (Figure 1.4).

The T4 cells decrease in numbers and the T4:T8 (helper: suppressor) cell ratio is reversed. HIV infection can suppress the function of infected cells without causing the structural damage. Infected T 4 cells do not appear to release normal amounts of interleukin-2, gamma interferon and other lymphokines [4]. This has marked effect on cell mediated immune response.

Though the major damage is to cellular immunity, humoral mechanisms are also affected. Helper T cell activity is essential for optimal B cell function, particularly in responding to thymus dependent antigens.

AIDS patients are unable to respond to new antigens.

An important feature in HIV infection is the polyclonal activation of B lymphocytes leading to hypergammaglobulinemia. All classes of immunoglobulins are involved but levels of IgG and IgA are particularly raised. The hypergammaglobulinemia is more hindrance than a help because it is composed mainly of misdirected immunoglobulins to irrelevant antigens and also autoantibodies. This may also be responsible for allergic reactions due to immune complexes and to ART drugs.

Monocyte macrophage function is also affected, apparently due to lack of secretion of activating factors by the T4 lymphocytes. As a result, chemotaxis, antigen presentation and intracellular killing by monocytes and macrophages are diminished. The activity of NK cells and cytotoxic T lymphocytes are also diminished.

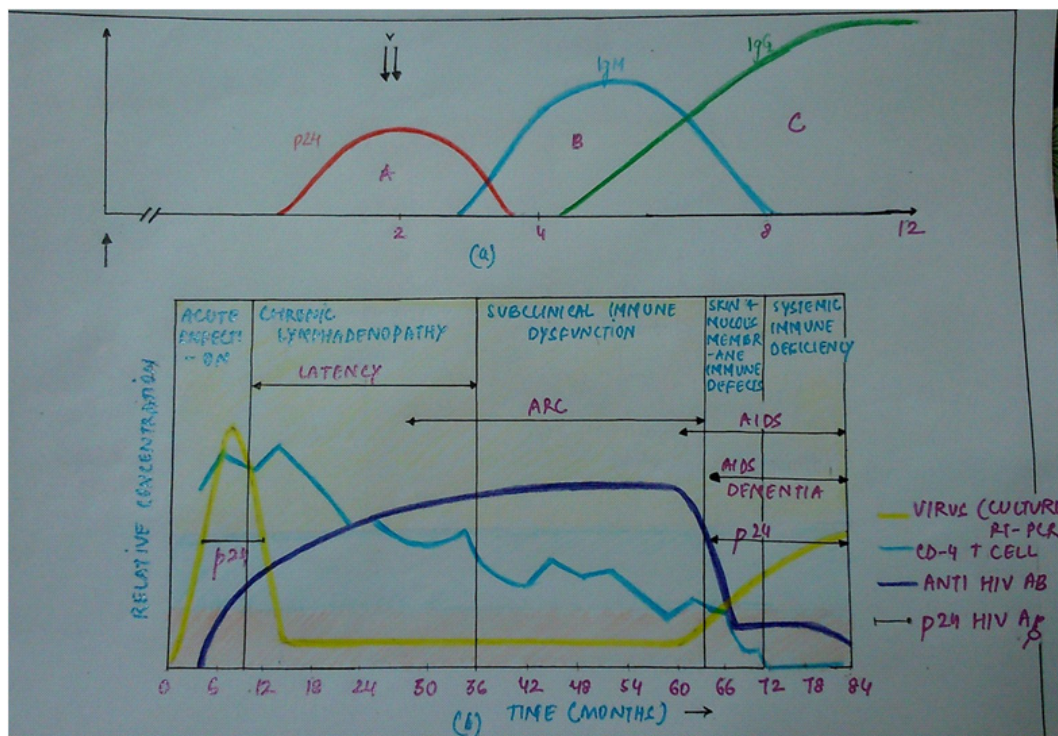


Figure 1.4: a) Sequence of appearance of p 24 antigen and antibodies after a massive HIV infection.

b) Illustration of the usual time course of immune response, viremia and disease resulting from untreated HIV 1 infection [6].

Some other immune cells also possess the CD4 antigen on the surface and so are susceptible to infection. Thus about 5-10% of B lymphocytes and 10-20% of monocytes and macrophages, including specialized macrophages such as alveolar macrophages in the lungs and Langerhans cells in the dermis, are susceptible. Glial cells and microglia in the central nervous system are also susceptible. Follicular dendritic cells from tonsils can be infected by HIV without the involvement of CD4.

The clinical manifestations in HIV infections are due not primarily to viral cytopathology but are secondary to the failure of immune responses. This renders the patient susceptible to opportunistic infections and malignancies.

Viral Set Point

Within 6 months, the host immune response is able to control the infection to a point where, the number of virus particles produced per day equals the number of particles destroyed per day. This steady state is called viral set point. The higher a patient's viral set point the greater the risk for disease progression [7].

The skin is the largest organ of the body covering the entire body. It is continuous with conjunctiva, tympanic membrane and mucous membranes of all orifices of the body. It is in contact with external environment and external injurious agents all the 24 hours. The external agents include living organisms like bacteria, fungi, viruses, parasites and harsh physical agents, which will be continuously damaging the structure and function of skin. Hence the dynamic skin has to deal with all these agents and has to maintain a physical and immunologic barrier to these external agents.

The CD4+ T cell count reflects the current immunological competence of the patient. Normal CD4+T cell count is 600-1200 cells/ml. When CD4+ T cells fall to 500/ml, seborrheic dermatitis and oral hairy leukoplakia first appear. As the CD4+ T cells decline, viral, bacterial, fungal infections and ectoparasitic infestations are noticed on the skin.

Therefore skin is the first line of defense after exposure to living agents and physical agents. As the immunity comes down, defense function of skin also comes down. Infections, inflammations and malignancies will be seen on the skin. Careful examination of skin will definitely reveal the early signs of HIV/AIDS disease, cutaneous markers of HIV/AIDS.

THE SKIN IMMUNE SYSTEM

The skin harbors specialized subsets of antigen presenting dendritic cells called Langerhans cells and dermal dendritic cells, that take up microbial and tissue antigens, migrate to peripheral lymph nodes, and present processed antigens to naïve T lymphocytes. The T lymphocytes are thereby inducted to become activated and expand in number, and the T cells so activated acquire the capacity to migrate preferentially to the skin, directed by specific homing receptors, where they exert their effector functions against relevant antigens. Impairment of the skin immune system, a well recognized consequence of pharmacological immunosuppression, leads to microbial and malignant invasion. Evidence that the properties of the skin immune system were distorted during the course of HIV infection came initially from the observation that the number of Langerhans cells is decreased in patients with AIDS.

Dermatological diseases are amongst the first recognized clinical manifestations of AIDS. They are seen at every stage of HIV infection and are often its presenting features. Approximately 90%

of HIV infected patients develop cutaneous disease. These skin manifestations not only act as markers but also reflect the underlying immune status.

Skin disease may provide the first suspicion of HIV infection, cause significant morbidity as the disease progresses, and point to important systemic implications. An exanthema occurs in approximately 70% of individuals with acute retroviral syndrome. The exanthema appears pink-to-red macules and papules, 5-10 mm in diameter, these remains discrete and occur over the upper trunk, palms and soles. Genital ulcers occur in 30-40% of individuals. Oropharyngeal manifestations occur in 70% of cases and include an enanthem, aphthous like ulcers, and candidiasis. The incidence and severity of several common cutaneous diseases are increased in patients with HIV infection and this correlates in many instances with absolute number of CD4 T helper cells (Figure 1.5) [8].

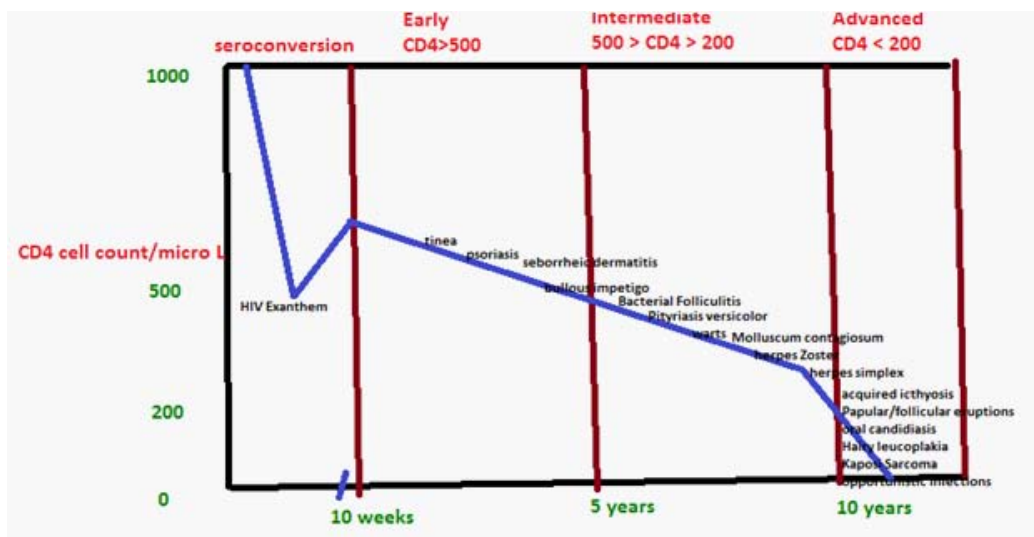


Figure 1.5: Sequence of appearance of dermatological diseases in relation to CD4 count and progression of the disease in years.

SKIN DISORDERS IN HIV INFECTED PATIENTS IN INDIA

The frequency of skin disorders in HIV infected patients has been found to vary from 40% to 50% in Indian studies. Infectious diseases constitute the largest category. Less frequently encountered dermatoses are papular pruritic eruptions/ eosinophilic folliculitis/ exaggerated insect bite reaction, seborrheic dermatitis, aphthous ulcerations, Xerosis/ ichthyosis; psoriasis and adverse cutaneous drug reactions are seen. Although the pattern of cutaneous lesions in HIV infected individuals is comparable with that of the west, there is striking lower incidence of Kaposi's sarcoma and other neoplasms in India.

Early Symptomatic HIV Disease

Because of early immune depletion, with the CD4 cell count declining to less than 500/

mm³, non-life threatening opportunistic infections occur. Tinea corporis, psoriasis, seborrheic dermatitis and bullous impetigo are seen.

Intermediate Stage of HIV Disease

This stage is defined by a CD4 cell count between 200 to 500 cells/mm³. Although the risk of developing new opportunistic infections during this stage is relatively greater than at an early stage, most patients remain asymptomatic or demonstrate only mild manifestations, predominantly dermatological and mucocutaneous lesions. Bacterial folliculitis, pityriasis versicolor, warts, molluscum contagiosum and herpes zoster are seen.

Late Stage Disease

The stage is characterized by severe immune depletion, with CD4 cell count varying between 50/mm³ and 200 cells/mm³. Dermatological manifestations are oral hairy leukoplakia, eosinophilic folliculitis, molluscum contagiosum, they are multiple, more than 1 cm in size and are located on face. Herpes zoster will be multidermatomal and disseminated. Oropharyngeal and genital candidiasis are common. Kaposi's sarcoma and invasive squamous cell carcinoma are more common in late stages. Acquired ichthyosis, Norwegian scabies and other opportunistic infections like cryptococcosis, penicilliosis, and cutaneous tuberculosis are seen.

CLASSIFICATION OF CUTANEOUS MANIFESTATIONS IN HIV INFECTION

Infections and Infestations

- **Fungal:** Candidiasis, Dermatophytosis, Pityrosporum infection, Cryptococcosis, Penicilliosis, Aspergillosis, Histoplasmosis.
- **Viral:** Varicella zoster virus infection, Herpes simplex infection, Cytomegalovirus infection, Epstein virus infection (oral hairy leukoplakia), Molluscum contagiosum, Human papilloma virus infection, Hepatitis B virus and hepatitis C virus.
- **Bacterial:** Staphylococcus aureus infection, Bacillary angiomatosis, Mycobacterial diseases, STDs.
- **Parasitic infestations:** Scabies, Demodicidosis.

Inflammatory Disorders

Seborrheic dermatitis, Psoriasis, Reiter's syndrome, Ichthyosiform dermatoses, Pruritus associated with HIV, Adverse cutaneous drug reactions.

Neoplasms

Kaposi's sarcoma, Lymphoma, Squamous cell carcinoma.

Miscellaneous Cutaneous Disorders

Generalized hyperpigmentation, Hidradenitis suppurativa, and miscellaneous skin conditions.

Hair Alterations and Nail Changes

Hypertrichosis of eyelashes and very long eye lashes [9], alopecia areata [10], premature graying of hairs, proximal white subungual onychomycosis, nail dyschromia as a result of antiretroviral therapy are noted.

CONCLUSIONS

Early recognition of the mucocutaneous manifestations of HIV infection is an important challenge. Careful examination of the skin and mucosae may be highly rewarding in evaluating the stage of HIV disease. An increasing number of dermatoses in an HIV infected individual points toward progression of HIV, and dermatological evaluation may detect prognostic indicators. The natural history of opportunistic infections has changed during the HAART era. In individuals responding to HAART, the incidence of all opportunistic infections, with the exception of HPV infection, is markedly reduced.

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