***CHAPTER***

***BIOLOGY AND PATHOGENESIS OF HIV INFECTION***

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**ASTRACT:**

HIV/AIDS has always been one of the most thoroughly global of diseases. The human

immunodeficiency virus (HIV) is a lent virus that causes HIV infection and AIDS. AIDS is a

condition in humans in which progressive failure of the immune system allows life-threatening

infections and cancers to thrive. Infection with HIV occurs by the transfer of blood, semen, vaginal

fluid, breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus

within infected immune cells. HIV infects vital cells in the human immune system such as helper

CD4 T cells, macrophages. HIV infection leads to low levels of T cells through a number of

mechanisms, including pyroptosis of infected T cells. The symptoms of AIDS are primarily the

result of conditions that do not normally develop in individuals with healthy immune systems.

Most of these conditions are opportunistic infections caused by bacteria, viruses, fungi and

parasites that are normally controlled by the elements of the immune system that HIV damages.

When condoms are used consistently by a couple in which one person is infected, the rate of HIV

infection is less than 1% per year. There is some evidence to suggest that female condoms may

provide an equivalent level of protection.

**Keywords:** HIV,CD4 T Cells,AIDS,Macrophage.

**INTRODUCTION:**

 The human immunodeficiency virus (HIV) was unknown until the early 1980's when increasing numbers of cases of unusual opportunistic infections and Kaposi sarcoma in persons with lymphadenopathy in the setting of impaired cell-mediated immunity were reported.[1,2] Since then HIV has infected millions of persons in a worldwide pandemic. The result of HIV infection is relentless destruction of the immune system leading to onset of the acquired immunodeficiency syndrome (AIDS).

 The AIDS pandemic has already resulted in the deaths of over half its victims. All HIV-infected persons are at risk for illness and death from opportunistic infectious, neoplastic complications, and comorbidities because of the inevitable manifestations of AIDS as well as long term treatment of HIV.[3,4] Once HIV infection became established in humans, the spread of HIV has been driven by multiple factors. The advent of quick air travel in the 20th century provided a means for spread not present in past human pandemics. Urbanization has led to increased numbers of persons at risk in close proximity. Human sexual practices with promiscuity have included a larger number of persons in populations around the world. A practical and easily available means for delivery of drugs of abuse through injection became more widespread in the 20th century.[3]

 The AIDS pandemic has evolved over time, with four main phases of evolution. In the initial phase, HIV emerged from endemic rural areas to spread among urban populations at an accelerating rate. In the second phase, dissemination occurred and involved definable risk groups. Behaviors in these risk groups, including sexual promiscuity and injection drug use, led to the third phase of escalation, which occurred through the 1980’s. A fourth phase of stabilization has occurred in some regions such as western Europe, North America, and Australia, where control measures appear to be having a positive effect. However, some regions such as central Africa and Asia continued to experience escalation of the pandemic through the 1990's and into the 21st century.[5,6] Although the HIV infection rate in the United States increased rapidly in the 1980's, peaked in the 1990’s, and has declined since, the reservoir of HIV-infected persons developing AIDS and requiring therapy continued to increase through the 1990's and into the 21st century. At the end of 2019, 1.19 million persons were living with HIV in the U.S., including 0.159 million whose infection remained undiagnosed.[7,8]

Globally, the incidence of new HIV infections probably peaked in 1997. At the end of the 20th century, over 21 million persons worldwide had died from AIDS, over 34 million were living with HIV infection, and over 95% of HIV infected persons resided in developing nations. Nine countries in southern Africa, with 2% of the world’s population, accounted for a third of all HIV-infected persons.[9] At the start of the 21st century, the worldwide prevalence of HIV infection stabilized at about 0.8%. The age group most affected, young persons from 15 to 24 years of age, accounted for 45% of new HIV infections. Worldwide, over half the victims of AIDS are women, and a consequence of this is perinatal infection resulting in children born with HIV infection. The scope of the AIDS pandemic has already led to serious consequences, not only for health care systems of countries unable to cope with many AIDS victims, but also for the national economies of those countries because of the loss of young to middle aged persons who are economically most productive.[10] Three advances helped to address the burden of HIV infection. The first was development and deployment of effective multi-drug antiretroviral therapy (ART) at the end of the 20th century. The second was recognition that suppression of viremia through ART could prevent HIV transmission. The third was instigation of ART early in the course of HIV infection, regardless of CD4 lymphocyte counts, to reduce subsequent immunologic damage and prolong lifespan of infected persons. This is the test and treat strategy. Thus, universal testing to detect persons infected with HIV is key to this strategy. However, the stigma of HIV infection and possible punitive measures taken against infected persons remain as barriers to universal testing.[11] Worldwide, new HIV infections decreased from 3.3 million in 2002, to 2.3 million in 2012. In 1990 there were an estimated 300,000 deaths from AIDS. Global AIDS-related deaths peaked at 2.3 million in 2005 and decreased to 1.6 million by 2012. An estimated 9.7 million people in low-income and middle-income countries had started antiretroviral therapy by 2012. In 2010, the 1.5 million estimated deaths from AIDS represented 2.8% of the 52.8 million worldwide deaths that year. AIDS was the 6th leading cause of years of useful life lost (YLL) worldwide in 2010.[4,12]

Considerable effort has been placed into education of persons potentially at risk for acquiring HIV.[19] A proper understanding of AIDS issues, including the nature of HIV and its means of spread, should precede decisions regarding allocation of health care resources and control measures.[20] Prevention strategies for HIV will require ongoing education, despite a general public perception, particularly among young persons, that AIDS is a peripheral threat that does not call for changes in lifestyle.[21] The battle against AIDS will require political alliances that allow prevention strategies to be implemented across national borders. A single strategy does not apply to all venues. The reservoir of infected persons is so large, global human interaction so broad, and costs of AIDS so high that everyone on earth is affected in some way by the AIDS pandemic.[22] Prevention strategies can include the following:[23]

* Make HIV testing a routine part of medical care.

 • Implement new models for diagnosing HIV infections outside medical settings.

 • Prevent new infections by working with persons diagnosed with HIV and their partners.

 • Provide antiretroviral drugs to infected persons who need them.

 • Further decrease perinatal HIV transmission.

 

 Fig: HIV Infection Fig:HIV Skin Lesions

**PATHOGENESIS OF HIV INFECTION:**

RELEASE.-- Release of HIV from the host cell occurs in several steps. The p55 protein of HIV directs formation of a capsid (CA) protein that surrounds the RNA of HIV, a nucleocapsid (NC) protein that interacts with the RNA within the capsid, and matrix (MA) protein that surrounds the capsid and lies just beneath the viral envelope. A protease enzyme encoded by the pol gene of HIV cleaves the large precursor proteins to produce the MA, CA, and NC proteins. Budding virions utilize host cell membrane to help form the outer virion envelope of the budding virion necessary for production of infectious particles. The process of viral budding from the infected host cell surface relies upon cellular endosomal sorting complexes required for transport (ESCRT) that sort proteins and form multivesicular bodies (MVBs) that are intermediates in the formation of secretory lysosomes. [24,25,26]

Dendritic cells play a key role in HIV infection. DCs can be classified as plasmacytoid (pDC) and myeloid (mDC) DCs. The mDCs display high surface levels of CD11c and HLA-DR while pDCs are CD11c−HLA-DR+ cells characterized by surface expression of the C-type lectin BDCA2, high levels of the alpha chain of the receptor for interleukin-3 (CD123) and the immunoglobulin superfamily receptor immunoglobulin-like transcript 7 (ILT7). They specialize in the recognition of different pathogen associated molecular patterns (PAMPs) due to the unique distribution of pattern recognition receptors (PRRs) such as toll-like receptors, C-type lectins and intracellular nucleic acid sensors. Both mDCs and pDCs can induce CD4+ and CD8+ T cell responses against different types of pathogens. Both mDCs and pDCs are also capable of interacting with natural killer (NK) cells, which are particularly relevant during viral infections . Therefore, the contribution of different DC subtypes to immune responses against microbial infections seems to be highly complex and be influenced by context- and pathogen-dependent factors.[27]

Most HIV infections likely begin from a single virus—a "founder" virus, or just a few viral genetic variants, from which subsequent clones develop. The initial infectious process is inefficient because the virus persists poorly in the environment and must find a host cell quickly, so most virions perish. Host cells elaborate an antiviral apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like-3G (APOBEC3G) with cytidine deaminase activity that leads to defective viral replication. In addition, the HIV gene for encoding reverse transcriptase has a high mutation rate and a high rate of error for reverse transcription. Thus, most initial HIV interactions with host cells do not result in established infections.[28]

**HUMAN IMMUNODEFICIENCY VIRUS SUBTYPES:**

 There are four major groups of HIV-1, based upon phylogenetic analysis, which likely arose from different transmission events in history among chimpanzee and gorilla primates and humans. These groups are defined as M (major), N (nonmajor and non-outlier), O (outlier), and P. These groups are very similar to simian immunodeficiency viruses SIVcpz (M and N) and SIVgor (O and P).[29] Groups M and N appear to be derivatives of simian immunodeficiency virus (SIV) found in the chimpanzee Pan troglodytes troglodytes. Groups O and P are more closely related to the SIV found in lowland gorillas (Gorilla gorilla). The vast majority of HIV-1 infections have been with group M. Groups N, O, and P have been reported rarely and have their highest prevalence (less than 2% of all HIV infections) in West and Central Africa, with Cameroon as the epicenter. Only about 100,000 infections with group O have occurred, and group N and P infections remain rare.[30,31] Even within HIV-1 subtypes, genetic diversity can average 8 to 17% but reach 30%; between subtypes, it is 17 to 35% but up to 42%. Different subtypes of HIV-1 that have arisen and will continue to arise in the course of the AIDS pandemic have been identified with certain geographic distributions, though movement of individuals among populations creates more variability over time. Variability of HIV subtypes may also confound testing strategies, because diagnostic sensitivity and specificity of laboratory tests may not be the same across all subtypes. [32] There is increasing diversity of HIV-1 in the form of recombination of subtypes. Recombinants between subtypes are termed circulating recombinant forms (CRFs) with nearly 100 documented. The term unique recombinant form (URF) is used to designate strains of HIV1 not meeting these criteria. The most common CRFs are A-G (CRF02\_AG), most prominent in West Africa, and A-E (CRF01\_AE), seen mainly in East Asia and Southeast Asia. There has been a global increase in the proportion of CRFs and an overall increase in recombinants. The greatest diversity in subtypes and recombinants is in Africa.[33] The migration pathways of some subtypes and CRFs have been traced. Subtypes A and D appear to have originated in central Africa, but eventually established epidemics in eastern Africa. Subtype C is predominant in southern Africa from where it spread to India and other Asian countries. Subtype B that accounts for most HIV-1 infections in Europe and the Americas appears to have arisen from a single African strain first spread to Haiti in the 1960s and then onward to the US and other western countries.[34]

**OTHER HUMAN RETROVIRUSES HIV-2:-**

 The numerous strains of HIV-1 isolated from various geographic regions of the world are all immunologically similar and differ only slightly in their DNA sequences. The first report of a possible variant of HIV-1 was from Senegal in 1985.[35] This second retrovirus designated HIV-2 was first isolated from Portuguese patients in 1986, but it is most common in West African countries and to a lesser extent in locations in Western Europe and elsewhere that migration from West Africa occurred.[36,37] HIV-2 is believed to have been present in Africa as early as the 1940’s. HIV-2, which has greater homology to simian immunodeficiency virus (SIV) than to HIV-1, appears to have become established in human populations as a zoonotic infection from the primate reservoir of sooty mangabeys (Cercocebus atys atys), originating from SIVsmm.[38] Serologic studies suggest HIV-2 was circulating in West Africa since 1966. Zoonotic transmission is likely to have accounted for HIV-2 subtypes A to I, but only subtypes A and B became epidemic.HIV-2 infection is mainly found in West African nations, with the highest prevalence for subgroup A including Guinea-Bissau, Guinea, The Gambia, Senegal, Sierra Leone, Cape Verde, Angola, Mozambique, and Cote d'Ivoire. Subtype B may be most prevalent in Cote d'Ivoire, Ghana, Burkina Faso, and Mali. The prevalence elsewhere is in part a function of links to former colonies, so that Portugal and France are the non-African countries with up to 5% of all HIV infection as HIV-2. Up to 2 million people are infected, some with HIV-1 co-infection. HIV-2 is spread in a manner similar to HIV-1. The peak age of persons infected with HIV-2 appears to be higher than that of HIV-1, but there appears to be no sex difference in rates of infection. [38, 39] Persons infected with HIV-2 infection have a longer asymptomatic phase, higher CD4 lymphocyte counts, lower plasma viral RNA levels, slower progression to AIDS, and lower mortality than HIV-1 infection. The risk factors for transmission are the same as for HIV-1, but heterosexual transmission and maternal-to-child transmission is less efficient. Even in persons not receiving antiretroviral therapy, plasma viral RNA may be undetectable. Though HIV-2 has a higher mutation rate, this does not provide a selective advantage over HIV-1. Rather, the immunologic response with broadly neutralizing antibodies, rare in HIV-1 infection, are present with HIV-2 infection and their presence is equivalent to a vaccine response to reduce viral replication.[39]

**EPIDEMIOLOGY OF HIV/AIDS:**

 Considerable epidemiologic and clinical work has been performed to understand the transmission of HIV from one person to another. As in past epidemics, the spread of AIDS is facilitated by human travel. Syphilis in the 16th century, bubonic plague in the 17th century, and influenza early in the 20th century also arose from endemic foci to become widespread. Modern means of travel by jet aircraft readily available to many people provide an easy route for the spread of AIDS from one location or population to another.[40] However, unlike most infections in past epidemics, AIDS is distinguished by a very long latent period before the development of any visible signs of infection in affected persons. The average HIV-infected person may have an initial acute self-limited illness, may take up to several weeks to become seropositive, and then may live up to 8 or 10 years, on average without treatment, before development of the clinical signs and symptoms of AIDS. In virtually all past infectious disease epidemics, infected persons were soon easily recognized so that measures could be taken to prevent the spread of disease. But persons infected with HIV cannot be recognized by appearance alone, are not prompted to seek medical attention, and are often unaware that they may be spreading the infection.[41,42,43] The transmission of HIV is a function of both where the virus appears in the body and how it is shed. HIV can be present in a variety of body fluids and secretions, The presence of HIV in genital secretions and in blood, and to a lesser extent breast milk, is significant for spread of HIV. However, the appearance of HIV in saliva, urine, tears, and sweat is of no major clinical or social importance, as transmission of HIV through these fluids does not routinely occur, primarily because of the low concentration of HIV in these fluids.[44] Risk for HIV transmission by oral–genital sexual practices is substantially lower than that carried by genital–genital or genital–anal practices because exposure to saliva carries lower risk compared with exposure to blood because of inhibitory factors in saliva to HIV. Oral inflammation, ulceration, and bleeding may increase the risk of HIV transmission.[45] Though infectious particles of HIV are frequent in cerebrospinal fluid, contact with this fluid in daily life is extremely rare.[46] Transmission of HIV can occur from male to male, male to female, and female to male. Female to female transmission remains extremely rare, though women with same-sex contact are also often bisexual and have additional risk factors for HIV infection.[47,48] Even a partial modification of sexual behavior practices may help retard the rate and extent of HIV transmission. Amongst males having sex with males in the U.S. in the 1990's, the prevalence of HIV infection remained high at 7.2%, and the prevalence of unprotected anal intercourse over a prior 6 month period was 41%.[49]

**PATTERNS FOR HUMAN IMMUNODEFICIENCY VIRUS INFECTION :**

Worldwide, three patterns of spread of HIV infection have been identified. In pattern 1, which affected primarily urban areas of the Americas and Western Europe early in the pandemic, the majority of HIV infections occurred in males having sexual intercourse with other males (homosexual and bisexual males), followed by infections in injection drug users. Fewer cases were initially observed among heterosexuals. Pattern 2 occurred in those areas in which HIV had been present longer and the number of HIV-infected persons in the population was greater. Men and women were affected equally, and heterosexual intercourse was the major means of transmission for HIV. These areas included sub-Saharan Africa and parts of the Caribbean where HIV infection occurred throughout the heterosexual population, and congenital AIDS was a significant problem. Pattern 3 occurred in areas of the world in which HIV has been introduced only recently, defined risk groups have not emerged, and only sporadic cases are reported. In the 21st century, education, prevention, and treatment campaigns have modified and reduced the spread of HIV.[50]

**Methods to Reduce Rates of HIV Transmission:**

 • Treat HIV infection as an illness, not as a social stigma

• Reduce levels of poverty in society that lead to increased risks through drug abuse and promiscuity

 • Provide HIV testing and counseling to identify infected persons who can reduce their risk to others

• Provide educational programs for children and adults which describe how to avoid sexually transmitted diseases

• Promote sexual barrier precautions among high risk commercial sex workers and clients

• Provide clean needles for injection drug users

• Offer male circumcision

• Create health care programs with ongoing support to provide antiretroviral therapy for all persons living with HIV to extend life and reduce HIV transmission rates 60

• Give HIV-infected pregnant women antiretroviral therapy to reduce perinatal HIV transmission

 • Consider pre-exposure prophylaxis with antiretroviral drugs for at risk persons

• Provide antiretroviral therapy suppressing viral load to undetectable levels

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