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Epidemiology, Etiology, Prevention, and Treatment of HIV/AIDS: A Review

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ABSTRACT: ***The HIV-1 pandemic is a complicated mix of several diseases inside and across nations and regions throughout the globe, and it is without a doubt the world's most serious public-health problem. Our knowledge of how the virus multiplies, manipulates, and hides in an infected individual has improved thanks to research. Despite advances in our knowledge of etiology and transmission dynamics, as well as preventive strategies, a cure or protective vaccination remains elusive. In certain situations, antiretroviral therapy has turned AIDS from a deadly illness to a chronic, treatable condition. This change has yet to be realized in those areas of the globe where new HIV-1 infections continue to be disproportionately high, and where morbidity and death are rising at an alarming rate. This seminar will give an update on HIV-1 epidemiology, pathophysiology, therapy, and preventive strategies. Globally, an estimated 386 (334–460) million individuals are infected with HIV-1, with approximately 25 million having previously died. 1 There were 41 million new HIV-1 infections and 28 million AIDS deaths in 2005 alone. 1 The dynamic character of this developing pandemic in terms of temporal variations, geographic distribution, size, viral variety, and method of transmission is obscured by these estimations. This epidemic has now reached every corner of the globe.***

KEYWORDS: AIDS, Disease, Epidemiology, Etiology, HIV.

1. INTRODUCTION

Heterosexual transmission remains the dominant mode of transmission and accounts for about 85% of all HIV-1 infections. Southern Africa remains the epicentre of the pandemic and continues to have high rates of new HIV-1 infections.[3] Although overall HIV-1 prevalence remains low in the emerging epidemics in China and India, the absolute numbers, which are fast approaching those seen in southern Africa, are of concern.[1] Outside of sub-Saharan Africa, a third of all HIV-1 infections are acquired through injecting drug use, most (an estimated 8·8 million) of which are in eastern Europe and central and southeast Asia.[1] The rapid spread of HIV-1 in these regions through injecting drug use is of importance, since it is a bridge for rapid establishment of more generalised epidemics[1].

A defining feature of the pandemic in the current decade is the increasing burden of HIV-1 infections in women, which has additional implications for mother-to-child transmission. Women now make up about 42% of those infected worldwide; over 70% of whom live in sub-Saharan Africa. Overall, a quarter of all new HIV-1 infections are in adults aged younger than 25 years. HIV-1 infection rates are three to six times higher in female adolescents than in their male counterparts, and this difference is attributed to sexual coupling patterns of young women with older men. Population prevalence of HIV-1 infection, concurrent sexual relationships, partner change, sexual practices, the presence of other sexually transmitted diseases, and population mobility patterns for economic and other reasons (eg, natural disasters and wars) further increase the probability of HIV-1 acquisition. Emerging data accord with strong links between risk of sexual HIV-1 acquisition and episodic recreational drug or alcohol use[2].

Although sub-Saharan Africa continues to bear a disproportionate burden of HIV-1 infections, there is now an increasing number of countries reporting stabilisation or declines in prevalence (eg, Zambia, Tanzania, Kenya, Ghana, Rwanda, Burkina Faso, and Zimbabwe). There is some

evidence to attribute these reductions to effective changes in sexual behaviour, such as postponement of sexual debut, reduction in casual relationships, and more consistent condom use in casual relationships. However, increasing morbidity and mortality rates associated with a maturing HIV-1 epidemic need to be considered when interpreting these data. For example, the death of a few high-risk individuals who are key to transmission chains could exert a major effect on sexual networks and result in major reductions in infection rates. Additionally, since most HIV-1 estimates are based on surveys in antenatal populations, increasing morbidity and mortality could cause the numbers of women in this group to decrease, and thus lead to underestimates of the true prevalence in these countries[3].

Although the relative contribution of cell-free virus compared with cell-associated virus in HIV-1 transmission remains unclear, there is growing evidence that viral load is predictive of transmission risk. The highest levels of viraemia are seen during acute infection and advanced HIV-1 disease. Further, co-infections with other sexually transmitted diseases in asymptomatic HIV-1 infected people can increase viral shedding to levels similar to those seen during acute infection. Thus, sexually transmitted diseases could enhance HIV-1 transmission to rates similar to those seen during primary infection. This observation could help to explain why the efficiency of HIV-1 transmission exceeds, in some settings, the earlier mathematical projections. Thus, identification and treatment of recently infected people is an important means to reduce transmission. However, most people are unaware of their HIV-1 status during these crucial first months of infection. Several screening strategies based on laboratory testing and clinical algorithms are being developed and tested for efficient identification of early infection before antibody development. Additionally, a more aggressive management of sexually transmitted infections in settings with generalised epidemics has the potential to affect current epidemic trajectories. Based on their genetic make-up, HIV-1 viruses are divided into three groups (eg, M [main], N, and O group). These HIV-1 groups and HIV-2 probably result from distinct cross-species transmission events. Pandemic HIV-1 has diversified into at least nine subtypes (Figure 1) and many circulating recombinant forms, which encode genetic structures from two or more subtypes (eg, A/E=CRF01; A/G=CRF02). The continuously evolving HIV-1 viral diversity poses an immense challenge to the development of any preventive or therapeutic intervention[4].

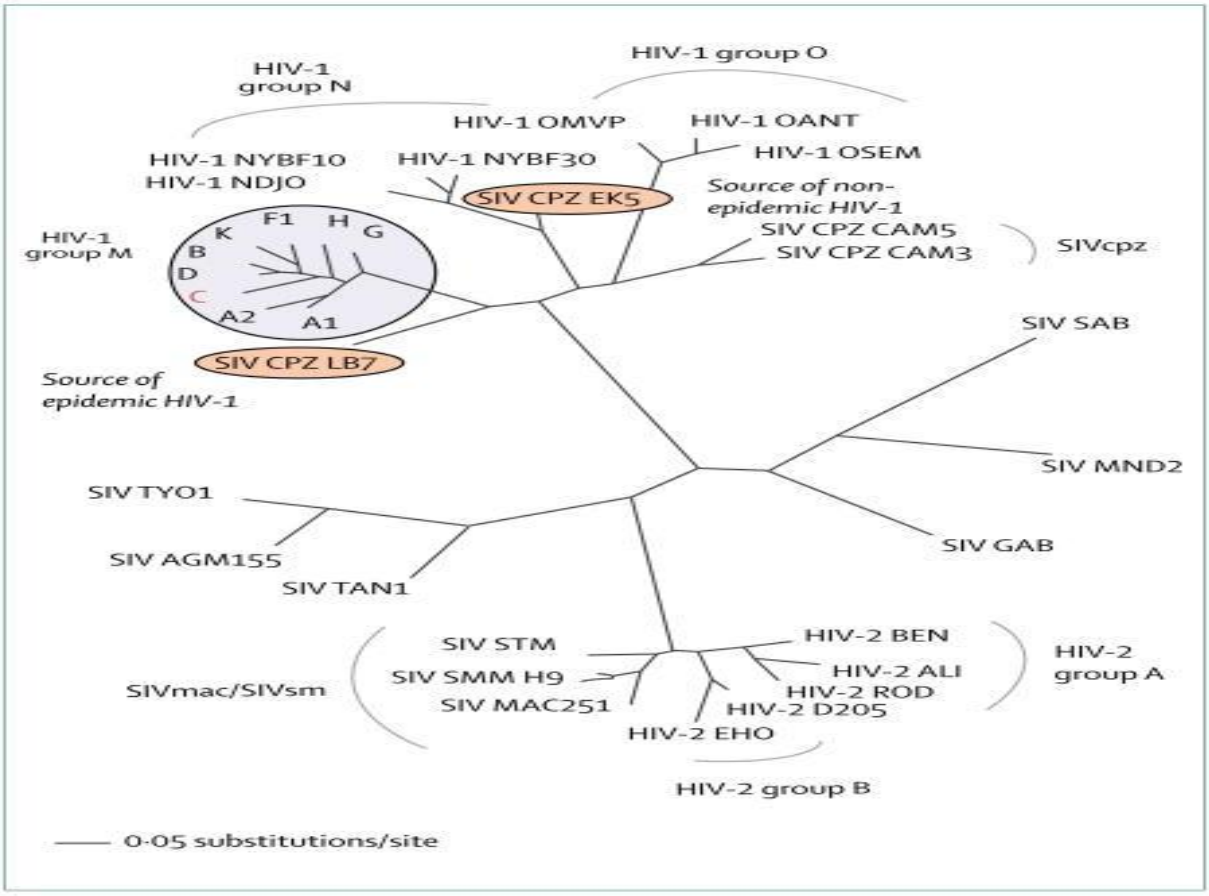

Figure 1: Phylogenetic relation of lentiviruses in man and non-human primates[5]**.**

Subtype C viruses continue to dominate in terms of viral variety, accounting for 55–60 percent of all HIV-1 infections globally. The virological features of non-subtype B isolates may vary from those of subtype B isolates (eg, viral load, chemokine co-receptor usage, transcriptional activation in specific biological compartments). The clinical implications of subtype differences, on the other hand, are unknown. Infection with two or more genetically different viruses may result in the emergence of novel recombinant viruses. Recombination occurs at a faster pace than previously thought30, with circulating recombinant versions accounting for up to 20% of infections in certain areas (eg, southeast Asia). These results are consistent with the incidence of co-infections with numerous isolates in a short period of time. Superinfections, in which viral acquisition occurs months to years apart, have also been reported, but they occur much less often than co-infections. These findings call into question the widely held belief that HIV-1 infection occurs only once with a single virus strain and that the infected person is thereafter immune to future infections. 40 The absence of immunization has serious consequences for vaccine development. New data indicates that among people with multiple infections, clinical progression to AIDS may be more fast. 35 and promoting better sex behaviors in viraemic HIV-1-infected individuals may be useful in reducing recurrent viral strain exposure[6].

2. REVIEW OF LITERATURE

S. S. Bloom in his study focus on AIDS and HIV, the virus that causes the illness, it's probable that a large portion of the world's population has heard of the condition. However, apart from the fundamental manner in which AIDS is communicated, the majority of individuals in most areas are unaware of the details of the illness continuum or effective strategies for halting the epidemic's spread. And the pandemic is just getting worse. The World Health Organization

(WHO) and the United Nations Program on HIV/AIDS (UNAIDS) estimated that 39.4 million individuals worldwide were living with HIV/AIDS at the end of 2004. Almost five million individuals were infected with HIV in 2004, and over three million people died as a result of the illness. Overall, around 1% of the worldwide population between the ages of 15 and 49 is infected with HIV. Women are being more affected by the pandemic, with almost half of all HIV/AIDS patients being female. However, as seen in the following discussion, the pandemic is expanding at a varied pace throughout the globe[7].

E. L. Korenromp et al. in his study discusses about 5 million people that have became HIV positive for the first time, more than in any prior year. Sub-Saharan Africa is still bearing the brunt of the epidemic, with over 25 million adults and children living with HIV/AIDS, the majority of whom reside in southern Africa, where prevalence rates are very high. Given this bleak picture, Gregson and colleagues' report on a substantial decrease in HIV prevalence in Zimbabwe on page 664 of this issue the first unambiguous evidence of a reduction in HIV prevalence linked with behavior modification in this area of Africa is good news. This is particularly true in light of Stover et alstudy.'s in this week's Science Expres on the cost-effectiveness of expanding HIV prevention programs[8].

J. A. Røttingen, in his study discloses about the Women that account for almost half of the 40 million individuals living with HIV-1 globally, with an even greater percentage in poorer countries, according to the human immunodeficiency virus type 1 (HIV-1) pandemic. Gender inequalities, poverty, cultural and sexual norms, lack of education, and violence are all social factors of female HIV-1 susceptibility. Hormonal changes, vaginal microbial ecology and physiology, and a greater incidence of sexually transmitted illnesses make women more vulnerable to HIV-1. The broad spectrum of gender disparities that increase HIV-1 transmission must be addressed in prevention efforts[9].

3. DISCUSSION

3.1 Pathogenesis of HIV-1:

The fact that HIV-1 has spread all across the globe shows that the virus is capable of overcoming innate, adaptive, and intrinsic immunity. Despite its small genome (less than 10 kb) and few genes (figure 2), HIV-1 excels at exploiting cellular pathways while neutralizing and hiding from various immune system components. Notably, research of subtype B viruses and non-human primate studies have frequently contributed to our knowledge of pathogenesis. The HIV-1 life cycle is complicated (figure 2), and the length and result are determined by the kind of target cell and the degree of cell activation. HIV-1 gets access to cells without inflicting immediate fatal harm in the early stages, although the procedure may activate intracellular signal cascades, which might aid viral replication. The exterior glycoprotein (gp120) and the transmembrane protein (gp41) on the HIV-1 envelope produce the spikes on the virion's surface. gp120 binds to the CD4+ receptor before attaching to the cell membrane during the entrance phase.

Following interactions between the virus and chemokine co-receptors (such as CCR5, CXCR4), irreversible conformational alterations occur. The real fusion process occurs within minutes as a result of pore formation, and the viral core is released into the cell cytoplasm. The viral genome is reverse transcribed into DNA by the virus's own reverse transcriptase enzyme when the core disassembles. Due to reverse transcriptase's error-prone nature and lack of proofreading activity, related but different viral variants may be produced throughout this process. The viral protein integrase, in collaboration with host DNA repair enzymes, inserts the viral genome into gene-rich, transcriptionally active regions of the host's chromosomal DNA during the midway of infection. LEDGF/p75 (lens epithelium-derived growth factor), an integrase-binding host factor, promotes integration, marking the turning point by permanently converting the cell into a

potential virus producer. In the final stages, both host-driven and virus-driven transcription are required for the production of viral particles. Viral proteins are delivered to the cell membrane and assemble there.

The vesicular sorting pathway (ESCRT-I, II, III), which usually promotes the budding of endosomes into multivesicular bodies, is used by the virus to exit the cell. HIV-1 binds TSG101 through its late domain, a small sequence motif in Gag p6, to get access to this protein-sorting pathway. The viral protease cleaves the Gag-Pol polyprotein, resulting in mature infectious virions. Because the producer cell's cytoplasmic molecules and components from its cell surface lipid bilayer are integrated into the new viral particle, virions take on the properties of the cells that generated them. Host chemicals may influence the virus's phenotypic in a variety of ways (eg, shape the replicative features in the next cycle of infection or mediate immune activation of bystander cells). In those who were diagnosed early after infection, there was a significant reduction in both activation and memory CD4+ T cells in the gut-associated lymphoid tissues.

Despite years of antiretroviral therapy, the preferential depletion of CD4+ cells in mucosal lymphoid tissues persists, a remarkable finding that contrasts with the fact that the number of CD4+ T lymphocytes in the peripheral blood may recover to normal. The characteristic of HIV-1 infection is the progressive loss of naïve and memory CD4+ T-lymphocyte populations, with AIDS being the final illness stage. HIV-1 replication remains dynamic throughout the illness, despite the lack of symptoms in the early and chronic phases. The half-life of a single virion is so brief that it replaces half of the plasma virus population in less than 30 minutes, and a chronically infected individual may generate more than 101P particles each day. During HIV-1 infection, lymphocyte turnover rates are increased by a factor of ten, while cell proliferation declines after viral replication is decreased by antiretroviral therapy. Various depletion mechanisms have been suggested, with a growing agreement favoring generalized immunological activation as the source of continuous CD4+ cell depletion[10].

Immune activation seems to be a key characteristic of pathogenic HIV-1 infections, since it predicts disease progression. Nef proteins from non-pathogenic SIV lineages have recently been shown to down-regulate CD3-T-cell receptors, resulting in decreased cell activation and apoptosis in their natural hosts (e.g., African green monkeys). HIV-1 Nef fails to stop T-cell activation, which may explain why infected individuals have such a high level of immunological activation[11].

By giving correlates of protection, understanding the processes that contribute to protection or long-term control of infection will guide vaccine development. Natural resistance to HIV-1 infection is uncommon and varies a lot from person to person. Long-term non-progressors and highly exposed chronically seronegative people have both been extensively researched in order to discover innate and learned protective factors. Human leukocyte antigen (HLA) haplotypes, autoantibodies, alterations in the promoter and coding areas of the co-receptors CCR5 and CCR2, as well as up-regulation of chemokine production, are all examples of host resistance factors. Individuals that encode a shortened form of CCR5 (CCR532; heterozygote) exhibit a slower illness development or are resistant to CCR5-using viruses (homozygote). MIP1, a CCR5 co-receptor ligand and chemokine with antiviral action, is encoded by the CCL3L1 gene. According to recent studies, the number of CCL3L1 gene duplications varies by person, and larger numbers of gene duplications decrease infection susceptibility, perhaps due to competing saturation of the CCR5 co-receptor. Some acquired variables, including as cytotoxic T-lymphocyte responses, helper T-cell activities, and humoral responses, influence the risk of transmission in highly exposed chronically seronegative individuals, and may also contribute to spontaneous replication control in long-term non-progressors. In seronegative sex workers and certain long-term non-progressors, the protective effect of cytotoxic T-lymphocyte activity has been proposed[12].

Studies of the early processes that occur after HIV-1 penetrates the mucosal barrier indicate that there is a window period during which viral propagation is not yet established and host defenses may be able to limit viral spread. Two chemokine receptors, CCR5 and CXCR4, are essential co-receptors for HIV-1 infection. Virus types that use CCR5 are responsible for the majority of new infections, regardless of how they are transmitted. CXCR4-tropic viruses emerge late in the infection cycle and have been linked to enhanced pathogenicity and disease progression. Vaginal transmission infects a limited number of CD4+ T lymphocytes, macrophages, and dendritic cells in the lamina propria, according to compelling data from nonhuman primate models (e.g., simian immunodeficiency virus [SIV] infection of rhesus macaques).

Endocytosis, transcytosis, and viral attachment to mannose C-type lectin receptors (e.g., DC-SIGN) on dendritic cells and macrophages are all possible routes for virus transmission. Initial replication occurs in localized lymph organs (e.g., draining lymph nodes) and is comprised of a small number of viral variations, resulting in limited primary amplification. Secondary amplification in the gastrointestinal tract, spleen, and bone marrow occurs when infected T lymphocytes or virions migrate into the circulation, resulting in widespread infection of vulnerable cells. Clinical symptoms may appear during primary HIV-1 infection and are closely related to the peak of viraemia (eg, 106 to 107 copies per mL plasma) The amount of viraemia in an individual's chronic phase of infection (viral set point) varies by one or two orders of magnitude from peak viraemia. This decrease is mostly due to HIV-1-specific CD8+ responses, although target cell restriction may also be a factor. Early after transmission, the viral population is most homogenous, but when viral quasi-species diversified in different biological compartments, mutant viruses resistant to antibody neutralization, cytotoxic T cells, or antiretroviral medicines are produced and stored in long-lived cells (ie, viral reservoirs). Mammalian cells do not create inviting micro-environments for endogenous and exogenous viruses, but instead deploy a defensive web to keep them at bay.

The capacity of HIV-1 to get through these defenses is as remarkable as its ability to exploit cellular machinery. APOBEC3G/3F and TRIM5 are two intrinsic restriction factors that are expressed constitutively in many cells. Both gene loci have been subjected to intense selection throughout primate evolution, suggesting an ancient requirement to neutralize foreign DNA and preserve genome integrity that predates the present HIV-1 epidemic. The superfamily of cytidine deaminases, a group of intracellular proteins with DNA/RNA editing ability, includes APOBEC3 enzymes (A3). The majority of APOBEC3 members have some mutagenesis potential and limit the spread of endogenous retroviruses and mobile genetic elements. The antiviral action of the deaminases A3G, A3F, and A3B is strong, with the first two being expressed in HIV-1-infected cells (T-lymphocytes, macrophages). HIV-1 avoids APOBEC3 mutagenesis by expressing Vif, which causes the degradation of APOBEC3G/3F but not A3B[13]. In Figure 2 shown the HIV-1 is a retrovirus that encodes three structural genes (Gag, Pol, and Env) and 3 HIV-1 infection defined by the level of viral replication.

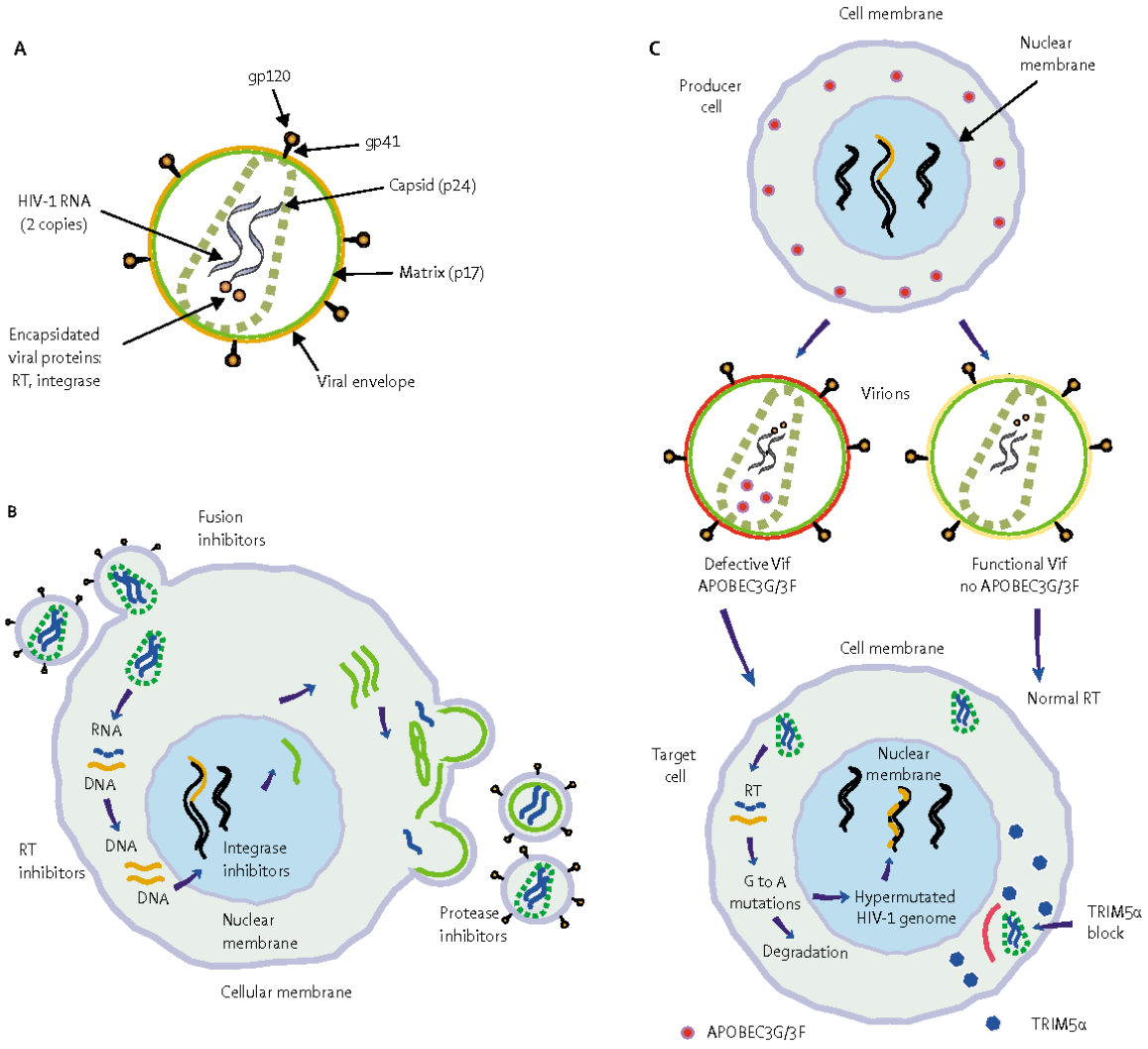

Figure 2: HIV-1 is a retrovirus that encodes three structural genes (Gag, Pol, and Env)[14].

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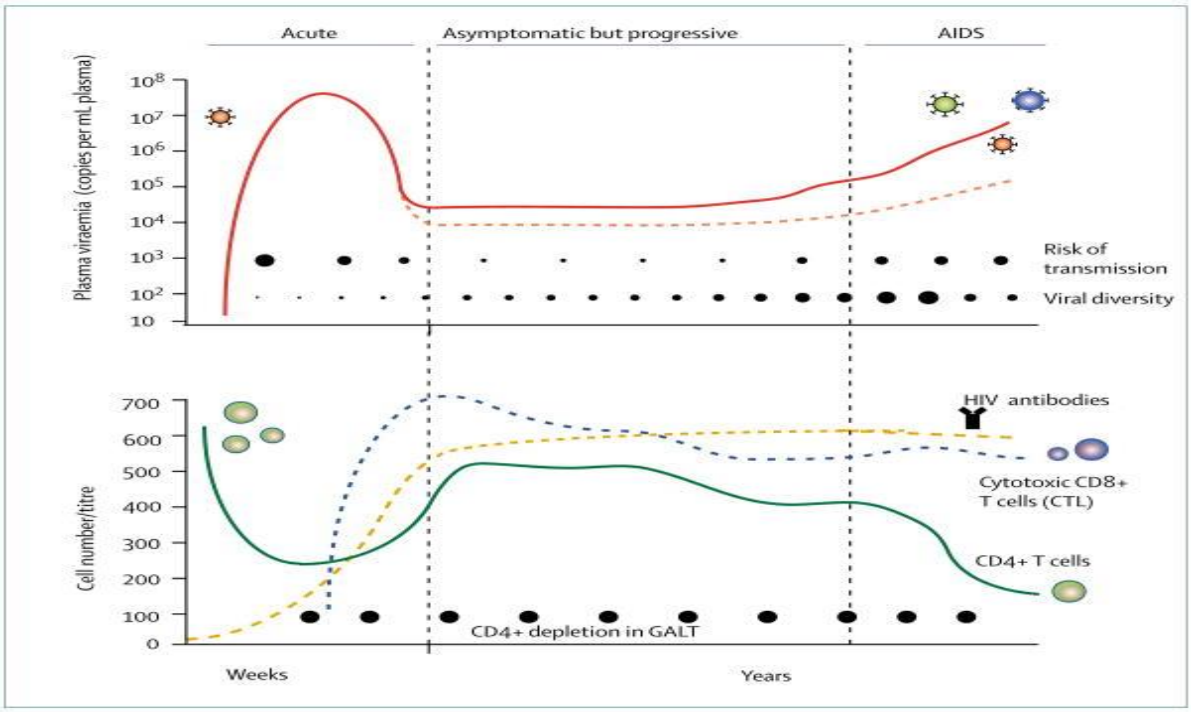

Figure 3: The course of HIV-1 infection defined by the level of viral replication[15].

4. CONCLUSION

Knowledge of HIV-1 status is a critical first step in both prevention and treatment. 207 Many people are hesitant to seek volunteer counseling and testing services because they are afraid of learning their status, which may lead to stigma and prejudice. 208 As antiretroviral treatments (prevention of mother-to-child transmission, antiretroviral therapy) become more widely available, chances for HIV-1 testing will expand, allowing for a prevention-care continuum to emerge, with voluntary counselling and testing as a point of entry. These changes will result in a shift in prevention efforts from a focus on people who are not infected with HIV-1 to a more effective continuum of prevention that includes people who are uninfected, recently infected, infected, and asymptomatic, as well as people who have advanced HIV disease and are on antiretroviral therapy. Given the urgency of the issue and the reality that the public sector supports the majority of research and programs, civil society is calling for more co-ownership of research and responsibility for the use of public money. On the one hand, this co-ownership demonstrates a vital synergy between activism and science, while on the other, it outlines a changing role and duty of science in society. Antiretroviral medication research, treatment availability in resource-constrained areas, and the scaling-up of measures to decrease mother-to-child transmission have all benefited from this collaboration.

The rising number of infected women and the disproportionate burden of infection in resource-poor settings necessitates a scientific urgency to guarantee that research is carried out for the individuals and in the places that will benefit the most. Many additional economic, political, and development problems confront the most afflicted nations, complicating multicentre and multicountry research. Women-specific research (such as the impact of sexual hormones on disease transmission and progression, viral variety, and antiretroviral efficacy) and women-specific preventive strategies, such as microbicides, are critical. In our reaction to the epidemic, we are arguably at one of the most hopeful and optimistic moments. There is undoubtedly more focus on HIV-1, more resources (panel), more civil society mobilization, more governments speaking out, more treatment options, and more evidence about which preventive and treatment

methods will succeed than in past years. The pandemic's relentless spread indicates that existing methods are insufficient. To stay up with the epidemic, we clearly need to do certain things differently while simultaneously expanding the scope and amplitude of existing measures. HIV/AIDS is a unique pandemic that requires a unique response. Despite many scientific and programmatic difficulties, significant progress has been achieved in a short period of time. Prevention and availability to antiretroviral therapy are the greatest alternatives for slowing down the HIV-1 pandemic in the absence of a protective vaccine or a cure. Improved infrastructure is required for widespread application of these concepts in resource-constrained areas, which have been and will continue to be the most impacted. The fact that HIV-1 is mostly spread via sexual contact and disproportionately affects those who are already socially or economically marginalized, or both, presents many ethical, social, economic, and political issues.

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