ЗМІСТ

HIV-infection = ВІЛ-інфекція: навчальний посібник (ВНЗ IV р. а.)

Про книгу

Навчальний посібник висвітлює питання епідеміології, патогенезу, особливості клінічного перебігу ВІЛ-інфекції на різних стадіях хвороби з урахуванням останніх наукових досліджень. У посібнику надані принципи діагностики, лікування та профілактики ВІЛ-інфекції згідно з відповідними протоколами ВООЗ, наведені сучасні статистичні дані стосовно розповсюдженості інфекції в Україні і світі. Викладений матеріал проілюстровано малюнками, таблицями, фотографіями. Посібник містить розділ із тестовими завданнями і ситуаційними задачами для самоконтролю.

Навчальний посібник призначений для студентів медичних ВНЗ IV рівня акредитації, а також буде корисним для інфекціоністів, лікарів-інтернів, лікарів сімейної медицини.

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HIV INFECTION

A TUTORIAL FOR MEDICAL STUDENTS

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1. Introduction

HIV infection poses a global threat today. An estimated 33.3 million people are living with HIV/AIDS, and there are some 2.6 million new infections each year. Globally, HIV/AIDS is the leading cause of mortality among women of reproductive age. Every day, more than 6800 people become infected with HIV and more than 5700 die, mostly because they have no access to HIV prevention, treatment and care services. Despite progress made in scaling up the response over the last decade, the HIV pandemic remains the most serious infectious disease challenge to global public health. Of eight key areas covered by the Millennium Development Goals, six – reduced poverty and child mortality, increased access to education, gender equality, improved maternal health and efforts to combat major infectious diseases – are being undermined by continuing transmission of HIV and its progression to AIDS.

Over the last years there have been major advances in our understanding of the epidemiology, molecular biology, pathogenesis, clinical management and prevention of HIV infection. Introduction of highly active antiretroviral therapy (HAART) has become a great achievement of clinical medicine. Optimal antiretroviral therapy (ART) increases the length and quality of life of HIV-infected patients, and reduces the onward transmission of the virus. But it is still unable to eliminate disease and to prevent infection globally. Disease remains poorly controlled in some developing coun-

tries. At global, national and local levels the HIV epidemic comprises a multitude of problems such as drug resistance, absence of vaccines for specific prevention and treatment of infection, poor availability of careful management and medical care in some regions with high level of morbidity, such as Sub-Saharan Africa. Therefore in such countries taken preventive measures have not significantly reduced the continuing spread of infection.

Effective control over HIV infection is in combining international medical, scientific, financial and humanitarian efforts to solve these problems.

The clinical effects of human immunodeficiency virus infection are diverse, ranging from an acute retroviral syndrome associated with primary HIV infection to a prolonged asymptomatic state to advanced HIV disease. Symptoms associated with acute HIV infection are nonspecific and may be attributed to any acute viral syndrome, such as flu, acute infectious mononucleosis, rubella and so on. Clinical manifestations of HIV-related diseases are extremely diverse. Despite remarkable advances in medical research, improving efficacy of laboratory diagnostics HIV infection remains difficult to diagnose. Early recognition and differential diagnoses of HIV/AIDS require considerable erudition from physicians of any specialization, experience, and extensive knowledge of all branches of clinical medicine to provide qualified medical care and essential treatment of patients. The background information on HIV infection, including the current epidemiologic situation in the world, strategies for HIV/AIDS control, and guidelines for the management of cases and contacts are needful for practical doctors, clinicians of any specialization and public health professionals. Knowledge of the practical aspects of clinical management and new scientific achievements in this field may improve local epidemic situation in any region and global HIV/AIDS control.

The purpose of this tutorial is to present the most current information available on the scope of the epidemic, on

its pathogenesis, treatment, and prevention, and on prospects for vaccine development. Above all, the aim is to provide a solid scientific basis and practical clinical guidelines for a state-of-the-art approach to HIV-infected patients. The tutorial contains tests and tasks for self-assessment to improve learning of the presented information.

4. Etiology

Etiological Agent

The etiological agent of AIDS is HIV, which belongs to the family of human retroviruses (*Retroviridae*) and the subfamily of *Lentivirus*. In order to replicate (duplicate), these RNA viruses must make a DNA copy of their RNA. Only HIV and other retroviruses use an enzyme called reverse transcriptase to convert their RNA into DNA. Lentiviruses or 'slow' viruses are characteristically responsible for long-duration illnesses with a long interval between initial infection and the onset of serious symptoms. Other lentiviruses infect nonhuman species, including sheep, horses, goats, cattle, cats, and monkeys. For example, the feline immunodeficiency virus (FIV) infects cats and the simian immunodeficiency virus (SIV) infects monkeys and other nonhuman primates. Like HIV in humans, these animal viruses primarily infect immune cells, often causing immune deficiency and AIDS-like symptoms. These viruses and their hosts have provided researchers with useful, albeit imperfect, models of the HIV disease process in people. The four recognized human retroviruses belong to two distinct groups: human T lymphotropic viruses (HTLV-I and HTLV-II), which are transforming retroviruses; and human immunodeficiency viruses (HIV). There are two species of HIV: HIV-1 and HIV-2. HIV-1 is the predominant virus that causes AIDS worldwide. It comprises several subtypes with different geographic distributions, and it is more virulent, more infective compared to HIV-2. HIV-2 was first identified in 1986 in West African patients and was originally confined to West Africa, because of its

relatively poor capacity for transmission. However, a number of cases that can be traced to West Africa or to sexual contacts with West Africans have been identified throughout the world. Unless specified otherwise, HIV generally refers to HIV-1.

HIV Morphology

HIV is a roughly spherical virus with a diameter of about 120 nm, around 60 times smaller than a red blood cell. Electron microscopy shows that the HIV virion is an icosahedral structure (Fig. 1) containing numerous 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 proteins, including major histocompatibility complex (MHC) class I and II antigens into its lipid bilayer.

The outer coat of the virus, known as the viral envelope, is composed of two layers of fatty molecules called lipids, taken from the membrane of a human cell when a newly formed virus particle buds from the cell. Embedded in the viral envelope are proteins from the host cell and about 70 copies of a complex HIV protein (frequently called "spikes") that protrudes through the surface of the virus par-

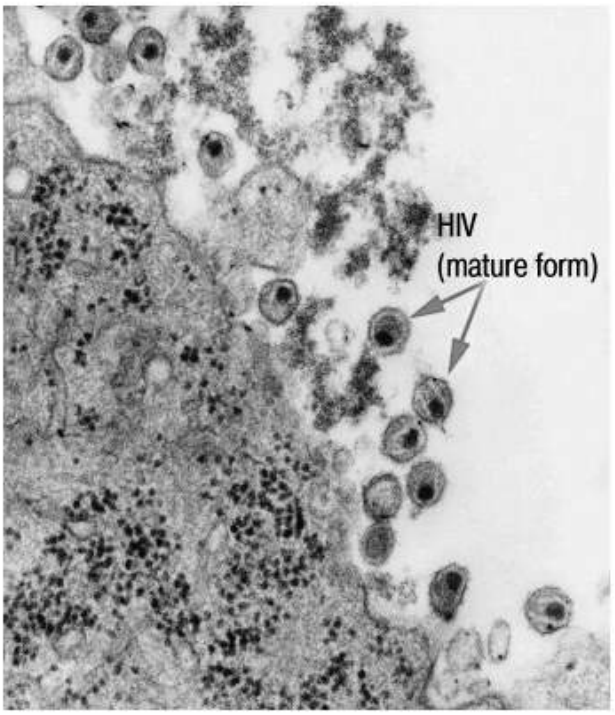

Fig. 1. Electron micrograph of HIV. HIV particles bud from a T-helper cell (*Source:* CDC/PHIL)

ticle. This protein, known as Env, consists of the external gp120 outer membrane and the gp41 transmembrane components. This glycoprotein complex enables the virus to attach to and fuse with target cells to initiate the infectious cycle. Both these surface proteins, especially gp120, have been considered as targets of future vaccines against HIV.

Within the envelope of a mature HIV particle is a bullet-shaped core or capsid made of 2,000 copies of another viral protein, p24. The capsid surrounds two single strands of HIV RNA, each of which has a copy of the virus's nine genes. The single-stranded RNA is tightly bound to nucleocapsid proteins and enzymes needed for viral replication such as reverse transcriptase, proteases, ribonuclease and integrase. A matrix composed of the viral protein p17 surrounds the capsid ensuring the integrity of the virion particle. The structure of HIV-1, including the gp120 outer membrane, gp41 transmembrane components of the envelope, genomic RNA, enzyme reverse transcriptase, p18 (17) inner membrane (matrix), and p24 core protein (capsid), is schematically diagramed in (see Fig. 2 in color insert).

The RNA genome consists of nine genes encoding at least 15 proteins (see Fig. 3 in color insert). Three of these genes, gag, pol, and env, contain information needed to make the structural proteins for new virus particles. The gag gene codes for a precursor protein that can be cleaved by the viral protease into four smaller proteins: p24 (capsid), p17 (matrix), p7 (nucleocapsid), and p6. The pol gene codes for a precursor protein that contains four enzymes: protease, integrase, ribonuclease, and reverse transcriptase. The env gene codes for a protein called gp160 that is broken down by the viral protease to form gp120 and gp41, the components of Env. The six remaining genes, tat, rev, nef, vif, vpr, and vpu (or vpx in the case of HIV-2), are regulatory genes for proteins that control the ability of HIV to infect cells, virus replication, or cause disease.

The ends of each strand of HIV RNA contain an RNA sequence called the long terminal repeat (LTR). Regions in

the LTR act as switches to control production of new viruses and can be triggered by proteins from either HIV or the host cell.

Molecular Heterogeneity of HIV-1

Molecular analyses of HIV isolates reveal varying levels of sequence diversity over all regions of the viral genome. For example, the degree of difference in the coding sequences of the viral envelope protein ranges from a few percent (very close, between isolates from the same infected individual) to 50 % (extreme diversity, between isolates from the different groups of HIV-1, M, N, and O). The changes tend to cluster in hypervariable regions. HIV can evolve by several means, including simple base substitution, insertions and deletions, recombination, and gain and loss of glycosylation sites. HIV sequence diversity arises directly from the limited fidelity of the reverse transcriptase. The balance of immune pressure and functional constraints on proteins influences the regional level of variation within proteins. For example, the envelope, which is exposed on the surface of the virion and is under immune selective pressure from both antibodies and cytolytic T lymphocytes, is extremely variable, with clusters of mutations in hypervariable domains. In contrast, reverse transcriptase, with important enzymatic functions, is relatively conserved, particularly around the active site. The extraordinary variability of HIV-1 is in marked contrast to the relative stability of HTLV-I and -II.

There are three groups of HIV-1: group M (major), which is responsible for most of the infections in the world; group O (outlier), a relatively rare viral form found originally in Cameroon, Gabon, and France; and group N, first identified in a Cameroonian woman with AIDS; only a few cases of the latter have been identified. The M group comprises nine subtypes, or clades, designated A, B, C, D, F, G, H, J, and K, as well as a growing number of major and minor circulating

recombinant forms (CRFs). CRFs are generated by infection of an individual with two subtypes that then recombine and create a virus with a selective advantage. These CRFs range from highly prevalent forms such as the AE virus, CRF01_AE, which is predominant in Southeast Asia and often referred to simply as E, despite the fact that the parental E virus has never been found, and CRF02_AG from West and Central Africa, to a large number of CRFs that are relatively rare. The subtypes and CRFs create the major lineages of the M group of HIV-1. The picture has been complicated somewhat when it was found that some subtypes are not equidistant from one another, while others contained sequences so diverse that they could not properly be considered to be the same subtype. Thus, the term "subsubtype" was introduced, and subtypes A and F are now subdivided into A1 and A2, F1 and F2. It has also been argued that subtypes B and D are really too close to be separate subtypes and should be considered subsubtypes; it was decided, however, not to increase the confusion by renaming the clades.

Seven strains account for the majority of HIV infections globally: HIV-1 subtypes A, B, C, D, G and two of the CRFs, CRF01_AE and CRF02_AG. The predominant subtype in Europe, Australia, and the Americas is subtype B. In Sub-Saharan Africa, home to approximately two-thirds of all individuals living with HIV/AIDS, > 50 % of infections are caused by subtype C, with smaller proportions of infections caused by subtype A, subtype G, CRF02_AG, and other subtypes and recombinants. In Asia, HIV-1 isolates of the CRF01_AE lineage and subtypes C and B predominate. CRF01_AE accounts for most infections in south and southeast Asia, while subtype C is prevalent in India. Sequence analyses of HIV-1 isolates from infected individuals indicate that recombination among viruses of different clades likely occurs as a result of infection of an individual with viruses of more than one subtype, particularly in geographic areas where subtypes overlap.

5. HIV Replication Cycle

The replication of HIV is a multistage process (Fig. 4). It consists of certain steps:

- Entry of HIV into the target cell, including receptor binding, attachment, membrane fusion and penetration.

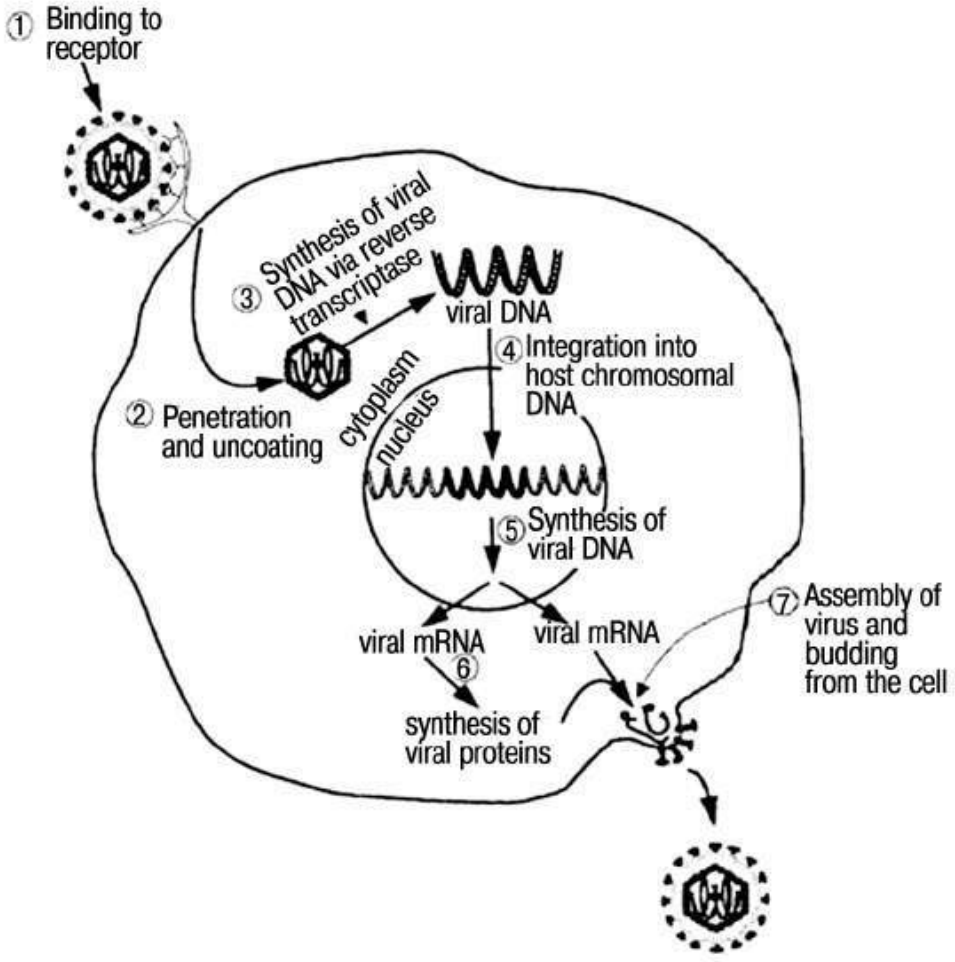

Fig. 4. Life cycle of HIV
(*Source:* University of Wisconsin)

- Reverse transcription (viral DNA synthesis).
- Integration of v-DNA into the host cell genome.
- Transcription.
- Translation.
- Assembly and budding.

Entry of HIV into the cell requires the presence of certain receptors on the host cell surface (see Fig. 5 in color insert). The replication cycle of HIV (see Fig. 6 in color insert) begins with the high-affinity binding of the gp120 protein via a portion of its V1 region near the N terminus to its receptor on the host cell surface, the CD4 molecule.

The CD4 molecule is a 55-kDa protein found predominantly on a subset of T lymphocytes that are responsible for helper function in the immune system. It is also expressed on the surface of monocytes/macrophages and dendritic/Langerhans cells. Cells that contain CD4 proteins are represented as CD4+ cells. Once gp120 binds to CD4, the gp120 undergoes a conformational change that facilitates binding to one of a group of co-receptors.

CCR5 and CXCR4, called co-receptors for HIV-1, are important determinants of the cellular tropism of the virus. Certain dendritic cells express a diversity of C-type lectin receptors on their surface, one of which is called DC-SIGN, that also bind with high affinity to the HIV gp120 envelope protein, allowing the dendritic cell to facilitate the binding of virus to the CD4+ T cell upon engagement of dendritic cells with CD4+ T cells. Following binding of the envelope protein to the CD4 molecule associated with the above-mentioned conformational change in the viral envelope gp120, fusion with the host cell membrane occurs via the newly exposed gp41 molecule penetrating the plasma membrane of the target cell and then coiling upon itself to bring the virion and target cell together. Following fusion, the preintegration complex, composed of viral RNA and viral enzymes and surrounded by a capsid protein coat, is released into the cytoplasm of the target cell.

HIV is an RNA virus whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme reverse

transcriptase. As the preintegration complex traverses the cytoplasm to reach the nucleus, the viral reverse transcriptase enzyme catalyzes the reverse transcription of the genomic RNA into DNA, and the protein coat opens to release the resulting double-stranded HIV DNA. At this point in the replication cycle, the viral genome is vulnerable to cellular factors that can block the progression of infection. In particular, the cytoplasmic TRIM5 protein in rhesus macaque cells blocks SIV replication at a point shortly after the virus fuses with the host cell. Although the exact mechanisms of TRIM5 action remain unclear, the human form is inhibited by cyclophilin A and is not effective in restricting HIV replication in human cells. The recently described APOBEC family of cellular proteins also inhibits progression of virus infection after the virus has entered the cell. APOBEC proteins bind to nascent reverse transcripts and deaminate viral cytidine, causing hypermutation of HIV genomes. It is still not clear whether (1) viral replication is inhibited by the binding of APOBEC to the virus genome with subsequent accumulation of reverse transcripts, or (2) by the hypermutations caused by the enzymatic deaminase activity of APOBEC proteins. HIV has evolved a powerful strategy to protect itself from APOBEC. The viral protein Vif targets APOBEC for proteasomal degradation.

With activation of the cell, the viral DNA accesses the nuclear pore and is exported from the cytoplasm to the nucleus, where it is integrated into the host cell chromosomes through the action of another virally encoded enzyme, integrase. HIV provirus (DNA) selectively integrates into the nuclear DNA preferentially within introns of active genes and regional hotspots. This provirus may remain transcriptionally inactive (latent) or it may manifest varying levels of gene expression, up to active production of virus.

Cellular activation plays an important role in the replication cycle of HIV and is critical to the pathogenesis of HIV disease. Following initial binding and internalization of virions into the target cell, incompletely reverse-transcribed