Scott M. Hammer, M.D.

HIV Diagnosis and Pathogenesis

I. Diagnosis

The diagnosis of HIV infection should be considered in anyone presenting with symptoms compatible with an HIV-related disorder or in an asymptomatic person with any risk factor for acquisition. A full sexual and behavioral history should be taken in all persons as assumptions of risk (or lack thereof) by clinicians are unreliable. A secure diagnosis is made via laboratory methods.

A. Established infection

HIV antibody detection is the basis for establishing the diagnosis in established (non-acute HIV infection). The initial test is typically an ELISA test that can be HIV-1 specific or may screen for both HIV-1 and HIV-2 (often used by blood banks). A positive ELISA antibody must be confirmed by a second test, typically a Western blot test. A Western blot detects serum antibodies to specific HIV proteins that are separated on a gel. Rapid HIV antibody tests are now widely available that can give results in 30 minutes to a few hours.

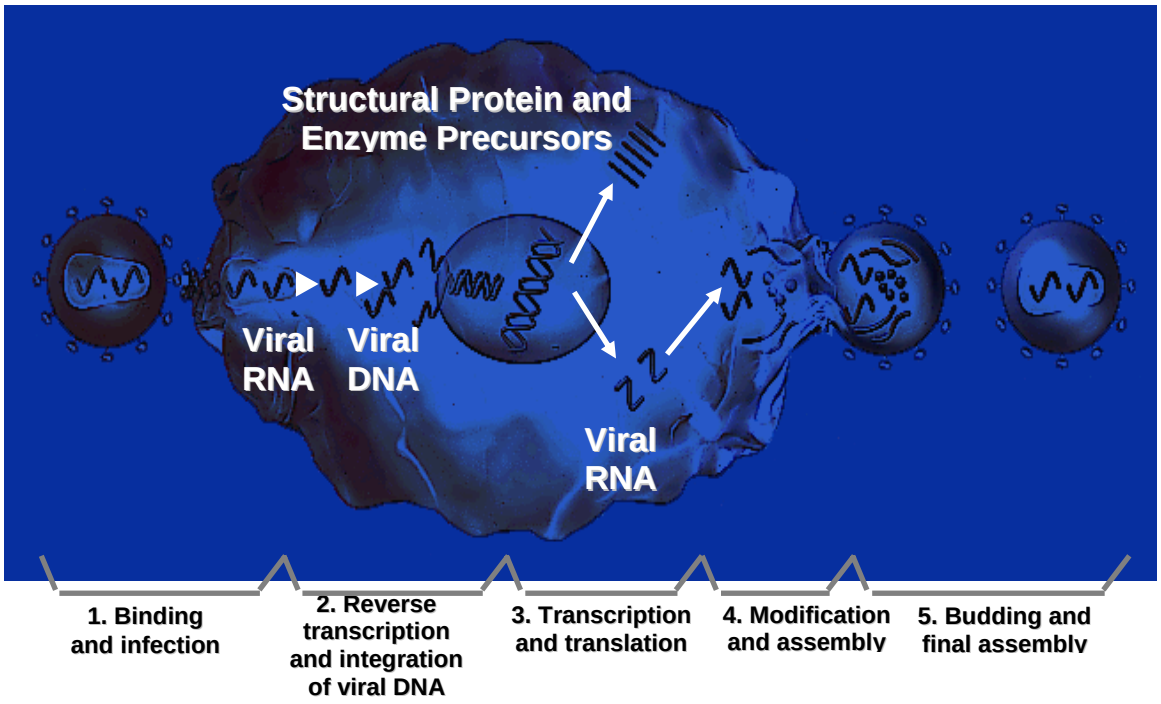
It is important to remember that an HIV test cannot legally be performed on any person without written permission. In addition, pre-test and post-test counseling must be provided to individuals agreeing to be tested. Counseling services are provided by individual care givers, institutions and local health departments.

B. Acute infection

In acute (or primary) HIV infection, a patient may present to a health care provider prior to full seroconversion. In these cases, an HIV antibody should be done but the ELISA may be negative or the ELISA may be positive with a negative or indeterminate Western blot. In these cases, a plasma HIV-1 RNA test should be done as the viral load (RNA concentration in plasma) is typically very high during the acute phase of HIV infection. A follow-up antibody test should be done to confirm that full seroconversion (positive ELISA and Western blot) has occurred.

II. HIV Structure

A. HIV is a member of the Retrovirus family. It is a single stranded RNA virus with an icosahedral nucleocapsid and a lipid envelope. The virion has two identical copies of RNA and carries a unique viral enzyme, the reverse transcriptase. The virus replication scheme is illustrated in the following figure:



B. The HIV genome is 10kB in length and consists of 3 major (Gag, Pol, Env) and 6 accessory genes:

1. Gag codes for internal structural proteins.

2. Pol codes for major enzymes of the virus – reverse transcriptase, protease and integrase.

3. Env codes for the gp120 envelope glycoprotein and the gp41 transmembrane protein. These proteins mediate attachment and entry of the virus into the cell.

4. Tat, Rev, Nef, Vif, Vpr and Vpu are accessory proteins which are involved in amplification of virus replication, infectivity and pathogenesis.

III. Viral Pathogenesis

The pathogenesis of HIV infection and disease is complex and still incompletely understood. The essential elements are:

A. For primary (acute) HIV infection, the pathogenetic steps are:

1. Virus – dendritic cell interaction is the first encounter the virus has following deposition on mucosal surfaces. Primary infection is typically with R5 (macrophage [M]-tropic) viral strains. DC-SIGN is recognized as an important HIV receptor on the surface of dendritic cells.

2. Delivery of virus to lymph nodes where very active replication takes place. In general, dendritic cells act as transporters of HIV and do not primarily support HIV replication.

3. High levels of viremia and viral dissemination occur. During this phase there is a massive loss of CD4+ T lymphocytes from the gut-associated lymphoid tissue (GALT) which is not fully reflected in the peripheral blood CD4 count. The GALT may contain up to 40% of the body's total lymphoid tissue.

4. Downregulation of virus replication by immune response occurs in the absence of any treatment. This is primarily mediated by CD8+ cytotoxic T cells. Neutralizing antibodies are formed but virus titers fall before these antibodies are fully developed.

5. A viral 'set point' is reached after approximately 6 months. The viral set point is predictive of the rate of subsequent disease progression.

B. Once HIV infection is established:

1. There is active viral replication present throughout the course of disease despite a long clinical latency period between the time of infection and the development of what is clinical AIDS (defined as a CD4 count $<200/mm^3$, or the development of an HIV-related opportunistic infection or malignancy).

2. Although one measures the virus in the peripheral blood, major reservoirs of infection exist outside of the blood compartment. These include lymphoreticular tissues (the major "factory" of HIV in lymph nodes, spleen and gastrointestinal tract), the central nervous system, and the genital tract.

3. The virus exists as multiple quasispecies or swarms of viruses. This means that mixtures of viruses with differential phenotypic and genotypic characteristics may coexist in the same body compartment or across body compartments. For example, viruses with different cell tropisms or drug resistance patterns may (and do) coexist in an infected person.

4. Viral production in the body is prolific with at least 10×10^9 virions produced and destroyed each day in the life of an infected individual. The turnover of HIV in the body is enormous with the half life ($T_{1/2}$) of HIV in plasma estimated to be <6 h and possibly as short as 30 minutes. As with all infectious diseases, the outcome of infection is a balance between the virulence of the pathogen and host factors. In the case of HIV, the strength of the innate and adaptive immune responses

(especially CD8+ cytotoxic T cells), the chemokine receptor status and HLA type of the infected person are important codeterminants of outcome.

5. Clinical illness (HIV-related symptoms, AIDS-defining opportunistic infections and malignancies) develops as the CD4 cell count falls, particularly as it falls below 200/mm^3. The risk is progressive as the CD4 cell count falls below this level. The average time from infection to clinical AIDS is typically 8-10 years. However, there are 'rapid progressors' who develop AIDS within 2 years or so of infection and 'long-term non-progressors' (LTNPs) who maintain normal CD4 cell counts and very low viral loads in the absence of treatment for >10-15 years. A subgroup of LTNPs has been termed "elite controllers". These are individuals who maintain plasma HIV-1 RNA (viral load) levels <50 copies/ml in the absence of antiretroviral therapy. These "elite controllers" form a very small percentage of the overall HIV infected population but are being studied intensively for the insights they may provide into the effective immune controls they exhibit which might be mimicked in an HIV vaccine.

6. "Non-AIDS" conditions. Since 2006, cardiovascular, hepatic and renal disease events, as well as a number of non-AIDS-defining malignancies, have been reported to be associated with ongoing HIV viremia even in persons with relatively well maintained CD4 counts (e.g., >350/mm^3). Direct effects of HIV, the immune activation associated with uncontrolled HIV replication, and/or subtle immune deficiency (in persons with higher CD4 counts) are hypothesized to be involved in the pathogenesis of the interactions of HIV disease with these diverse conditions but precise mechanisms have not been defined. Their presence, however, is beginning to influence clinical decision making related to the question of "When to start antiretroviral therapy?".