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HIV: Structure, Life Cycle, and Pathogenecity

Jonathan Richard Hughes
University of Tennessee - Knoxville

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Name: Jonathan Hughes

College: Arts & Sciences Department: BCMB

Faculty Mentor: Jeff MacCabe

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I have reviewed this completed senior honors thesis with this student and certify that it is a project commensurate with honors level undergraduate research in this field.

Signed: Jeff MacCabe, Faculty Mentor

Date: 5/6/02

Comments (Optional):

Human Immunodeficiency Virus: Structure, Life Cycle, and Pathogenecity

Jonathan Hughes

Viruses are the smallest infectious agents of animal and plant tissues. They range in size from 20 to 300 nm (1nm = one billionth of a meter). To cause a disease, viruses must enter living cells, unlike bacteria which are able to survive outside cells. Viruses are totally dependent on living cells to survive as they utilise the host cell's own replication processes, in order to reproduce themselves (Abbas, 2000).

HIV the causative agent of AIDS, was identified in 1983 following the first reported cases of Acquired Immunodeficiency Syndrome (AIDS) in 1981 and 1982.

HIV is a member of a class known as Retroviruses. These viruses store their genetic information as ribonucleic acid (RNA), unlike most viruses which store their genetic information as deoxyribonucleic acid (DNA). Before viral replication can take place, the RNA must be converted to DNA by reverse transcription, hence the Latin term *Retro*, meaning 'turning back' (Abbas, 2000).

HIV comprises an outer envelope consisting of a lipid bilayer with spikes of glycoproteins (gp), gp41 and gp120. These glycoproteins are linked in such a way that gp120 protrudes from the surface of the virus. Inside this envelope is a nucleocapsid (p17), which surrounds a central core of protein, p24. Within this core, are two copies of single-stranded RNA (the virus genome). Proteins, p7 and p9, are bound to the RNA and are believed to be involved in regulation of gene expression. Multiple molecules of the enzyme, reverse transcriptase (RT), are also found in the core. This enzyme is responsible for converting the viral RNA into proviral DNA (Abbas, 2000).

HIV only infects certain types of cells. In general, these are cells which carry CD4 receptors on their surface. Some cells in the immune system have these receptors, in particular, T4-lymphocytes or T-helper cells. These cells are often referred to as CD4 cells or T4 cells. Other cells carrying the CD4 receptor include other white blood cells (monocytes and macrophages), glial cells in the brain, chromaffin cells in the intestines and Langerhans' cells in the skin (Marr, 1998). AII of these cell types have been shown to be infected with HIV. It has also been shown, however, that cells which do not bear the CD4 receptor may still be infected by HIV which raises the possibility that other cellular receptors for the virus may exist.

When HIV comes into contact with T-lymphocytes (CD4 cells), the spikes of gp120 'slot into' the CD4 receptors (like a lock and key) allowing binding of the virus to the host cell. Once inside the cell, the virus loses its outer envelope and its contents are released into the host cell's cytoplasm, the most important of which, are the viral RNA and reverse transcriptase. Using the viral RNA as a template, reverse transcriptase catalyses the production of a single, complementary strand of DNA from nucleotides in the host cell (Abbas, 2000).

DNA is constructed of units called nucleotides. Each nucleotide is made up of a base (either adenine, guanine, thymine, or cytosine), a sugar and a phosphate molecule. The sequence in which the bases occur determines the genetic code of the virus. RNA differs from DNA in that uracil replaces thymine as a base and the sugar molecule is different. Once the single strand of DNA has been produced, it acts as a template in the production of a second strand of DNA. This replication step is also catalysed by reverse transcriptase and the resulting double-stranded DNA is known as proviral DNA (Abbas,

2000). This is then incorporated into the DNA of the host cell by the viral enzyme, integrase. It is this integration of the viral genetic material into the host cell's own genetic material that makes eradication of the virus, without damage to the host cell, a formidable goal.

Effectively, the virus has now hijacked the host cell's own replication system. As a result, when the cellular DNA is transcribed, so is the viral DNA to form an RNA transcript. Further processing of this RNA into messenger RNA (mRNA) and genomic viral RNA occurs.

The viral mRNA is then translated into viral proteins, which along with the genomic RNA, are assembled into new virus particles. This last stage requires the viral enzyme, protease (Marr, 1998). Finally, the new viral particles are released from the infected cell and go on to infect other cells in the body.

Known routes of HIV transmission include:

- Sexual contact (homosexual, bisexual or heterosexual)
- Contaminated needles - used for intravenous drug injection, or for general medical purposes In countries where disposable needles or sterilising equipment may be scarce
- Vertical transmission from mother to child
- Blood transfusions, blood products and organ/tissue transplants
- Injuries in healthcare settings, e.g. people working with blood products, needlestick injuries

(Negishi, 1993).

There is no significant evidence to support claims that HIV may be transmitted by the following:

- Insects, e.g. mosquitoes, which penetrate the skin and blood supply
- Saliva, e.g. kissing, sharing food and eating/drinking utensils
- Sneezing or coughing
- Shared use of facilities and equipment, e.g. toilets, swimming pools, towels, etc
- Casual social contact, e.g. shaking hands, hugging, etc.

(Negishi, 1993)

Sexual contact:

Based on cumulative global statistics from 1983 to 1995, the World Health Organization estimates that 70-80 per cent of AIDS cases are transmitted through heterosexual contact, and five to ten per cent of cases are transmitted through homosexual contact. At the beginning of the epidemic, homosexual sex was perceived to be the main route of transmission of HIV and accounted for the majority of known cases; however, heterosexual contact now accounts for the vast majority of cases of transmission. This is a worldwide figure, however, and it should not be forgotten that in much of Europe and the Americas, homosexual and intravenous drug-using populations remain the most affected by HIV (van Benthem, 2001). On the other hand, in sub-Saharan Africa, the predominant route of transmission is heterosexual. Results of a European Collaborative

Study on heterosexual transmission from HIV-infected persons to their stable heterosexual partners showed a cumulative transmission rate of 12.7 per cent (Marr, 1998). Oral sex of any form is not associated with a high risk of HIV transmission, but it should, nevertheless, be regarded as a potential means of transmission. Genital ulceration has been shown to increase the risk of transmission during sexual contact as has high viral load in the infected person (Marr, 1998).

The risk of sexual transmission can be decreased by a reduction in the number of sexual partners and the use of male and female condoms.

Perinatal (mother-to-child) transmission:

The World Health Organisation estimates that five to ten per cent of AIDS cases are caused by perinatal transmission. However, varying rates of mother-to-child transmission have been reported from 13 per cent in some European countries to 43 per cent in Kenya (although regional variations exist). There are a number of different possible routes of infection, including: *in utero* infection, during delivery and during breast feeding. The importance of each of these routes to the overall mother-to-child rate of transmission has not yet been determined. Several maternal factors appear to increase the risk of transmission, including high viral load and low CD4 count, particularly during the third trimester (Phrapradit, 1999). However, transmission has been reported across a wide range of maternal viral load measurements. Prematurity and low birth weight of the infant also appear to be associated with a higher risk of transmission.

The risk of perinatal transmission can be reduced through giving birth by caesarean section and refraining from breast feeding. The use of AZT during the later

stages of pregnancy and postnatal treatment of the neonate reduces transmission rates from approximately 25 per cent to 8 per cent (Sowell, 2001).

Intravenous drug use :

The World Health Organisation estimates that intravenous drug use is responsible for five to ten per cent of AIDS cases worldwide. The sharing of contaminated needles and syringes is the main route for viral transmission amongst intravenous drug users. This is believed to be an extremely 'efficient' means of HIV transmission, as direct blood-to-blood contact is possible. Refraining from sharing needles and syringes and the introduction of clean needle exchange programs can reduce the risk of HIV transmission through intravenous drug use.

Transfusions and transplants :

The risk of transmission through transfusion and transplants is very small. The World Health Organisation estimates that transfusions and transplants account for only three to five per cent of cases. The screening/testing of all blood, blood products and transplant tissues, and the discouragement of blood donations from those deemed to have a lifestyle which may put them at increased risk of infection has significantly reduced the risk of transmission through these routes.

Occupational exposure :

Transmission of HIV through healthcare injuries and occupational exposure is very rare, accounting for less than 0.0001 per cent of cases as estimated by the World Health Organisation. The risk of transmission from HIV-infected patients to healthcare

workers can be reduced by the use of protective clothing, including gloves; the implementation or revisiting of procedures for disposing of contaminated products and sharp instruments; and the use of antiretroviral therapy.

It should be noted, however, that education is potentially regarded as the most effective primary means of preventing infection by any mode of transmission.

Immune Responses:

The overall effect of infection with HIV and its interaction with the body's natural response mechanisms is severe damage to the immune system, destroying the means by which the human body naturally defends itself against infections.

Following entry into the host, HIV is disseminated via the blood and circulatory system to different tissues in the body. From this moment of infection, the virus is replicating at extremely rapid rates. As the virus replicates and spreads throughout the body, the immune system detects the presence of the virus and mounts an immediate antibody response. This usually occurs within two to four weeks of infection and is referred to as seroconversion (because antibodies to HIV can be detected in the blood) (Yoshida, 2001). Early in the course of infection, HIV is disseminated to the lymphoid tissues. The lymph system can be likened to a drainage system which filters out unwanted pathogens from the body and destroys them. Lymph vessels carry infectious agents to the lymph nodesr These nodes are located throughout the body and contain a sieve- or mesh-like structure of follicular dendritic cells (FDCs) in their germinal centres, which trap bacteria, fungi, and viruses (including HIV) (McMichael, 2001). The lymph nodes are also the site of a concentration of immune system cells, including T-lymphocytes (the

cells which orchestrate the immune response). As the pathogens are trapped by the FDC network, these immune system cells attack and destroy them.

During the earlier stages of infection, the FDC network is intact and is able to trap extra-cellular virions, which in combination with effective destruction of the virus by immune system cells results in apparently low levels of virus in other tissues as well as in blood and plasma. As viruses are trapped in greater concentrations, they infect the T-lymphocytes and other cells in the lymph nodes. Gradually, more and more cells in the lymph nodes begin expressing HIV. Eventually the FDC network completely breaks down. This destruction of lymph node architecture has been observed in lymph node biopsies (Orenstein, 2000). Finally, with this complete destruction of the lymph nodes, viruses, bacteria, and fungi 'spill over' into the blood system and around the body. At this stage, levels of HIV are so high that the virus is able to infect and destroy CD4 T-lymphocytes at a faster rate than the body is able to produce new immune cells (including CD4 T-lymphocytes). This leaves the body unable to mount an effective immune response against these pathogens, including HIV. Eventually, clinical symptoms of HIV appear, such as neurological deterioration (erg. AIDS dementia complex), as well as other opportunistic infections (erg. *Pneumocystis carinii* pneumonia) and cancers (e.g. Kaposi's sarcoma), indicating that the infection is in its advanced stages (Klatt, 1998).

This entire course of events varies considerably amongst individuals but is, on average, approximately 12 years.

Long-Term Non-Progressors :

This time course of infection and disease is likely to occur in the majority of patients. However, a small percentage (perhaps less than five per cent) of patients are known to live with HIV infection for prolonged periods of time without experiencing disease progression and the appearance of symptoms. These individuals are often referred to as long-term non-progressors (LTNPs) and appear to have some consistent features of their infection: Firstly, the lymph node architecture of LTNPs is usually completely preserved. In addition, the proportion of lymphoid tissue occupied by germinal centres in the early stages of disease is significantly lower, reflecting the state of activation of the lymph node. Also, LTNPs appear to have consistently lower levels (by approximately one log) of HIV RNA as compared with progressors. However, it is important to remember that the virus in LTNPs is still infectious and able to replicate. Levels of viraemia are, also, generally lower in LTNPs and may increase transiently without an obvious effect on the CD4 cell count. In addition, LTNPs tend to have a more robust immune response, with particularly high levels of neutralising antibodies. Although the exact reason why some individuals experience long-term non-progression is unclear and it is likely that they probably represent a heterogeneous group of patients with variable impacts from the virus and host factors (Propatio, 2001).

The pattern and rate of progression of HIV disease varies significantly between individuals and appears to be dependent upon the individual's age, sex, general health and mode of infection.

Course of infection :

In the 1990s, the time to development of AIDS after initial infection with the virus is approximately 10 to 12 years. In the mid 1980s, however, the average time from infection to AIDS was 8 to lO years (Klatt, 1998). This improvement in time to development of AIDS is due, in part, to improved diagnosis, increased use of antiretroviral therapy and improved management of opportunistic infections. Although the clinical, virological and immunological course of HIV infection varies, a generalised course of events can be determined.

During the initial days following infection, the levels of HIV RNA (a marker of HIV infection) rise steeply, mostly due to high rates of viral replication and the resulting large amount of virus in the blood. Some weeks after infection, the immune system mounts a response to the infection, producing antibodies to HIV, which lower the amount of virus in the blood. However, viral levels in the whole body still remain relatively high. This stage of infection, seroconversion, usually occurs between two to four weeks after infection, but it may take as long as six months (Ashebir, 1996). A significant drop of CD4 cells is also observed, which, although transient in nature, usually never fully returns to pre-infection levels. Clinically, patients at this stage of infection experience no symptoms. However, seroconversion may be characterised by a rash, fever, fatigue and lymphadenopathy. Following seroconversion a period of clinical latency is observed which may last for approximately ten years. However, this should not be mistaken for a period of virological and immunological latency. As previously mentioned, the levels of viral replication and immune cell turnover are extremely high. Whilst levels of the infectious virus in the peripheral blood are low during this period, higher levels are observed in the plasma and in specific tissues (especially lymphoid tissues). Overall, the

level of the virus in the body is seen to rise over time. Concurrently, CD4 counts decline gradually during the same period. Whilst these two markers of infection are the most accurate determinants of the status of infection, changes in other laboratory markers are often observed. Typically, these include an increase in levels of p24 antigen, $beta_2$-microglobulin and serum neopterin; and a decrease in levels of p24 antibody haemoglobin, neutrophils, platelets, lymphocytes, and interleukin-2-receptors (Chibatamoto, 1996) .

As the infection continues, viral load and replication rates reach such a magnitude that lymphoid tissues are completely destroyed and the turnover of CD4 T-lymphocytes can not match the destructive actions of the virus. Thus, CD4 cell counts are seen to decline at an increasingly faster rate and, with a weakening immune system, levels of viral RNA begin to increase once again. These virological and immunological events mark the onset of the more advanced stage of infection, characterised by the onset of clinical symptoms.

At this stage of infection, viral load in individuals may be extremely high, around one million copies/ml, although individual variation is significant. Although CD4 cell counts may also vary, individuals with CD4 counts below 2OO cells/mm^3 are at the greatest risk of developing opportunistic infections (note that CD4 cell counts of healthy individuals are usually above lOOO cells/mm^3) (Chibatamoto, 1996).

The first clinical symptoms of this advanced stage vary considerably and include: persistent thrush (candidiasis, oral and genital), oral hairy leukoplakia and herpes. Other

signs include impaired neurological function, night sweats, weight loss, fever, diarrhoea, malaise and fatigue (Hays, 1992).

As this advanced stage continues, clinical diseases often increase in their severity and may include Kaposi's sarcoma, *Pneumocystis carinii* pneumonia, tuberculosis, and neurological dysfunction. Eventually, infected individuals reach a stage when their condition is classified as Acquired lmmunodeficiency Syndrome. Whilst this classification does not make a positive contribution to patients, the staging of the disease course using clinical, virological, and immunological markers is very useful in the context of clinical trials. Survival times following a diagnosis of AIDS vary and often depend on the opportunistic infections that a person may have and the management options available.

Categorization of AIDS:

The CDC in Atlanta, Georgia, has developed a widely-used system by which the disease status of HIV-infected adolescents and adults is categorised on the basis of clinical conditions associated with HIV infection and CD4 cell counts. The system divides CD4 cell counts into three categories: Category A consists of one or more of the conditions listed in the slide with documented HIV infection. Conditions in Category B or Category C must not have occurred. Category B consists of symptomatic conditions, some of which are listed in the slide, that are not included in Category Cr The clinical conditions must meet at least one of the following criteria: (1) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity, (2) the

conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection (CDC).

A patient with any disease included in Category C (C1, C2 or C3) is considered to have AIDS, as is any patient with a CD4 cell count of below 2OO cells/mm^3 .

Opportunistic infections (Ols) are caused by organisms (bacteria, viruses, fungi, parasites) that the immune system would normally fight off. People with HIV are vulnerable to infection with these organisms because of the destruction of their immune system. Some of the more common Ols are listed in the following slides, in addition to other symptoms of advanced disease.

Skin and mouth infections and symptoms :

- *Seborrhoeic dermatitis*, a type of eczema, is one of the most common infections and occu rs as a red, scaly rash on the face and scalp.
- *Tinea* is a fungal infection which affects the feet (athlete's foot) and groin.
- *Candida albicans* is a fungus which can cause thrush in the mouth, vagina, or oesophagusr
- *Oral hairy leukoplakia* is white, warty-like growths on the sides of the tongue and cheeks and is usually painless, although its appearance worries many individuals. It is caused by Epstein Barr virus.
- *Impetigo* is an irritating and contagious bacterial skin infection

- *Herpes simplex virus* is sexually transmitted and symptoms may range from mild irritation in genital and anal areas to painful, deep ulcers.

- *Varicella zoster virus* causes shingles, which, if it becomes widespread throughout the body, can be fatal.

- *Kaposi's sarcoma* is a cancer which is diagnostic of AIDS. It frequently occurs as raised purplish patches on the skin. A herpes-like virus has been implicated in the development of Kaposi's sarcomar

(Schneider, 2000).

Effects on the nervous system :

A wide spectrum of neurological complications affecting each part of the nervous system has been described in HIV-infected individuals. These include otherwise rare opportunistic infections and neoplastic diseases, such as cerebral toxoplasmosis, cryptococcal meningitis and primary central nervous system (CNS) lymphoma, as well as syndromes caused by or directly related to, HIV infection, such as dementia and various neuromuscular complications (Krebs, 2000). Today, at least 7O per cent of HIV-infected individuals exhibit some type of neurological complication, and neuropathological abnormalities are found in 80 to 9O per cent of patients at autopsy (Krebs, 2000).

HIV was first isolated from the brain and cerebrospinal fluid of people with AIDS with neurological disorders in 1985. Whilst it is now generally accepted that HIV infection of the brain results in the clinical syndrome known as AIDS dementia complex (ADC), many questions about the pathogenesis of ADC remain unanswered. There is

evidence that the virus infects the brain early in infection but that the neurones themselves are rarely infected (Wesselingh, 2001). This presents an intriguing paradox - how does HIV cause disease in the brain? The answer seems to lie in a combination of direct and indirect effects of HIV on cells of the CNS.

- *AIDS dementia complex (ADC)* is an AIDS defining illness characterised by symptoms including slowed thought, impaired concentration, memory deficit, confusion, clumsiness, loss of co-ordination, tremor, inability to walk, incontinence, social withdrawal, noticeable change in personality and irrational behaviour. Since the introduction of AZT in 1987, the incidence of ADC has been greatly reduced, from approximately 53 per cent to 10 per cent in one study [3]. Further studies have confirmed the therapeutic efficacy of zidovudine in the treatment of ADC. It is apparent that no other antiretroviral agents have demonstrated comparable efficacy and safety to AZT in preventing and reversing the effects of ADC.

- *Peripheral neuropathy* (destruction of nerve tissue) occurs in 10 to 15 per cent of individuals with AIDS. It can cause severe pain in the legs, feet and extremities.

- *Cryptococcus neoformans*, a common fungi found in soil, is a recognised cause of meningitis. It can also cause generalised infection in the body which is life-threatening in approximately ten per cent of individuals with AIDS.

- *Toxoplasma gondii*, a protozoal parasite, causes toxoplasmosis of the brain, a condition which is associated with headache, confusion, personality changes and seizures and can result in coma and death.

- *Cytomegalovirus* is often associated with retinitis which can lead to blindness and may also be associated with neurological illnesses, including encephalitis (inflammation of the brain).

- *Lymphoma* (a tumour of the lymphoid tissue) can occur in the brain, causing headaches, confusion, seizures, and problems with vision.

(Tardieu, 1999).

Other Systems Affected:

Effects on the respiratory system :

- *Pneumocystis carinii* pneumonia (PCP) was the most common OI in people with AIDS. Prophylaxis of PCP has drastically reduced the incidence of this infection from around 60 per cent of patients with AIDS in the USA in the mid 1980s to around 5 per cent today. Symptoms of PCP include a dry cough, shortness of breath, and sometimes, pneumonitis, making breathing painful.

- *Tuberculosis (TB)* is caused by the bacterium *Mycobacterium tuberculosis*. Many countries have seen a rise in the number of cases of TB, with the increasing incidence of HIV infection. Drug-resistant strains of TB are becoming a significant worldwide problem as many patients do not take their full course of therapy. This infection, unlike many others associated with HIV, is infectious to all individuals. This infection flourishes in conditions of deprivation and overcrowding. It is endemic in many developing countries.

- *Mycobacterium avium intracellulare* occurs in approximately 5O per cent of individuals who have low CD4 counts. Symptoms are generally non-specific and include fever, weight loss, anaemia, enlarged liver and chronic diarrhoea.

- *Bronchitis* and pneumonia, caused by a variety of bacteria, occur more often in people with HIV

- *Kaposi's sarcoma* and other cancers are often the cause of lung complaints in people with AIDS.

(de Leon, 1995).

Effects on the gastrointestinal (Gl) system :

- *Candida albicans* (thrush) is one of the early signs that the immune system is faltering. It often infects the oesophagus and causes pain and difficulty when swallowing.

- *Herpesvirus* infections can cause inflammation and ulceration all along the GI tract, from the mouth to the anus.

- *Cryptosporidium muris* and *microsporidium* are protozoa which are frequently the cause of severe diarrhoea.

- *Kaposi's sarcoma* of the Gl tract is found in many people who die of AIDS.

(Knox, 2000).

Cancers :

- *Kaposi's sarcoma* is a malignant, life-threatening cancer of the blood vessels which occurs initially as flat, purplish patches on the skin. The cancer may, however, affect any part of the body, and young male homosexuals appear to be most vulnerable to this cancer. A herpes-like virus has been implicated in the development of Karposi's sarcoma.

- *Non-Hodgkin's lymphoma (NHL)* is a life-threatening cancer for people with advanced HIV infection and is increasing in incidence. Around 3O per cent of HIV-infected individuals with NHL have some involvement of the brain.

- *Other cancers* have been noted in people with HIV and AIDS, including rectal cancer, head and neck cancer and melanoma.

(Clarke, 2001).

HIV Screening:

Most of the currently used first-line screening systems to diagnose HIV infection employ enzyme-linked immunosorbent assay (ELISA) techniques. These assays detect the presence of antibodies to HIV in blood samples (although kits are now available to test urine and saliva samples) (Kosko, 2000). Automated processing of multiple samples using microwell plates enables large-volume throughput, essential to the screening of blood donations. Combination assays for detecting both HIV-1 and HIV-2 are often used in countries where both strains may be prevalent. The use of these combined assays is increasing worldwide.

If any samples are found to be positive in the first-line screening procedure, further confirmatory tests are required to ensure that the initial results are not inaccurate, so-called 'false positives'. Currently, many laboratories use Western Blot technique (antibody reaction to viral proteins and glycoproteins) as a second line testing procedure. A positive result generally requires the presence of bands correlating to p24, p31, gp41, and gp120 or gp160 (Roberts, 1994).

One weakness of these methodologies is that they measure the presence of antibodies to HIV rather than the presence of the viral components themselves. It is, therefore, possible that infection may not be diagnosed in individuals who have not yet developed an antibody response to the virus.

A number of other techniques have been developed and refined in recent years to enable the accurate monitoring of HIV over the course of infection. These include:

Polymerase chain reaction (PCR) :

This technology is able to detect the presence of viral genetic material (both RNA and DNA) and involves three distinct steps: denaturation, annealing, and polymerisation. Repeated cycles of this process produce microgram quantities of viral DNA or RNA. This methodology has been developed further, with the inclusion of internal standards in commercially available kits (known quantities of genetic material) to allow accurate quantification of viral RNA/DNA. In addition, this technology has been automated to allow high-volume processing of numerous samples (Klatt, 1998).

Branched-chain DNA (b-DNA) :

This approach differs from other assays in that it is based on signal amplification rather than target amplification. Quantitation is determined by comparing the chemiluminescence of samples with a four-point standard curve assayed in each microwell plate (Klatt, 1998).

Nucleic acid sequence-based amplification (NASBA) :

This technology involves isolation by lysis and binding to silicon dioxide particles, followed by an isothermal amplification procedure. Three levels of calibration, or internal standards, are included and detection is based on an enzyme-linked gel assay or electrochemiluminescence (Kosko, 2000).

These technologies have made it possible to quantitatively measure plasma viral levels in individuals, from which, disease status and risk of disease progression can then be determined.

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