Retroviridae & AIDS

HIV-1 Genotypes

- There are 3 HIV-1 genotypes; M (Main), O (Outlayer), and N (New)
- M group comprises of a large number subtypes and recombinant forms
  - Subtypes - (A, A2, B, C, D, F1, F2, G, H, J and K)
  - Recombinant forms - AE, AG, AB, DF, BC, CD
- O and N group subtypes not clearly defined, especially since there are so few N group isolates.

As yet, different HIV-1 genotypes are not associated with different courses of disease nor response to antiviral therapy.

HIV half-lives

- Activated cells infected with HIV produce and die within 1-2 days.
- i.e virus present in the plasma.
- HIV life-cycle = 1.5 days.
- Resting cells infected produce virus only after immune stimulation; these cells have a half-life of at least 5-6 months.
- •Some cells are infected with defective virus that cannot complete the virus life-cycle. Such cells are very long lived, and have an estimated half-life of approximately 3-6 months.
- Such long-lived cell present a major challenge for anti-retroviral therapy.

Transmission & Epidemiology

Transmission of HIV occurs primarily by **sexual contact** and by **transfer of infected blood**. **Perinatal transmission from infected mother** to neonate also occurs, either across the placenta, at birth, or via breast milk. Infection occurs by the transfer of either HIV-infected cells or free HIV (i.e., HIV that is not cell-associated). Although small amounts of virus have been found in other fluids, e.g., saliva and tears, there is no evidence that they play a role in infection. In general, transmission of HIV follows the pattern of hepatitis B virus, except that HIV infection is much less efficiently transferred, i.e., the dose of HIV required to cause infection is much higher than that of HBV. People with sexually transmitted diseases, especially those with ulcerative lesions such as syphilis, chancroid, and herpes genitalis, have a significantly higher risk of both transmitting and acquiring HIV. Uncircumcised males have a higher risk of acquiring HIV than do circumcised males.

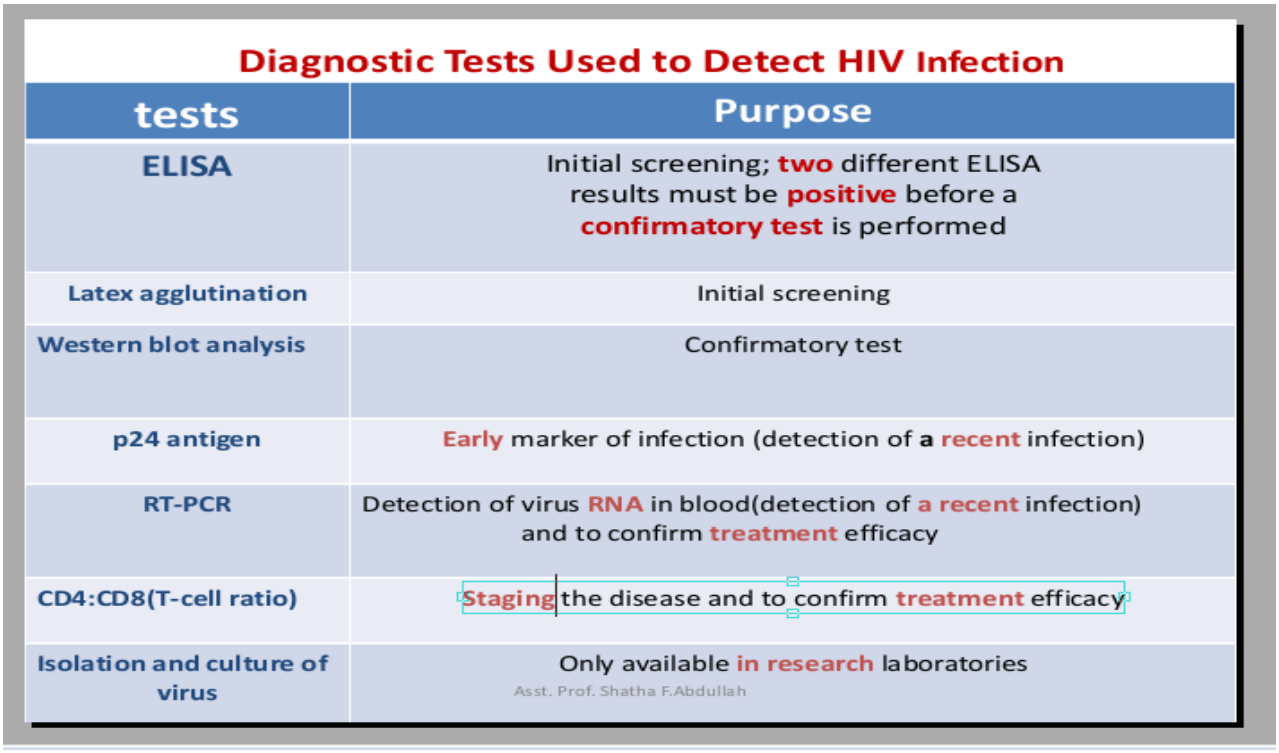
Transmission of HIV via blood transfusion has been greatly reduced by screening donated blood for the presence of antibody to HIV. However, there is a "window" period early in infection when the blood of an infected person can contain HIV but antibodies are not detectable. Blood banks now test for the presence of p24 antigen in an effort to detect blood that contains HIV.

Laboratory Diagnosis

The diagnosis of HIV infection is made by the detection of antibodies by **ELISA.** Because there are some false-positive results with this test, the definitive diagnosis is made by **Western blot** analysis.

HIV can be grown in culture from clinical specimens, but this procedure is available only at a few medical centers. The polymerase chain reaction (PCR) is a very sensitive and specific technique that can be used to detect HIV DNA within infected cells. Some individuals who do not have detectable antibodies have been shown by this test to be infected. As already mentioned, the amount of viral RNA in the plasma (i.e., the viral load) can also be determined using PCR-based assays.

During the first month after infection, antibody tests may be negative. These false-negative tests are due to insufficient antibody being made early in infection to be detected in the ELISA test. The average time for seroconversion is 10 to 14 days and most, but not all, will have seroconverted by 4 weeks.



Diagnostic Tests Used to Detect HIV Infection

tests	Purpose
ELISA	Initial screening; two different ELISA results must be positive before a confirmatory test is performed
Latex agglutination	Initial screening
Western blot analysis	Confirmatory test
p24 antigen	Early marker of infection (detection of a recent infection)
RT-PCR	Detection of virus RNA in blood(detection of a recent infection) and to confirm treatment efficacy
CD4:CD8(T-cell ratio)	Staging the disease and to confirm treatment efficacy
Isolation and culture of virus	Only available in research laboratories

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Prognostic tests

To monitor the patient for: signs of disease progression and response to antiviral chemotherapy.

- HIV viral load - detect HIV-RNA e.g.
- RT-PCR (bad >10,000 copies)
- HIV Antigen tests
- serial CD4 counts.

Treatment

The treatment of HIV infection has resulted in a remarkable reduction in mortality and improvement in the quality of life of infected individuals. The specific goals of treatment are to restore immunologic function that reduces the incidence of both opportunistic infections and certain malignancies as well as to reduce viral load, which reduces the chance of transmission to others.

Treatment of HIV infection typically involves multiple antiretroviral drugs. The use of a single drug (monotherapy) for treatment is not done because of the high rate of mutation to drug resistance.

The choice of drugs is complex and depends on several factors, e.g., whether it is an initial infection or an established infection, the number of CD4 cells, the viral load, the resistance pattern of the virus, and whether the patient is pregnant or is coinfected with HBV or HCV.

In general, initial antiretroviral therapy consists of one of two regimens, each one of which consists of three drugs. One regimen has two nucleoside reverse transcriptase inhibitors (NRTI), such as lamivudine and zidovudine plus a protease inhibitor, such as fosamprenavir. The second regimen has the same two NRTI plus a nonnucleoside reverse transcriptase inhibitors (NNRTI), such as Nevirapine.

These combinations are known as **HAART,** which is an acronym for "highly active antiretroviral therapy." It is very effective in prolonging life, improving quality of life, and reducing viral load but does not cure the chronic HIV infection, i.e., replication of HIV within CD4-positive cells continues indefinitely. Discontinuation of HAART almost always results in viremia (a return of the viral load to its pretreatment set point) and a fall in the CD4 count.

Antiretroviral Drugs Used in HAART

Class of Drug	Mechanism of Action	Name of Drug
Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)	inhibit HIV reverse transcriptase.This prevents virus replication and spread	**zidovudine(AZT), didanosine (DDI), lamivudine (3TC)**
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	**=**	**Efavirenz (EFV), nevirapine,**
Protease inhibitors (PIs)	inhibit the retroviral protease from cleaving the viral proteins. slow the spread of the virus to other uninfected cells.	**ritonavir, indinavir**
Fusion entry inhibitors	interferes with the viral gp41 and prevents fusion of HIV with the host cell.	**Enfuvirtide**
CCR5 entry inhibitors	block binding of the HIV virion to the surface of	**Maraviroc**

Also, in 2007, the FDA approved the use of raltegravir (Isentress), the first drug to **inhibit the HIV-encoded integrase.** It is recommended for use in patients who have been treated with other antiretroviral drugs but continue to produce significant levels of HIV.

Prevention

No vaccine is available. Prevention consists of taking measures to avoid exposure to the virus, e.g., using condoms, not sharing needles, and discarding donated blood that is contaminated with HIV. Postexposure prophylaxis, such as that given after a needle-stick injury or a high-risk nonoccupational exposure, consists of two drugs, e.g., lamivudine and zidovudine for low-risk exposures and the same two drugs plus lopinavir/ritonavir for high-risk exposures. Two steps can be taken to reduce the number of cases of HIV infection in children: ZDV or nevirapine should be given perinatally to HIV-infected mothers and neonates, and HIV-infected mothers should not breast feed. In addition, the risk of neonatal HIV infection is lower if delivery is accomplished by cesarean section rather than by vaginal delivery. Circumcision reduces HIV infection.

Several drugs are commonly taken by patients in the advanced stages of AIDS to prevent certain opportunistic infections. Some examples are trimethoprim-sulfamethoxazole to prevent *Pneumocystis* pneumonia, fluconazole to prevent recurrences of cryptococcal meningitis, ganciclovir to prevent recurrences of retinitis caused by cytomegalovirus, and oral preparations of antifungal drugs, such as clotrimazole, to prevent thrush caused by *Candida albicans*.

Why is it difficult to develop a vaccine for HIV and AIDS?

There are **many reasons** for this, including:

- Nobody has ever recovered from HIV infection, so there is no natural mechanism to imitate
- HIV destroys the immune system cells that are meant to fight against it
- Soon after infection, HIV inserts its genetic material into human cells, where it remains hidden from the immune system .
- HIV occurs in several subtypes, each of which is very different from the others
- Even within each subtype, HIV is highly variable and constantly changing
- There are no good animal models to use in experiments although the use of non human primate (NHP) models could become a more significant model for HIV vaccine design and testing in the future.