Chapter 42

Arboviruses

-- **Arboviruses** means **arthropod-borne viruses**.

-- All **arboviruses** are transmitted by arthropods primarily **mosquitoes** and **ticks.**

-- There are at least **400 members**.

-- They are **named** after either the **disease** they cause or the **place** where they were first isolated.

-- **Roboviruses** are viruses **transmitted directly to humans from rodents**, generally by inhalation of dried excreta.

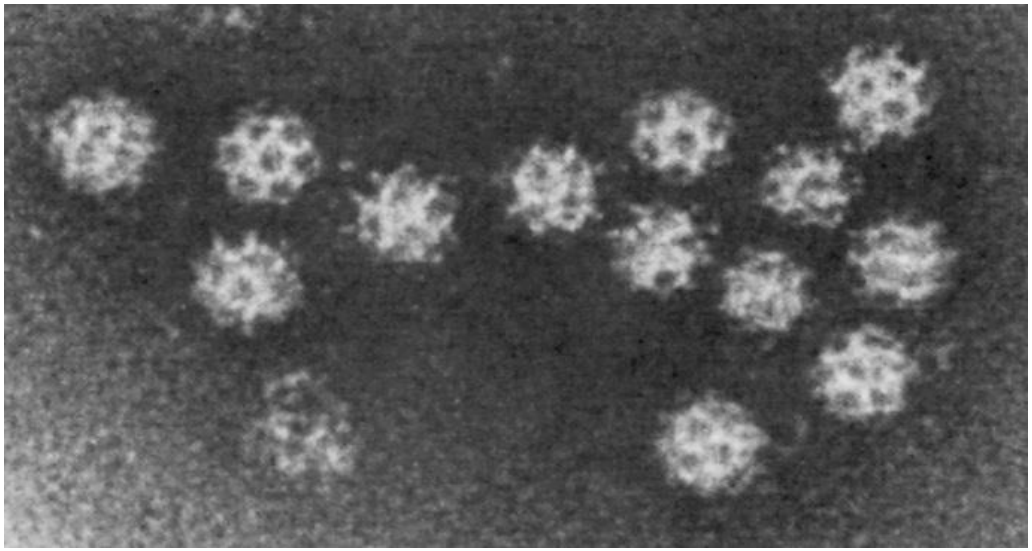
Important properties

-- There are three families, **togaviruses**, **flaviviruses**, and **bunyaviruses**.

-- **Togaviruses** have an **icosahedral nucleocapsid** surrounded by **an envelope** and have **single-stranded, positive polarity RNA genome.**

-- They are **70 nm** in diameter.

-- **Flaviviruses** are **similar** to **togavirus** but size is only **40-50 nm.**



Transmission

-- The life cycle is based on the ability of these viruses to **multiply in *both* the vertebrate host and the bloodsucking vector.**

-- For **effective transmission**, virus should be present in **sufficiently high numbers** to be **infective in small volume of blood** sucked by insect.

-- After ingestion, virus **replicates in gut of insect** and **then move to other organs** including **salivary glands**.

-- **Only female insect is relevant** because only she **needs proteins in blood for producing progenies**.

-- **Extrinsic incubation period** is the **time between sucking of virus by insect and its presence in sufficient numbers in saliva.**

-- In most cases, it is **7-14 days**.

-- Some viruses are transmitted **vertically from mother tick**.

-- It is called **“transovarian”** passage.

-- It has **important survival value** for the virus if a vertebrate host is unavailable.

-- Usually **humans are dead end hosts** because concentration of virus in blood is **too low** and period of **viremia** is **too small** for the next bite to transmit the virus.

-- However in diseases such **as yellow fever** and **dengue**, there is **high level viremia** and **humans can act as a reservoir.**

-- Usually **arbovirus** infections are **asymptomatic in insect and animal host**.

Yellow fever

-- **Yellow fever virus** is a **flavivirus**.

-- Disease is characterized by **jaundice** and **fever**.

-- It is a **severe, life-threatening disease** that begins with the **sudden onset of fever**. **Liver, kidneys** and **heart** become involved **at a later stage**.

-- Diagnosis depends on **virus isolation** or **detection of antibody**.

-- **No antiviral therapy** is available and **mortality rate is high**.

-- There is **no chronic stage** and immunity is **life long**.

-- **Yellow fever** occurs primarily in the **tropical areas of Africa** and **South America**.

There are **two distinct cycles** in nature:

-- **Jungle yellow fever** is a disease of **monkeys** transmitted primarily by treetop mosquitoes of ***Haemagogus*** species.

Humans such as **tree cutters** are accidental hosts.

-- **Urban yellow fever** is a disease of humans transmitted by ***Aedes aegypti***, which breeds in stagnant water.

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-- Prevention involves **mosquito control** and **immunization with vaccine** containing live, attenuated yellow fever virus.

Dengue virus

-- **Dengue virus** is also a **flavivirus**.

-- It is estimated that about **20 million** people are infected with dengue virus **each year worldwide**.

-- Dengue is **the most common insect-borne viral disease** in the world.

-- **Classic dengue (break bone fever)** begins **suddenly** with **an influenza like syndrome** consisting of **fever, malaise, cough** and **headache**.

-- **Severe pain** in **muscles** and **joints** occur.

-- **Enlarged lymph nodes**, a **maculopapular rash**, and **leucopenia** are common.

-- **After a week** or so the **symptoms regress** but weakness may persist. This typical form is **rarely fatal** and has **few sequelae**.

-- In contrast, **dengue hemorrhagic fever** is much more **severe disease** with nearly **10% fatality rate**.

-- **Initial picture** is **similar to classic dengue** but then **shock** and **hemorrhage** esp. into the **GIT** and **skin** develop.

-- It occurs particularly in **Southern Asia** whereas the **classic form** is found in **tropical areas worldwide**.

-- **Hemorrhagic shock syndrome** is due to the **production of large amounts of cross-reacting antibody** at the time of **second dengue infection by a different serotype**.

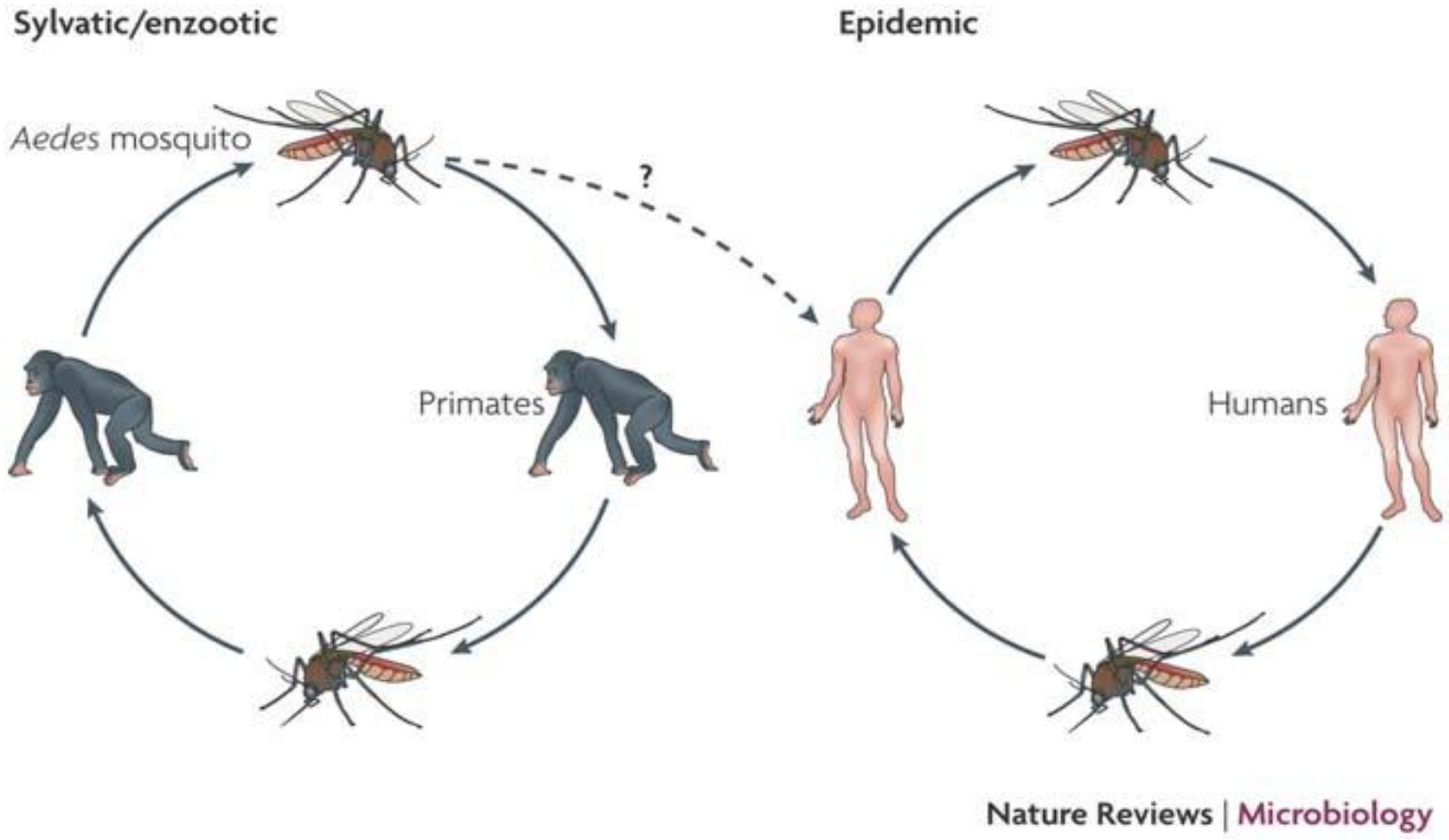
-- An **anamestic, heterotypic response** occurs and large amount of **cross reacting antibody** to **first serotype** is produced.

-- The **subsequent events** may be due to **immune complexes composed of virus and antibody** which **activate complement** causing **increased vascular permeability** and **thrombocytopenia**.

-- It is also possible that **antibodies increase the entry of virus into monocytes and macrophages** with consequent **liberation of a large amount of cytokines**.

Dengue virus is transmitted by ***A. aegypti*** **or** ***A. albopictus***.

Humans are reservoirs but a **jungle cycle involving monkeys** as reservoir and other ***Aedes*** species as vectors is suspected.



-- The **diagnosis** can be made by **virus isolation** or **serology** that demonstrate the **presence of IgM antibody** or a **four-fold or greater rise in antibody titer** in acute and convalescent sera.

-- **PCR** can be useful.

-- **No antiviral therapy or vaccine** is available.

-- Outbreaks are controlled by using **insecticides, draining stagnant water** and **wearing clothes that cover entire body.**

These eight billionaires own the same wealth as the 3.6bn people who form the poorest half of the world's population

$75bn
Bill Gates

$67bn
Amancio Ortega

$61bn
Warren Buffett

$50bn
Carlos Slim

$45bn
Jeff Bezos

$45bn
Mark Zuckerberg

$44bn
Larry Ellison

$40bn
Michael Bloomberg

Source: Forbes/Oxfam

BBC

Chapter 45

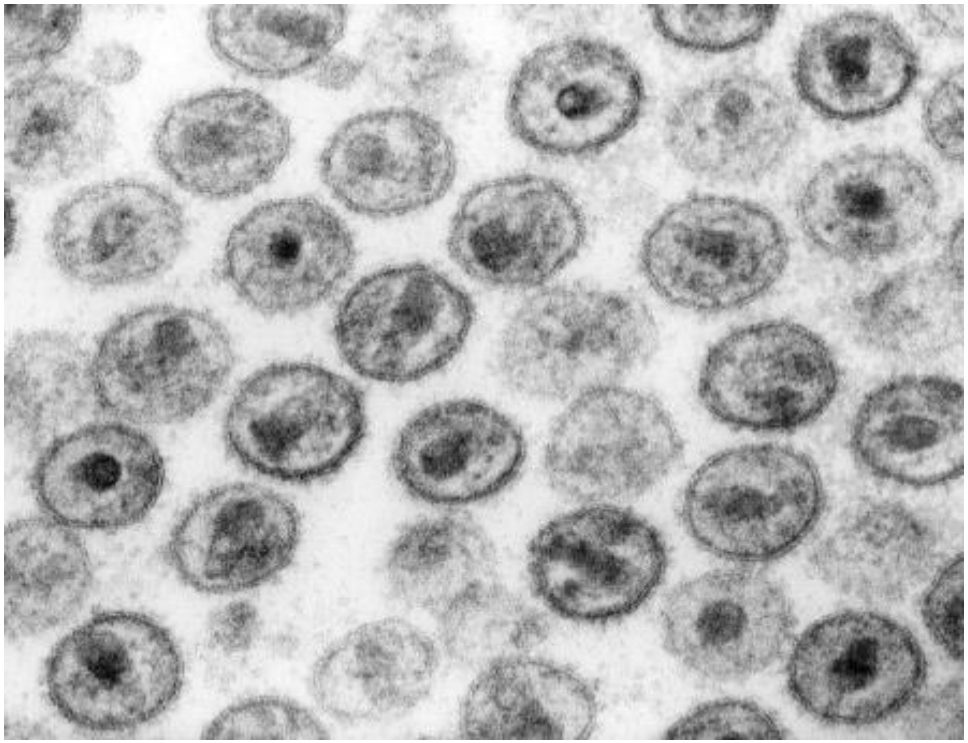
Human Immunodeficiency virus (HIV)

HIV is the cause of **acquired immunodeficiency syndrome (AIDS)**.

Both **HIV-1** and **HIV-2** cause **AIDS.**

HIV-2 is found primarily in **West Africa**.

Generally **HIV** is reference to **HIV-1**.



Important Properties

-- **HIV** is one of two important human **T-cell lymphotropic retroviruses** (other is human T-cell leukemia virus).

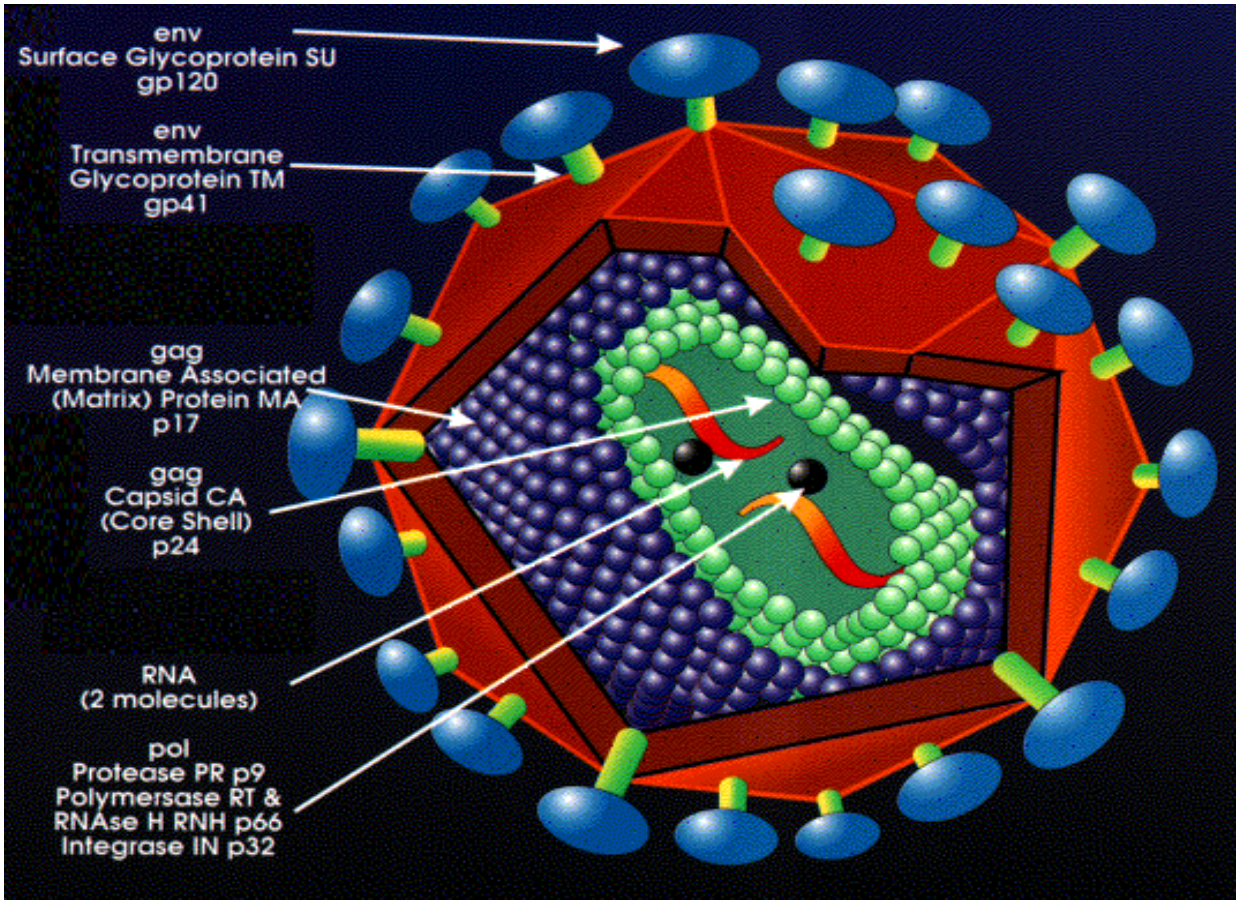
-- **HIV** preferentially **infects and kills helper (CD4) T lymphocytes** resulting in **loss of cell-mediated immunity** and a **high probability** that host will **develop opportunistic infections**.

-- Other cells, e.g., **macrophages** and **monocytes**, that have **CD4 proteins on their surfaces** can also be infected.

-- **HIV** is an **enveloped retrovirus**.

HIV has a **bar-shaped (type D)** core surrounded by an **envelope** containing virus **specific glycoproteins gp120 and gp41.**

Genome consists of **two identical molecules** of **single-stranded, positive polarity RNA** and is said to be **diploid**.



There are several important antigens of **HIV**:

gp120 and gp41

-- **gp120** and **gp41** are **type specific envelope glycoproteins**.

-- The **gp120** protrudes from the surface and **interacts with CD4 receptor** on the cell surface.

-- The **gp41** is embedded in the envelope and **mediates the fusion of the viral envelope with cell membrane** at the time of infection.

-- **Gene** coding for **gp120** mutates rapidly, resulting in **many antigenic variants**.

P24

-- The **group specific antigen p24** is **located in the core** and is **not known to vary**.

-- Antibodies against it are **not neutralizing** but serve as important **serological markers** of infection.

-- Natural host range is **limited to humans** although some primates can be infected in laboratory.

-- It is generally thought that **chimpanzees** are source of infection of **HIV1** for **humans**.

-- **HIV2** proteins are **40%** identical to original **HIV** isolates.

-- It remains localized primarily in **West Africa** and is **much less transmissible** than **HIV-1**.

Transmission and Epidemiology

-- Transmission **is primarily by sexual contact** and by **transfer of infected blood**.

-- **Perinatal transfer also occurs** either across the placenta, at birth, or via breast milk.

-- More than half infections are at the time of delivery.

-- There is **no air, water or insect borne transmission**.

-- Infections occur by **the transfer of either HIV infected cells** or **free HIV**.

-- In general **transmission pattern is similar to HBV except** that **much higher** viral dose is needed.

-- People with **venereal** diseases are at **much greater risk**.

-- **Uncircumcised** males are at higher risk.

-- **Worldwide**, it is estimated that **app. 33 million people** are infected, two third in sub-Saharan Africa.

-- AIDS is the **4th leading cause of death globally** after ischemic heart disease, cerebrovascular diseases and acute lower respiratory disease.

-- Initially the disease was confined to **homosexuals**, **iv drug users** and **hemophiliacs** but now **heterosexual transmission** is also on rise esp. in African countries.

-- Due to high infective dose, infection of health care workers is rare.

Pathogenesis and Immunity

-- **HIV** infects helper T cells (**CD4 +ve cells**) and **kills them to suppress CMI**.

-- It makes the host **susceptible to various opportunistic infections** and **certain cancers** such as Kaposi's sarcoma and lymphoma.

-- **Initial infection** in genital tract is in **mucosal dendritic cells** followed by infection of **helper T cells**.

-- **HIV** appears in blood **4-11 days** after infection.

-- A **subset** of CD4 +ve cells, **Th17 cells**, related to mucosal immunity in GI, is **most vulnerable**.

-- Their death means that **IL 17** is **not produced** and **neutrophils are not attracted** to the site of infection, exposing the person to **colon bacterial infections**.

-- **HIV** also infects **brain monocytes** and **macrophages** producing **syncytia** by action of **gp41**, and significant **CNS symptoms**.

-- The cells **ultimately die** as they are also **attacked by cytotoxic CD8 +ve cells**.

-- But effectiveness of **cytotoxic CD8 +ve cells** is reduced to **disruption in synthesis of MHC 1 molecules** by viral **Tat** and **Nef** proteins.

-- **HIV infection is for life** due to **integration of viral DNA in cellular DNA**.

-- **Less than 1%** of those infected have **no detectable HIV in blood**.

-- They are called **elite controllers**. Their **CD4 counts are normal**.

-- Gender or race is **not important**.

-- The reason for **considerable gap** between **HIV infection and AIDS** is cytotoxic **CD8 T cells** which remain step in step by making changes against viral mutations.

-- But when **helper cells** which produce **IL-2** necessary for **CD8** function are **largely eliminated**, they lose the battle and clinical symptoms appear.

-- **Antibodies** against viral proteins are produced but they **act poorly *in vivo*** and have little effect on course of disease.

Clinical findings

Clinical picture of **HIV** can be divided into four stages.

Stage 1: Primary HIV Infection

-- This stage of infection **lasts for a few weeks** and is often accompanied by a **short flu-like illness**.

-- During this stage there is a **large amount of HIV in the peripheral blood** and the immune system begins to respond to the virus by producing **HIV antibodies and cytotoxic lymphocytes**.

Stage 2: Clinically Asymptomatic Stage

-- This stage lasts for an average of **ten years** and, as its name suggests, is **free from major symptoms**, although there may be swollen glands.

-- The level of **HIV** in **the peripheral blood drops to very low levels** but **antibody tests will show a positive result**.

-- Research has shown that **HIV** **is not dormant during this stage**, but is **very active in the lymph nodes**.

Stage 3: Symptomatic HIV Infection

Over time the **immune system becomes severely damaged by HIV**.

This is thought to happen for **three** main reasons:

- The **lymph nodes** and **tissues** become **damaged or "burnt out"** because of the years of activity.
- **HIV mutates and becomes more pathogenic**, in other words stronger and more varied, leading to **more T helper cell destruction**.
- **The body fails to keep up with replacing the T helper cells that are lost**.

As the **immune system fails, symptoms develop**.

-- **Symptomatic HIV infection** is mainly caused by the emergence of **opportunistic infections** and **cancers** the immune system **would normally prevent.**

-- These can occur in **almost all the body systems**.

-- **Symptomatic HIV infection** is often characterized by **multi-system disease**.

-- Treatment for the specific infection or cancer is often carried out, but the **underlying cause is the action of HIV** as it erodes the immune system.

-- Unless **HIV** itself can be slowed down the symptoms of immune suppression will continue to worsen.

Stage 4: Progression from HIV to AIDS

As the immune system becomes more and more damaged the illnesses that occur become **more and more severe** leading eventually to an **AIDS diagnosis**.

Laboratory Diagnosis

-- The **presumptive diagnosis of HIV infection** is made by the **detection of antibodies in the patient's serum** to the **p24 protein** of **HIV** using **ELISA**.

-- **ELISA** may give **false positive** results.

-- **Definitive diagnosis** is made by **Western Blot (Immunoblot)** analysis in which viral proteins are separated by gel electrophoresis, transferred to nitrocellulose paper and reacted with patient's serum.

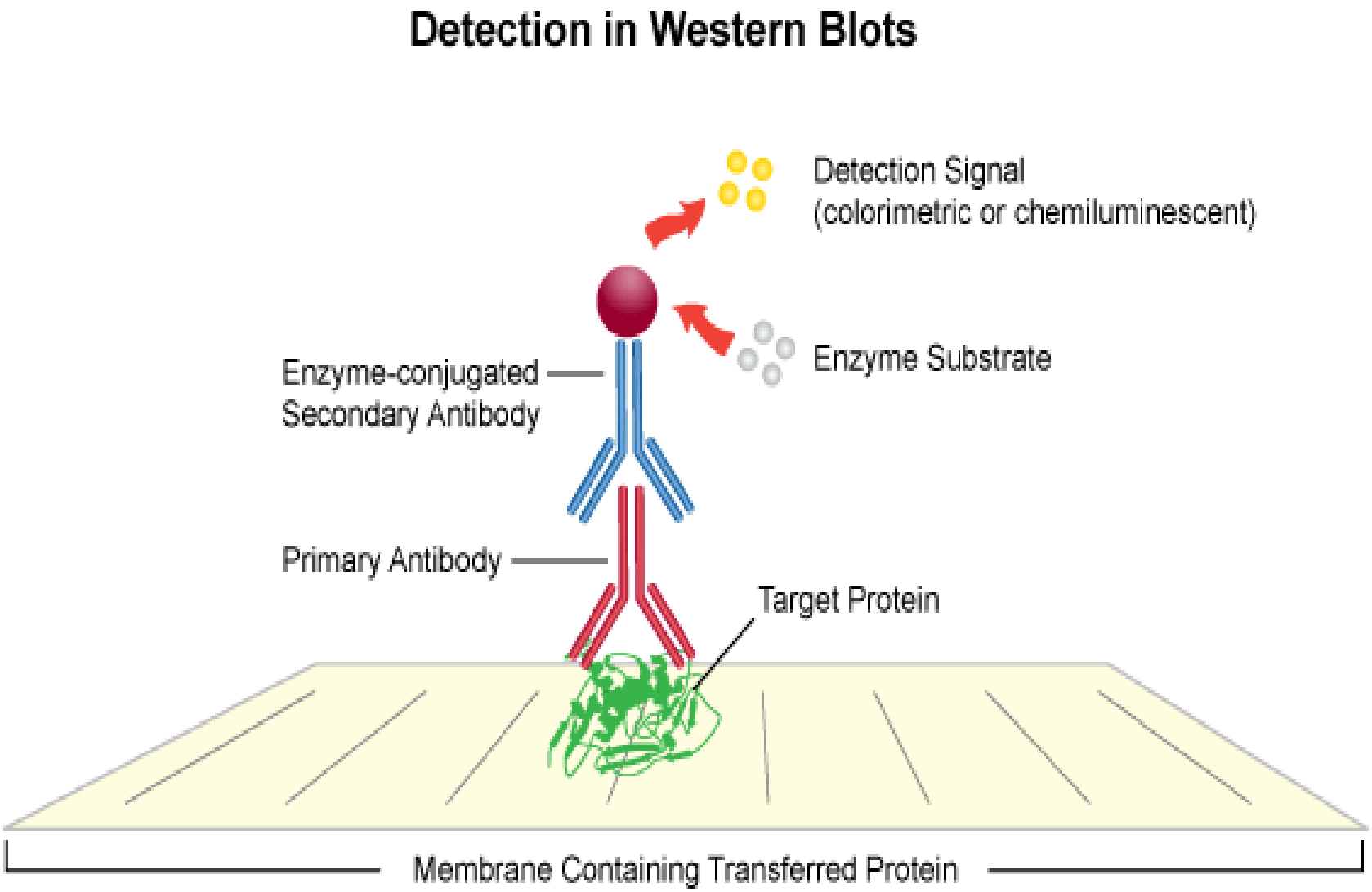


Diagram 2: *Illustration of detection in Western Blots.*

-- **HIV** can be cultured but **not commonly done**.

-- **PCR is very sensitive** and is widely used.

-- The **viral load** can be measured by **real time PCR**.

-- During **first month**, antibody tests may be negative due to **insufficient amount** of antibody.

-- Average time for **seroconversion is 10-14 days** and most patients become positive in 4 weeks.

-- So in early stage **HIV RNA** detection by **PCR is the best option**.

-- The **p24** antigen test or viral culture can also be used.

Treatment

-- At this time, there is **no cure for AIDS**, but medications are **effective** in fighting **HIV** and its complications.

-- Most medications have **side effects**.

-- Individuals **respond differently** to medications and side effects may vary.

-- Drug treatments help **reduce the HIV virus** in the body, **keep immune system as healthy as possible** and **decrease the complications** that may develop.

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

-- These drugs **interrupt the virus from duplicating**, which may slow the spread of **HIV** in the body.

-- They include **Abacavir**, and **Didanosine.**

-- Common side effects include **fever, rash, fatigue, vomiting, diarrhea, abdominal pain, malaise** or **fatigue**, **loss of appetite** and **respiratory symptoms.**

Protease Inhibitors (PI)

-- These drugs **interrupt virus replication at a later step** in the virus life cycle.

-- Protease inhibitors include **Amprenavir** and **Atazanavir.**

-- Side effects from protease inhibitors vary, depending on the individual.

-- These include nausea, diarrhea, vomiting, rash, numbness around the mouth and abdominal pain.

-- About 1 % of people have **serious skin reactions**, including **Stevens-Johnson syndrome.**

Fusion Inhibitors

-- Fusion inhibitors are a new class of drugs that act against **HIV** by **preventing the virus from fusing** with the inside of a cell, preventing it from replicating.

-- The group of drugs includes **Enfuvirtide.**

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

-- Non-nucleoside reverse transcriptase inhibitors (**NNRTIs**) **block the infection of new cells** by **HIV**.

-- These drugs may be prescribed in combination with other anti-retroviral drugs.

-- NNRTs include **Delvaridine** and **Efravirenz.**

Highly Active Antiretroviral Therapy (HAART)

-- In 1996, highly active antiretroviral therapy (**HAART**) was introduced for people with **HIV** infection and **AIDS**.

-- **HAART** — often referred to as the **anti-HIV "cocktail"** — is a combination of three or more drugs, such as protease inhibitors and other anti-retroviral medications.

-- The treatment is **highly effective in slowing the rate at which the HIV virus replicates itself**, which may slow the spread of **HIV** in the body.

-- The goal of HAART is to **reduce the amount of virus** in the body, or the viral load, to a level that can no longer be detected with blood tests.


Thank You!