AIDS

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Introduction

- AIDS- Acquired Immunodeficiency Disease.
- It is a disease caused by the retrovirus human immunodeficiency virus (HIV) and characterized by profound immunosuppression that leads to opportunistic infections, secondary neoplasms and neurological manifestations.
- The acquired immune deficiency syndrome AIDS was first recognized in 1981 in US.
- Centers for Disease Control and Prevention reported the unexplained occurrence of *Pneumocystis jiroveci* pneumonia in five previously healthy homosexual men in Los Angeles and of Kaposi's sarcoma with or

without *P. jiroveci* pneumonia in 26 previously healthy homosexual men in New York and Los Angeles.

ETIOLOGY

- AIDS is caused by HIV, a human retrovirus.
- Two types- HIV I and HIV II which are genetically different but has related forms.
- HIV I is most common type associated with AIDS in US, Europe and Central Africa.
- HIV II causes similar disease in West Africa and India.
- HIV-II is transmitted less efficiently than HIV-I.

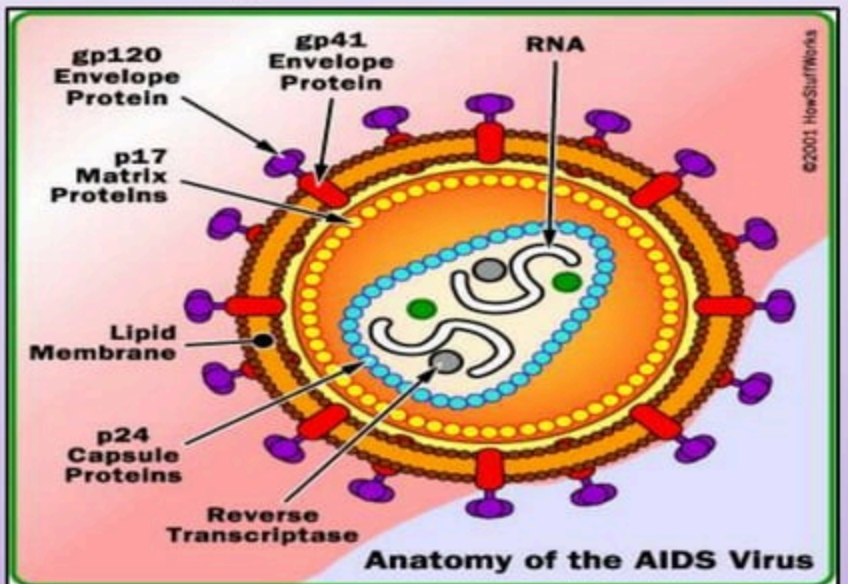
STRUCTURE

- HIV is a typical retrovirus with a small RNA genome of 9300 base pairs.
- Is a spherical and contains nucleocapsid core surrounded by a lipid bilayer or envelop derived from host cell membrane.
- The viral genome encodes 3 major open reading frames-

1. *gag* encodes a polyprotein that is processed to release major structural proteins of virus.
2. *pol* encodes 3 important enzymes are RNA dependent DNA polymerase or reverse transcriptase with RNAse H, Protease and integrase.

3. *env* encodes for large transmembrane envelop proteins responsible for cell binding and entry.

- Several small genes encodes regulatory proteins that enhances virion production or combat host defence.



PATHOGENESIS

- HIV can infect many tissues, there are 2 major targets

  -Immune system

  -Central nervous system.
- Primarily affect cell mediated immunity.
- Results in severe loss of CD4+ T cells and impairment in the function of helper T cells.
- Macrophages and dendritic cells also infected.

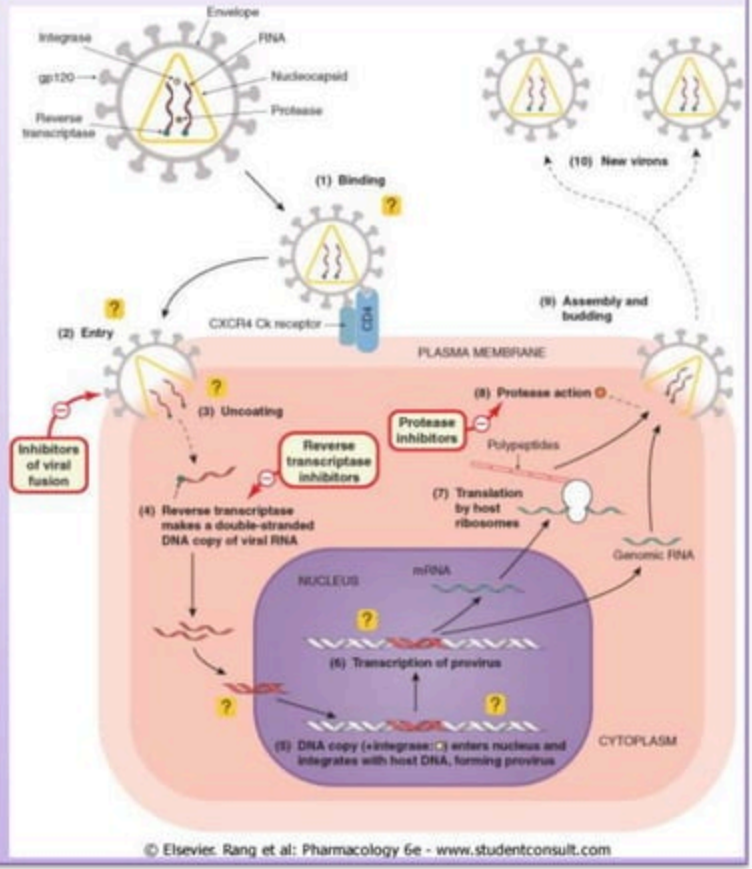
LIFE CYCLE OF HIV

- STEP'S INVOLED

1.INVASION
 a) Attachment
 b) Fusion

2.MATURATION
 a) Reverse transcriptase
 b) Integration

3.RELEASE
 a) Budding
 b) Exit from cell



ROLE OF ENZYMES

1. REVERSE TRASCRIPTASE (RT)

- Multifunctional enzymes having RNA dependent DNA polymerase activity
- Also having RNase H (helicase) activity
- Catalyses formation of double stranded proviral DNA from singal stranded RNA genome
- Due to its central role in the viral replication RT is prime target for anti aids therapy

- Inhibitors of RT can be classified as
  1.nucleoside RT inhibitor(NRTI)
  2.non nucleoside RT inhibitor(NNRTI)
- NRTI are competative in nature while NNRTI are non competative

2. PORTEASE

- Protease essential for production of mature, infectious virions
- HIV protease is responsible for posttranslatio-nal processing of poly proteins & protolytic activity

- Inhibition of these protease enzyme is also attractive target for anti aids therapy

3. Intigrase

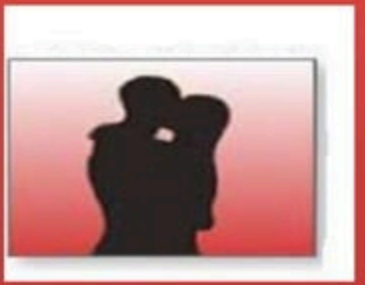
- Catalyses the integration of double stranded DNA copy of their RNA genome into chromosome of a host cell
- Inhibition of integrase enzyme is prime target for anti aids therapy

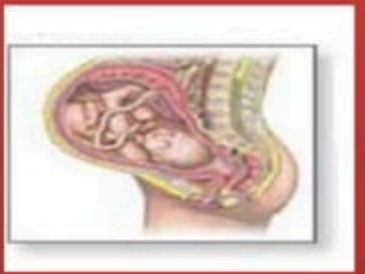
COMMAN SIGN & SYMPTOMS

- Severe impairment or suppression of immune system.
- Pneumocystis carinii pneumonia (pcp) is mostly seen.
- Opportunistic infection
- CD4+T- cells count falls below 200 cells/mm3 of blood.
- In healthy adult it's value is 600-1500 cells/mm3 of blood.

- Weight loss
- Pharyngitis
- Neurological symptoms.
- Rash
- Headache
- Fever
- Lymphadenopathy

MODES OF HIV/AIDS TRANSMISSION





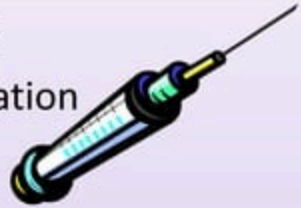
Through Bodily Fluids

- Semen
- Vaginal fluids
- Breast Milk

HIV enters the bloodstream through

- Open Cuts
- Breaks in the skin
- Mucous membranes
- Direct injection

- Sharing Needles
  - Without sterilization



Through Sex

- Intercourse
- Oral
- Anal

Mother-to-Baby

- During pregnancy transplacently transmitted.
- During post-partum period through contamination with maternal blood, infected amniotic fluid or breast milk

DIAGNOSIS

BLOOD DETECTION TEST

- Enzyme-Linked Immunosorbent Assay/Enzyme Immunoassay (ELISA/EIA)
- Radio Immunoprecipitation Assay/Indirect Fluorescent Antibody Assay (RIP/IFA)
- Polymerase Chain Reaction (PCR)
- Western Blot Confirmatory test

URINE TEST

- Urine Western Blot
- As sensitive as testing blood
- Safe way to screen for HIV
- Can cause false positives in certain people at high risk for HIV

Orasure

- The only FDA approved HIV antibody.
- As accurate as blood testing
- Involves collecting secretions between the cheek and gum and evaluating them for HIV antibodies.

ANTIRETROVIRAL AGENTS

1. Nucleoside/Nucleotide Analogues

- Abacavir Didanosine Emtricitabine Lamivudine Stavudine Tenofovir Zalcitabine

2. Non nucleoside Reverse Transcriptase Inhibitors

- Delavirdine, Efavirenz ,Etravirine ,Nevirapine

3. Protease Inhibitors

- Amprenavir,Atazanavir ,Darunavir Fosamprenavir, Indinavir, Lopinavir/Ritonavir Nelfinavir ,Ritonavir, quinavir

4. Fusion Inhibitors

- Enfuvirtide

5. Chemokine Coreceptor Antagonists

- Maraviroc

6. Integrase Inhibitors

- Raltegravir

NUCLEOSIDE/NUCLEOTIDE ANALOGUES

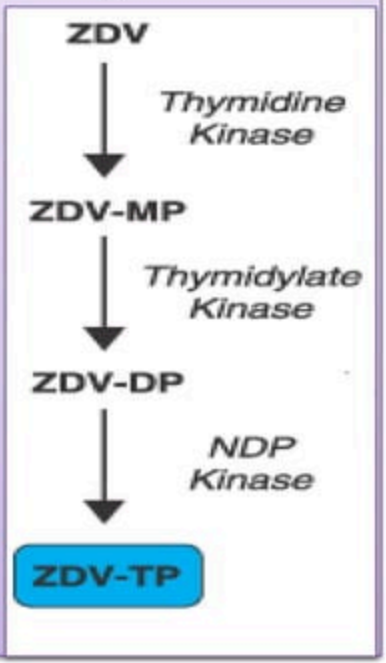
- Nucleoside and nucleotide reverse transcriptase inhibitors prevent infection of susceptible cells but have no impact on cells that already harbor HIV.
- Nucleosides that must be triphosphorylated at the 5'-hydroxyl to exert activity.
- *tenofovir,* is a nucleotide monophosphate analog that requires two additional phosphates to acquire full activity.

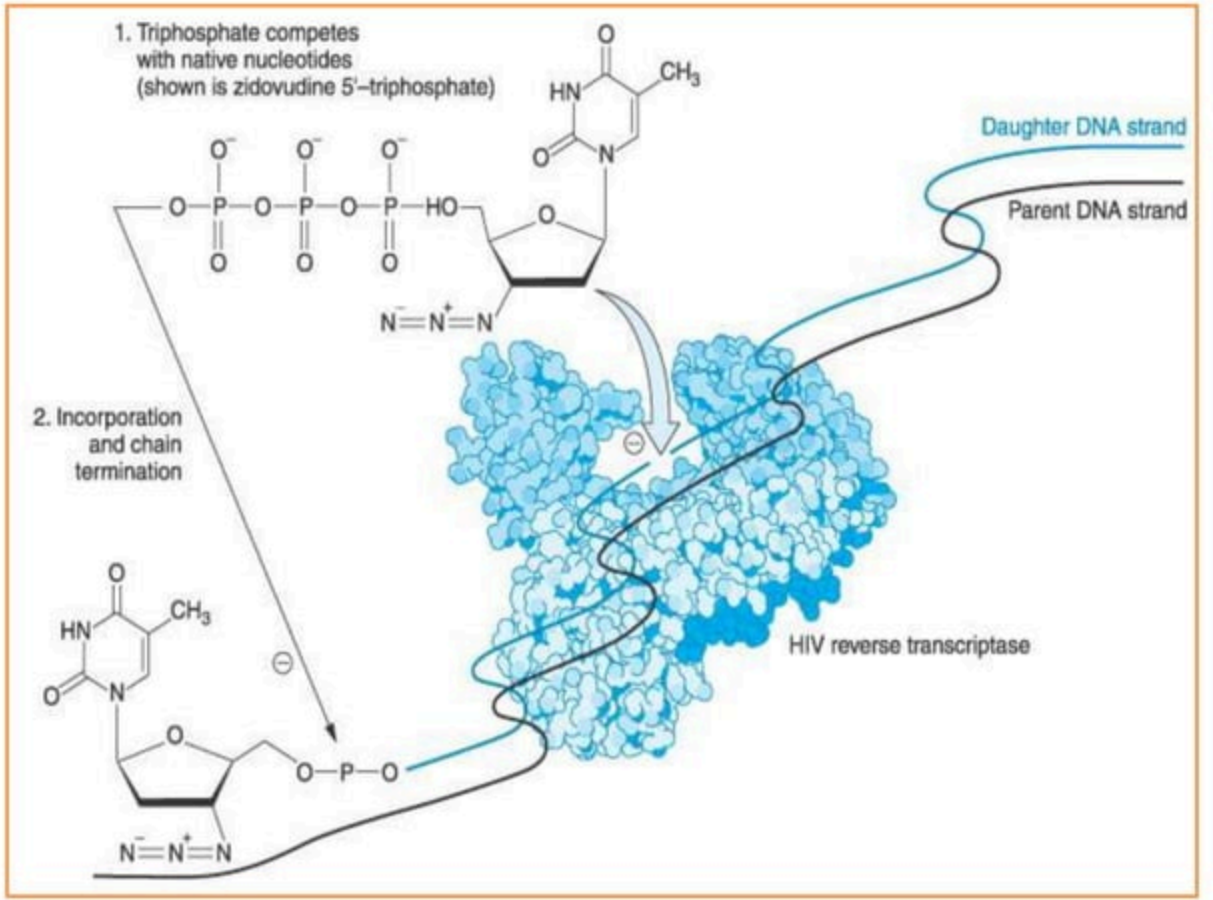
ZIDOVUDINE:

- 3’ azido- 3’ deoxythymidine.
- Synthetic thymidine analogue with potent broad spectrum activity.

Mechanism of Action:

- due to similar structure it incorporate in to growing DNA strand and terminate synthesis due to lack of OH group.




1. Triphosphate competes with native nucleotides (shown is zidovudine 5'–triphosphate)
Daughter DNA strand
Parent DNA strand
2. Incorporation and chain termination
HIV reverse transcriptase

Untoward Effects

- They mainly due to partial inhibiton of cellular DNA polymarase.
- Fatigue, malaise, myalgia, nausea, anorexia, headache, and insomnia.
- Bone marrow suppression, mainly anemia and granulocytopenia.
- Gastrointestinal disturbances
- Abnormal liver functions
- hyperlipidemia

Therapeutic Uses.

- Zidovudine is FDA approved for the treatment of adults and children with HIV infection and for preventing mother-to-child transmission of HIV infection.
- It is also recommended for postexposure prophylaxis in HIV-exposed healthcare workers, also in combination with other antiretroviral agents.

NONNUCLEOSIDE REVERS TRANSCRIPTASE INHIBITORS

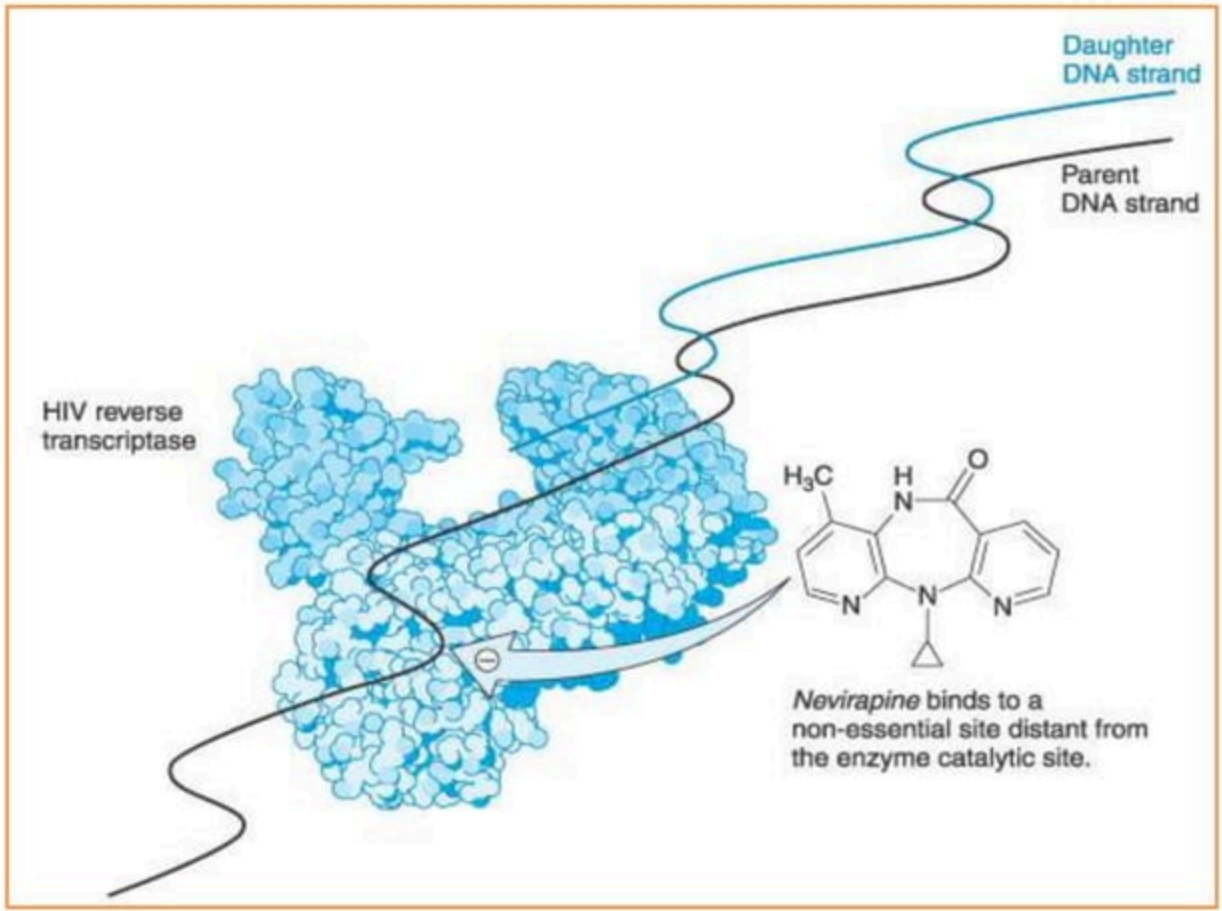
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs) include a variety of chemical substrates that bind to the HIV-1 reverse transcriptase.
- These compounds induce a conformational change in the three-dimensional structure of the enzyme that greatly reduces its activity, and thus they act as noncompetitive inhibitors

NEVIRAPINE:

- Is a dipyridodiazepinone NNRTI with potent activity against HIV-1.
- nevirapine does not have significant activity against HIV-2 or other retroviruses.

Mechanism of Action:

- Nevirapine is a noncompetitive inhibitor that binds to a site on the HIV-1 reverse transcriptase that is distant from the active site, inducing a conformational change that disrupts catalytic activity.


Daughter
DNA strand
Parent
DNA strand
HIV reverse
transcriptase
H3C
H
N
O
N
N
N
Nevirapine binds to a
non-essential site distant from
the enzyme catalytic site.

Untoward Effects:

- Hepatotoxicity
- Stevens-Johnson syndrome
- Rash
- Pruritus
- Fever, fatigue, headache, somnolence, and nausea.

Uses

- Pregnant women
- Used to prevent mother to infant HIV infection
- HIV-1 infection in adults and children in combination with other antiretroviral agents.

PROTEASE INHIBITORS

- HIV protease inhibitors are peptidelike chemicals that competitively inhibit the action of the virus aspartyl protease.
- This protease is a homodimer consisting of two 99-amino-acid monomers; each monomer contributes an aspartic acid residue that is essential for catalysis.

SAQUINAVIR:

- A peptidomimetic hydroxyethylamine HIV protease inhibitor.
- Inhibits both HIV-1 and HIV-2 replication.

Mechanisms of Action

- Reversibly binds to the active site of HIV protease, preventing polypeptide processing and subsequent virus maturation.
- Potently inhibiting the HIV-encoded protease but not host-encoded aspartyl proteases.

Untoward Effects

- Nausea, vomiting, diarrhea, and abdominal discomfort.
- Lipodystrophy.

Therapeutic Use

- Reduction of viral load with other nucletide analogues.

FUSION INHIBITORS

- *Enfuvirtide* is the only available HIV entry inhibitor.
- Enfuvirtide is a 36-amino-acid synthetic peptide whose sequence is derived from a part of the transmembrane gp41 region of HIV-1.
- Not active against HIV-2.
- The peptide blocks the interaction between the N36 and C34 sequences of the gp41 glycoprotein by binding to a hydrophobic groove in the N36 coil

- This prevents formation of a six-helix bundle critical for membrane fusion and viral entry into the host cell.
- Treatment-experienced adults who have evidence of HIV replication despite ongoing antiretroviral therapy.

CCR5 antagonists

- In order to enter a human cell, HIV must first attach itself to proteins on the cell's surface.
- The next stage involves proteins called co-receptors, two main types: CCR5 and CXCR4. Some strains of HIV use CCR5, others use CXCR4,.
- CCR5 antagonists are drugs that bind to the CCR5 co-receptor so that HIV cannot exploit it to gain entry to a cell.
- The main drawback of these drugs is that they don't work against all strains of HIV.
- Maraviroc is a example for this class.

Raltegravir: first in class HIV integrase inhibitor

- The integration of HIV-1 proviral DNA into the host cell genome
- Integrase mainly involved in integration of viral DNA in to host DNA.
- Inhibition of this enzyme prevents integration.
- Impressive antiviral potency in heavily treatment-experienced patients.

RECENT THERAPY FOR AIDS

Drug class	Recently approved	Phase III	Phase II
Entry inhibitor (CCR5)	Maraviroc (Aug. 2007)	Vicriviroc	PRO 140
Entry inhibitor (CD4)			TNX-355
Integrase inhibitor	Raltegravir (Oct. 2007)	Elvitegravir	
Maturation inhibitor			Bevirimat
NNRTI	Etravirine (Jan. 2008)	Rilpivirine	
NRTI		Apricitabine	KP-1461 Racivir Elvucitabine

GENE THERAPY

- RNA-interference is damage to a certain RNA sequence with participation of a different, "defending" RNA molecule.
- This system prevents viral infection, unless viruses had learned to cut it off in the course of evolution.
- Researchers from countries including Russia are developing the artificial RNA-interference system.
- It is non-injurious to the patient and, due to high specificity of action, does not damage its own RNA in cells infected by the virus.

- To fight HIV, Russian biologists have created three genetic structures.
- These structures contain short nucleotide against sequences that find the most conservative molecules among all RNA molecules, that is, sequences that do not change quickly and are important to the virus.
- These sequences are then "damaged".
- Genetic structures significantly suppress viral reproduction.

VACCINE

Difficulties in developing an HIV vaccine

- Classic vaccines mimic natural immunity against reinfection generally seen in individuals recovered from infection; there are almost no recovered AIDS patients.
- Most vaccines protect against disease, not against infection; HIV infection may remain latent for long periods before causing AIDS.
- Most effective vaccines are whole-killed or live-attenuated organisms; killed HIV-1 does not retain antigenicity and the use of a live retrovirus vaccine raises safety issues.

- Most vaccines protect against infections through mucosal surfaces of the respiratory or gastrointestinal tract; the great majority of HIV infection is through the genital tract.

Phase I

- Most initial approaches have focused on the HIV envelope protein.
- Thirteen different gp120 and gp160 envelope candidates have been evaluated.
- Most research focused on gp120 rather than gp41/gp160.

Phase III

- AIDSVAX vaccine.
- This is the first successful HIV vaccine trial in history.
- The percentage rate reduced to 26% compared with those who had been given a placebo.

Planned clinical trials

- Novel approaches, including modified vaccinia Ankara (MVA), adeno-associated virus, Venezuelan equine encephalitis (VEE).

MONOCLONAL ANTIBODIES

- monoclonal antibodies, produced after immunizing mice, have binding characteristics that look similar to two well-known broadly neutralizing human monoclonal antibodies, known as **2F5** and **4E10**, which also bind to HIV-1 protein and lipid.
- That might be useful in an effective HIV-1 vaccine.

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