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Safe Use of Antiretroviral Agents in HIV

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Abstract: ***HIV (Humanimmuno deficiency Virus) is retro viruses that gradually attack the immune system, which protects human body against illness. HIV infected person becomes an easy target for opportunistic infection and disease. This virus multiplies in T-helper cell (CD4) and gradually platelets them he two main types areHIV-1and HIV-2 is the most common type found wild life, however HIV-2 is found mainly in western Africa, with some case In India and Europe. Currently around 15 molecules are being use in different treatment regimen store at HIV infection however, issue like treatment failure due to drug resistance and toxicity remains crucial issue.***

1. Introduction

A) Descriptions

HIV (Human immunodeficiency Virus) is retroviruses that gradually attack the immune system, which protects human body against illness. HIV infected person becomes an easy target for opportunistic infection and disease. This virus multiplies in T- helper cell (CD4) and gradually platelets them.

The two main types are HIV-1 and HIV-2 is the most common type found wildlife, however HIV-2 is found mainly in western Africa, with some case In India and Europe. Currently around 15 molecules are being use in different treatment regimens to treat HIV infection however, issue like treatment failure due to drug resistance and toxicity remains crucial issue. The purpose of this review is to brief about newer antiretroviral drugs (pharmacokinetics and pharmacodynamics) for HIV, which are recently approved and newer promising drugs in pipeline i.e. phase-2 and Phase-3 trials.

By the end of 2017, unite state food and administration (USFDA) had approved 43 antiretroviral drugs for clinical use include 29 single tablet and 14 fixed dose combination. The identity of the search for novel antiretroviral compound has slowed over the last 10 years and several traditional agents are still in and several traditional agents are still in phase-3 clinical trials in the next decade to improve drug safety, adherence and efficacy. The development of new anti HIV-1 drug will focus on long acting formulations oral attachment inhibitor, maturation and new initiatives to cure the disease.

The first decade of antiretroviral drug therapy, these agents did not fundamentally change the density of these with HIV infection althoughthey could decrease viral load, increase CD4 cell number and prolong survival over the short term. The major shortcoming was drug toxicity, drug resistance and high drug cost.

B) Types of Virus

1) Human Endogenous and Exogenous Retroviruses

Similar to other vertebrate animals, humans possess retroviruses that exist in two forms: as normal genetic elements in their chromosomal DNA (endogenous retroviruses) and as horizontally-transmitted infectious RNA-containing viruses which are transmitted from human-to-human (exogenous retroviruses, e.g. HIV and human T cell leukemia virus, HTLV).

- HIV virus
- Human T- cell Leukemia virus
- DNA virus
- RNA virus

a) HIV Virus

- The human immunodeficiency virus is acquired immunodeficiency syndrome (AIDS), a condition in human in which progressive failure of the immune system allows opportunistic infection and cancers to prosper.
- Unlike some other viruses, the human body cannot get rid of HIV. That means that one you have HIV, you have it for life.
- Asymptomatic infection.
- Acute infection with symptoms that may include fever, sweats, myalgia, throat, lymphadenopathy, nausea, vomiting, diarrhea, headaches, and rash.
- Acquired immune deficiency syndrome (AIDS), characterized by progressive immune deficiency accompanied by a wide range of opportunistic infections, neoplasms, and neurologic abnormalities, including progressive dementia and peripheral neuropathy.

b) Diagram of HIV virus

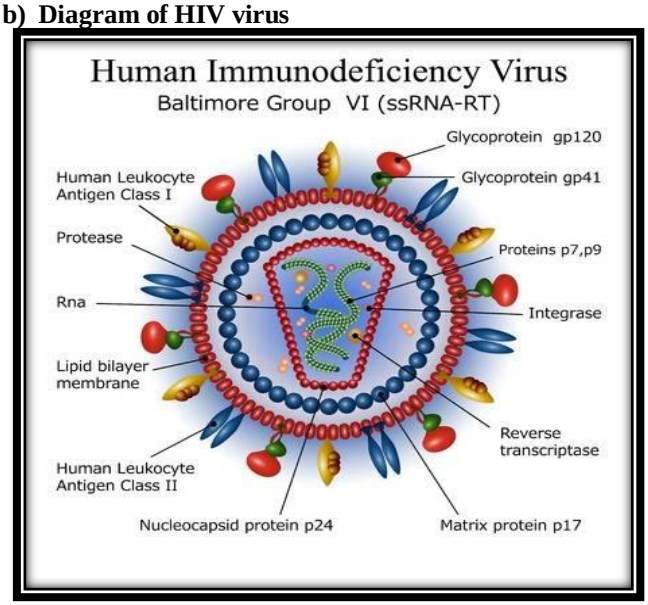


Figure 1: Human Immunodeficiency Virus.

Morphology of HIV virus-

- The virus is spherical with a diameter is about 110 nm.
- It contains a core , surrounded by a lipid envolop derived from host plasma membrane .
- The core of the HIV has two strands of genomic RNA
- The Proteins components are namely after its molecular weight.

- The RNA genome consist of 9 genes – Three of these genes, gag, pol and env,contain information needed to make the structural proteins for new virus particles.
- Inside of capsid are three enzymes required for HIV replication- reverse transcriptase, Integrate and protease.
- Matrix composed of the viral proteins P17 surrounds the capsid ensuring the integrity of the version particles.
- A matrix is surrounded by phospholipid- 2 layer – embedded by 70 copies of complex HIV proteins.

B) Human T-Cell Leukemia viruses

- Human T- Cell leukemia virus is a retroviral infection that affects the T- cell (A type of White blood cell). Although this virus generally courses no sing or symptoms, some affected people may letter develop adult T-cell leukemia?
- HTLV is spread by blood transfusion, sexual contact and sharing needles.
- It can also be spread from mother to child during birth or breast feeding.
- There is no cure or treatment of HTLV and it is considered a long life condition ; However , most (95%)infected remains no symptoms through life
- Human T-cell leukemia viruses are horizontally transmitted from human-to-human (i.e. exogenous virus) and are associated with development of some rare diseases. They are believed to have originated from highly-related simian viruses.

Symptoms

- Fatigue
- Swollen lymph nodes
- Nausea and Vomiting
- Fever
- Skin and bone Abnormalities
- Enlarge liver
- Progressive Weakness
- Stiff muscles
- Weak bladder

Causes

- Human T-cell leukemia virus
- Sexual contact and sharing needle

Diagram of T-Cell Leukemia viruses-

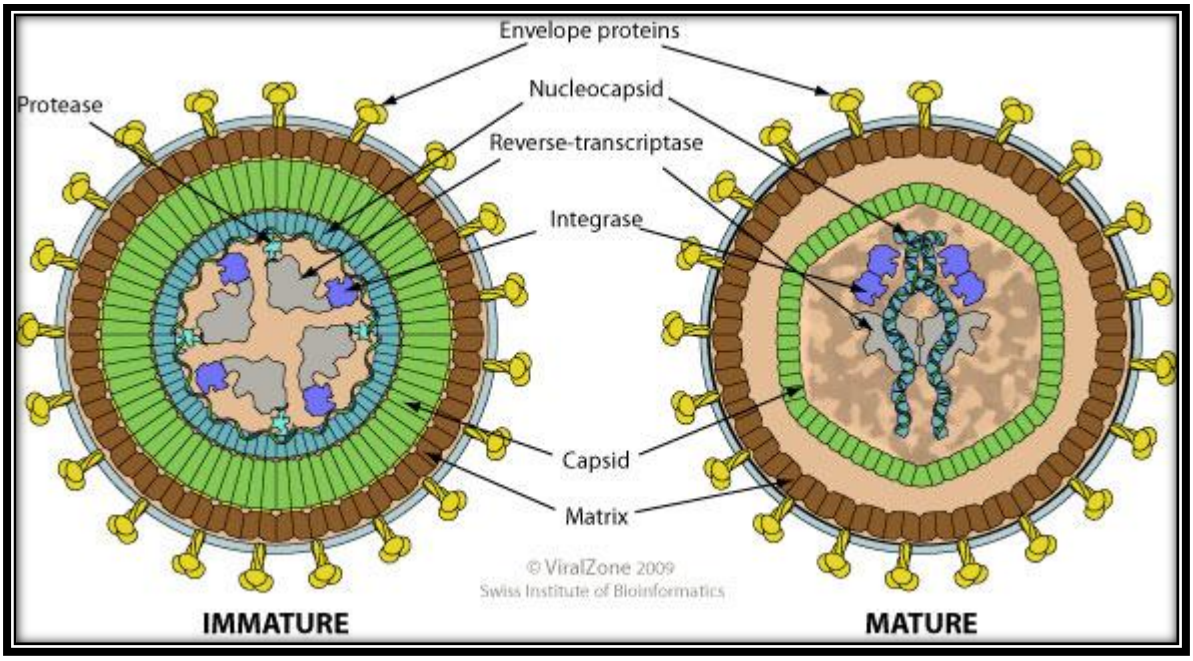


Figure 2: T-Cell Leukemia viruses

Morphology of T-cell Leukemia Virus

- Capsid- Icosahedral with helical nucleoprotein
- Compositions- RNA (2%), Protein (60%), Lipid(35%), Carbohydrates (3%).
- Proteins- Reverse transcriptase-enzyme contained inside the virision.

c) DNA virus

- A DNA virus that has DNA material and replicate using a DNA dependent DNA polymerase.
- The nucleic acid is usually double–stranded DNA but may also be single stranded DNA
- Single stranded DNA is usually expanded to double – strand in infected cell.
- Although group V|| virus such as hepatitis B contain a DNA genome ,they are not considered DNA viruses
- Such disease is caused by DNA virus are smallpox,herpes, and chickenpox etc.

Diagram of DNA, RNA virus

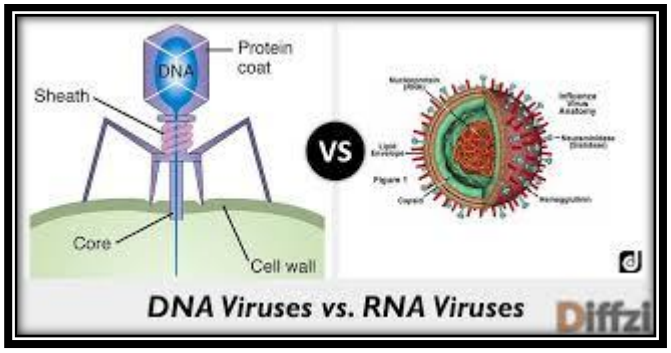


Figure 3: DNA and RNA virus

Morphology of DNA, RNA virus

- Single virus particles, are 20–250 nanometres in diameter.
- In the past, viruses were classified by the type of nucleic acid they contained, DNA or RNA, and whether they had single- or double-stranded nucleic acid.
- Molecular analysis of viral replicative cycles is now more routinely used to classify viruses.
- It consists of nucleic acid and they are confirmed with DNA and RNA

2) Basic Principal of HIV

There are some principles of HIV infectious disease are as follows.

1) Ongoing HIV replication leads to immune system damage and progression to AIDS, HIV infection is always harmful, and long term survival free of clinically significant immune dysfunction is unusual.
2) Plasma HIV RNA levels indicate the magnitude of HIV replication and its associated rate of CD4 +T Cell destruction, whereas CD4 +T cell counts indicates the extent of HIV induced immune damage already suffered. Regular, periodic measurement of plasma HIV, RNA never CD4+T cell counts is necessary to determine the risk of disease progression in an HIV-infected person and to determine when to initiate or modify antiretroviral treatment regimen.
3) As rate disease progression differ among HIV infected persons, treatment decision should be individualize by level of risk indicated by plasma HIV RNA levels and CD4+T cell count.
4) The use of potent combination antiretroviral therapy to suppress HIV replication to below the level of detection of sensitive plasma HIV RNA assay limits the potential for selection of antiretroviral resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay disease progression. Their fore maximum achievable suppression of HIV replication should be a goal of therapy.
5) The most effective means to accomplish durable suppression of HIV replication is the simultaneous initiationof combinations of effective Anti- HIV drugs with which the patients has not been previously treated and that are not cross resistant with antiretroviral agents with which the patients has been treated previously.
6) Each of the antiretroviral drugs used in combination therapy regimens should always be used according to optimum schedule and dose.
7) The available antiretroviral drugs are limited in number and mechanism of action, and cross resistance between specific drugs has be documented. Their fore, any changes in antiretroviral therapy increase future therapeutic contain.
8) Women should receive optimal antiretroviral therapy regardless of pregnancy status.
9) HIV – Infected person, they are avoiding sexual and drug use behavior that are associated with both transmission and other infectious pathogen.

3) HIV virus Life cycle

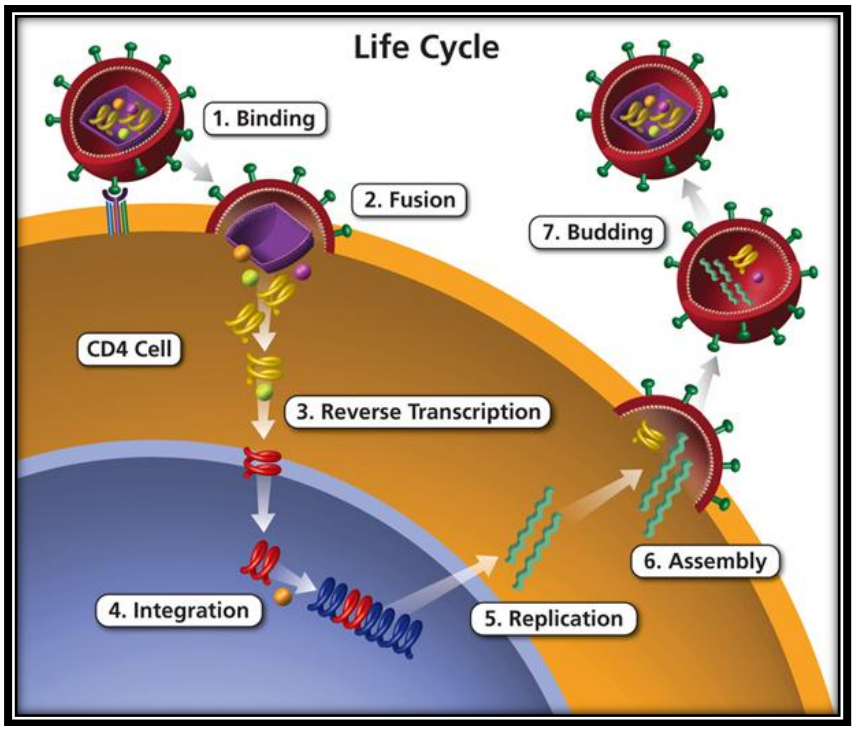


Figure 4: Life cycle of HIV

4) Stages of HIV life Cycle

1) Viral genome and reverse transcriptase entre cell.
↓
2) DNA copy synthesized by reverse transcriptase.
↓
3) RNA degraded second DNA strand Synthesized.
↓
4) DNA circularizes or integrated function to incorporate DNA in to host cell genome.
↓
5) With host cell activation, viral DNA is transcribed yielding messenger RNA and viral genome RNA.
↓
6) Viral RNA are translated yielding viral enzymes (Including Protease) and structural protein.
↓
7) Viral membrane protein is transported to host cell membrane.
↓
8) Final viral assembly and budding take place.
↓
9) Infection are Takes place in host cell

5) Classification of antiretroviral Agent

Antiretroviral Agents are classified in to six Main classes –

1) Nucleoside reverse transcriptase inhibitor

Examples
- Zidovudine
- Stavudine.
- Lamivudine
- Abacavir
- Didanosine
- Zalcitabine

2) Non- Nucleoside reverse transcriptase inhibitor

Examples
- Delavirdine
- Etravirine
- Rilpavirine
- Nevirapine

3) Protease inhibitor –

Examples
- Atazanavir
- Darunavir
- Indinavir
- Nelfinavir
- Ritonavir
- Tipranavir

4) Lopinavir

5) Fusion inhibitor –

Examples – 1) Enfuvirtide

6) Entry inhibitor -

Examples- 1) Maraviroc

7) Integrase inhibitor -

Examples
- Dolutegravir
- Elvitegravir

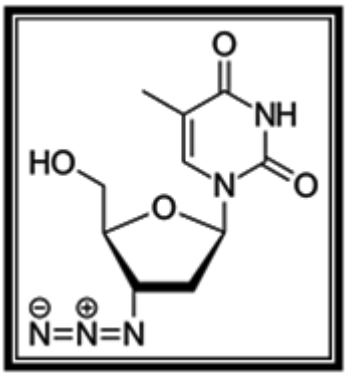
1) Nucleoside Reverse transcriptase inhibitor-

NRTIs were the first class of drugs to be approved by the FDA.NRTIs are administered as pro drugs, which require host cell entry and phosphorylation by cellular kinases before enacting an antiviral effect. Nucleoside reverse transcriptase is antiretroviral agents in HIV drug class. Nucleoside reverse transcriptase inhibitors (NRTIs) block reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

DrugsTherapy-

1) Zidovudine-

Structure



MOA of Zidovudine
- Zidovudine (ZDV), also known as AZT (other names Azidothymidine) is an important drug used for treatment of HIV infection.
- A deoxythymidine analoge.
- Enters the cell via passive diffusion
- Must be converted to the triphosphate from by mammalian thymidine kinase
- Competitively inhibit deoxythymidine triphosphate for reverse transcriptase enzyme
- Couse chain termination occourse.
- AZT is a thymidine analogue. AZT works by selectively inhibiting HIV's reverse transcriptase, the enzyme that the virus uses to make a DNA copy of its RNA.
- Reverse transcription is necessary for production of HIV's double-stranded DNA, which would be subsequently integrated into the genetic material of the infected cell .

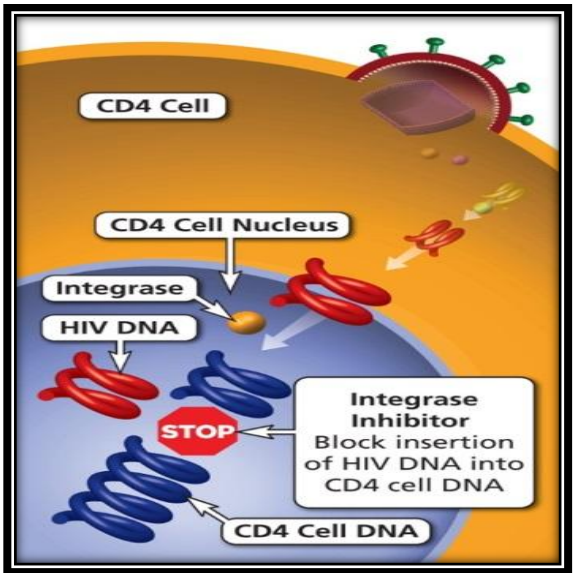


Figure 5: Nucleoside reverse transcriptase inhibitor

Uses of Zidovudine-

- This drug is used with other HIV medications to help control HIV infection
- It helps to decrease the amount of HIV in your body so your immune system can work better. This lowers your chance of getting HIV complications (such as new infections, cancer) and improves your quality of life.
- Zidovudine is used in pregnant women to prevent passing the HIV virus to the unborn baby.
- This medication is also used in newborns born to mothers infected with HIV to prevent infection in the newborns.
- Zidovudine is not a cure for HIV infection. To decrease your risk of spreading HIV disease to others, do all of the following
  (1) Continue to take all HIV medications exactly as prescribed by your doctor.

Side Effect

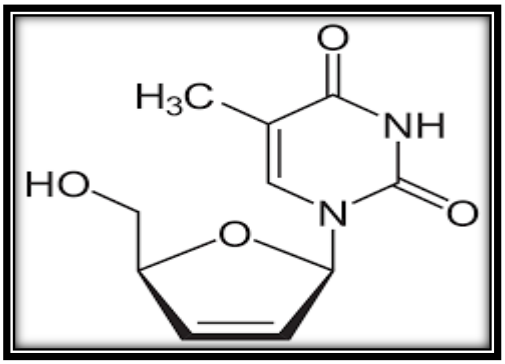
- Most common side-effects include-
- nausea,
- vomiting,
- acid reflux (heartburn),
- headache,
- cosmetic reduction in abdominal body fat,
- light sleeping,
- Loss of appetite.
- Faint discoloration of fingernails and toenails, mood elevation, occasional tingling or transient numbness of the hands or feet.

Dose

- Adult - 300 mg BD
- Children – 180 mg (max 200 mg) 8 hourly.)

2) Stavudine

- Structure



Mechanism of action of Stavudine

- Stavudine, a nucleoside analogue of thymidine, inhibits the replication of HIV in human cells in vitro.
- Stavudine is phosphorylated by cellular kinases to the active metabolites Stavudine triphosphate.
- Stavudine triphosphate inhibits the activity of HIV reverse transcriptase both by competing with the natural substrate deoxythymidine triphosphate (Ki = 0.0083 to 0.032 µM), and by its incorporation into viral DNA causing a termination of DNA chain elongation because Stavudine lacks the essential 3'-OH group.
- Stavudine triphosphate inhibits cellular DNA polymerase beta and gamma, and markedly reduces the synthesis of mitochondrial DNA.

Side effect of Stavudine

- Get emergency medical help if you have signs of an allergic reaction: hives; difficult breathing;
- Swelling of your face, lips, tongue, or throat. Mild
- Symptoms of lactic acidosis may worsen over time, and this condition can be fatal. Get emergency medical help if you have: unusual muscle pain, trouble breathing, stomach pain, vomiting, irregular heart rate, dizziness, feeling cold, or feeling very weak or tired.
- Numbness, tingling, or weakness in your legs, feet, arms, or hands; pain in your hands or feet
- Liver problems--swelling around your midsection, right-sided upper stomach pain, loss of appetite, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes)
- Signs of a new infection--fever, night sweats, swollen glands, cold sores, cough, wheezing, diarrhea, loss; trouble speaking or swallowing, problems with balance or eye movement, weakness or prickly feeling.
- Nausea, vomiting, diarrhea; headache

Uses of Stavudine

- This drug is used with other HIV medications to help control HIV infection.
- It helps to decrease the amount of HIV in your body so your immunesystem can work better
- This lowers your chance of getting HIV complications (such as new infections, cancer) and improves your quality of life.
- Stavudine belongs to a class of drugs known as nucleoside reverse transcriptase inhibitors (NRTI).
- Stavudine is not a cure for HIV infection. To decrease your risk of spreading HIV disease to others, do all of the following:

(1) Continue to take all HIV medications exactly as prescribed by your doctor,
(2) Always use an effective barrier method (latex polyurethane condoms/dental dams) during all sexual activity,
(3) Do not share personal items (such as needles/syringes, toothbrushes, and razors) that may have contacted blood or other body fluids.

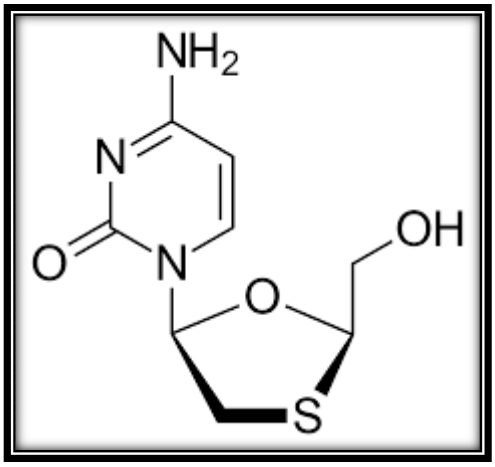
- Consult your doctor or pharmacist for more details.

Dose of Stavudine

- 30 mg BD
- Stag, stavir, virostav 30 mg capsule

3) Lamivudine

Structure



Mechanism of action lamivudine-

- Lamivudine is an analogue of cytidine.
- It can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B virus.
- It is phosphorylated to active metabolites that compete for incorporation into viral DNA.

Side effect of Lamivudine

- The more common side effects that can occur with lamivudine include:
- cough
- diarrhea
- fatigue
- headache
- malaise (general discomfort)
- nasal symptoms, such as a runny nose

Serious side effects

- Lactic acidosis or severe liver enlargement. Symptoms can include:
- stomach pain
- shallow breathing
- muscle pain
- weakness
- feeling cold or dizzy

Uses of Lamivudine-

- This drug is used with other HIV medications to help control HIV infection.
- It helps to decrease the amount of HIV in your body so your immune system can workbetter.
- This lowers your chance of getting HIV complications (such as new infections, cancer) and improves your quality of life. Lamivudine belongs to a class of drugs known as nucleoside reverse transcriptase inhibitors-NRTI.
- Lamivudine is not a cure for HIV infection. To decrease your risk of spreading HIV disease to others, do all of the following:
  (1) continue to take all HIV medications exactly as prescribed by your doctor,
  (2) always use an effective barrier method (latex or polyurethane condoms/dental dams) during all sexual activity,
  (3) Do not share personal items (such as needles/syringes, toothbrushes, and razors) that may have contacted blood or other body fluids.

Dose of Lamivudine-

For HIV infection- 150 mg BD
Or 300mg OD

2) Non – Nucleoside reverse transcriptase inhibitor-

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are promising drugs for thetreatment of HIV when used in combination with other anti-HIV drugs such as nucleosidereverse transcriptase (RT) inhibitors and protease inhibitors.
- The first generation of NNRTIs has, however, suffered from the rapid development of resistance.
- Non-nucleoside reverse-transcriptase inhibitors (NNRTIs) are antiretroviral drugs used in the treatment of human immunodeficiency virus (HIV). NNRTIs inhibit reverse transcriptase (RT), an enzyme that controls the replication of the genetic material of HIV.
- Antiretroviral (ARV) HIV drug class. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind to and block HIV reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription).
- Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.
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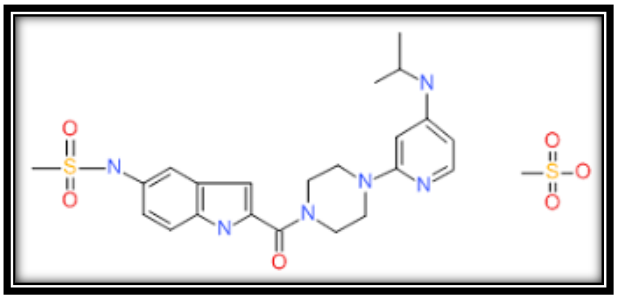
Drug Therapy

1) Delavirdine

Structure



Mechanism of action Delavirdine

Delavirdine binds directly to viral reversetranscription(RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by disrupting the enzyme's catalytic site.

Side effect of Delavirdine

- Diarrhea
- Headache
- Tiredness
- Changes in the shape and location of body fat (especially in your arms, legs, face, neck, breasts, and waist)
- Worsening of a previous medical condition (such as an old infection)
- Itching
- Rash, or
- Cold symptoms (stuffy nose, sneezing, or sore throat).

Use of Delavirdine

- This drug is used with other HIV medications to help control HIV infection.
- It helps to decrease the amount of HIV in your body so your immune system can work better. This lowers your chance of getting HIV complications and improves your quality of life. Delavirdine belongs to a class of drugs known as non-nucleoside reverse transcriptase inhibitors (NNRTIs).
- Delavirdine is not a cure for HIV infection. To decrease your risk of spreading HIV disease to others, do all of the following:

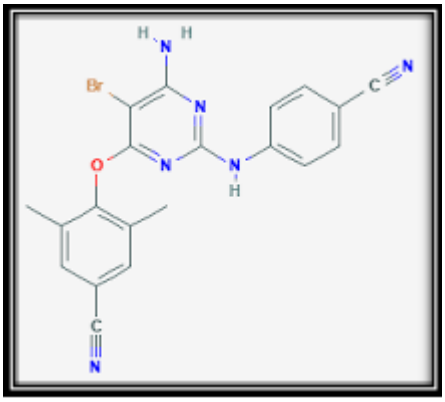
(1) Continue to take all HIV medications exactly as prescribed by your doctor,
(2) Always use an effective barrier method (latex or polyurethane condoms/dental dams) during all sexual activity, and
(3) Do not share personal items (such as needles/syringes, toothbrushes, and razors) that may have contacted blood or other body fluids. Consult your doctor or pharmacist for more details.

Dose of Delavirdine

- 100 mg Tablet
- 200 mg after Meals.

2) Etravirine

Structure



Mechanism of action Etravirine

Etravirine exerts its effects via direct inhibition of the reverse transcriptase enzyme of human immunodeficiency virus type 1 (HIV-1). It directly binds reverse transcriptase and consequently blocks DNA-dependent and RNA-dependentpolymerase activity. Etravirine does not inhibit human DNA polymerase alpha, beta or gamma.

Side effect of Etravirine

- Some side effects of etravirine can be serious. Serious side effects of etravirine include severe skin rash and allergic reactions. Changes in body fat (including gain or loss of fat).
- Changes in your immune system (called immune reconstitution inflammatory syndrome or IRIS). IRIS is a condition that sometimes occurs when the immune system begins to recover after treatment with an HIV medicine. As the immune system gets stronger, it may have an increased response to a previously hidden infection.
- Tingling, numbness, or pain in your hands or feet (peripheral neuropathy) (in adults).
- Diarrhea (in children).

Uses of Etravirine

- Etravirine is used with other HIV medications to help control HIV infection.
- It helps to decrease the amount of HIV in your body so your immune system can work better. This lowers your chance of getting HIV complications (such as new infections, cancer) and improves your quality of life.
- This medication is usually prescribed to people who have taken other HIV medications (e.g., efavirenz, nevirapine, delavirdine) that did not work well enough to control their HIV. Etravirine is known as a non-nucleoside reverse transcriptase inhibitor (NNRTI). It blocks the virus from growing and infecting more cells.

Dose of Etravirine-

- 100 mg tablet.
- 200 mg BD after meals.

Protease Inhibitor

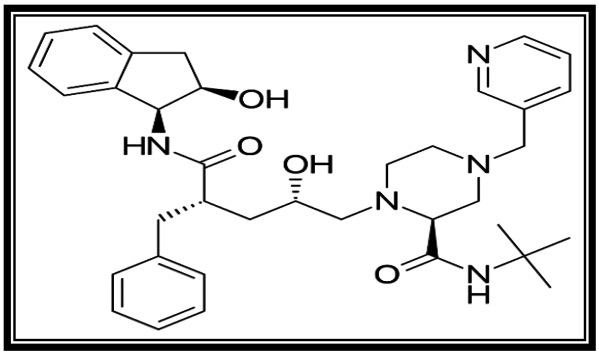
Drug Therapy

1) Indinavir

Mechanism of action Indinavir-

Indinav irinhibits the HIV viral protease enzyme which prevents cleavage of the gag- polpolyprotein, resulting in non infectious, immatureviral particles.

Structure



Side effect of Indinavir

- Gastrointestinal disturbances (abdominal pain, diarrhea, nausea, vomiting)
- General malaise and fatigueNephrolithiasis/urolithiasis (the formation of kidney stones), which sometimes may lead to more severe condition including kidney failureMetabolic alteration
  including hyperlipidemia (cholesterol or triglyceride eleva tions) and hyperglycemia
- Increased levels of Bilirubin, causing skin and white parts of the eyes to turn yellow
- Inhibits urinary nitrous oxide production and may inhibit nitric oxide production.
- Renal abnormalities, sterile leukocyturia, and reduced creatinine clearance.
- Impairs endothelial function in healthy HIV-negative men and may accelerate atherosclerotic disease.

Uses of Indinavir

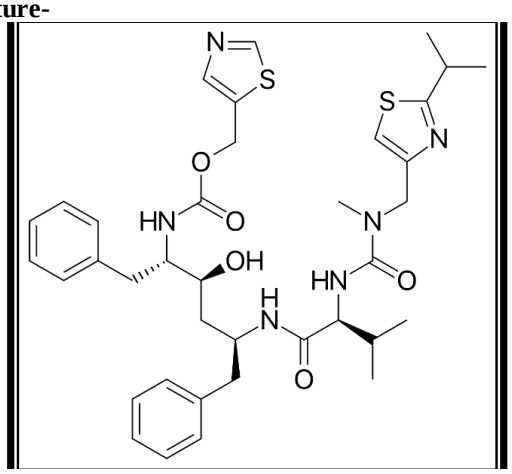
- Indinavir is an antiviral medicine that prevents human immunodeficiency virus (HIV) from multiplying in your body.
- Indinavir is used to treat HIV, the virus that can cause acquired immunodeficiency syndrome (AIDS).
- Indinavir does not cure HIV/AIDS, but it can extend the length of a person's life for several years by slowing the progression of the disease.
- The type that is widely used and created by Merck is indinavir sulfate. The pills are created from sulfate salts and are sold in dosages of 100, 200, 333, and 400 mg of indinavir.
- It is normally used as one of the three drugs in a triple-combination therapy for the HIV virus.

Dose of Indinavir-

800 mg TDS (BD if taken with 100 mg RTV)

2) Ritonavir

Structure-



Mechanism of action Ritonavir

- Ritonavir inhibits the HIV viral proteinase enzyme that normally cleaves the structural and replicative proteins that arise from major HIV genes, such as *gag* and *pol*.
- *Gag* encodes proteins involved in the core and the nucleocapsid, while *pol* encodes the HIV reverse transcriptase, ribonuclease H, integrase, and protease.
- The *pol*-encoded proteins are initially translated in the form of a larger precursoe polypeptide, *gag-pol*, and needs to be cleaved by HIV protease to form other complement protein.
- Ritonavir prevents the cleavage of the *gag-pol* polyprotein, which results in noninfectious, immature viral particles.

Uses of Ritonavir

- Ritonavir is used along with other medications to treat HIV/AIDS.

Side effect Ritonavir

- Ritonavir may cause side effects. Many side effects from HIV medicines, such as nausea or occasional dizziness, are manageable. Some side effects of ritonavir can be serious.
- Serious, life-threatening side effects of ritonavir include inflammation of the pancreas (pancreatitis), heart rhythm problems, severe allergic reactions, liver problems, and drug interactions.
- Other possible side effects of ritonavir include:

Dose of Ritonavir

- 100 mg BD.

4) Fusion inhibitor

- Entry inhibitors, also known as fusion inhibitors, are a class of antiretroviral drugs, used in combination therapy for the treatment of HIV infection.
- This class of drugs interferes with the binding, fusion and entry of an HIV virion to a human cell.

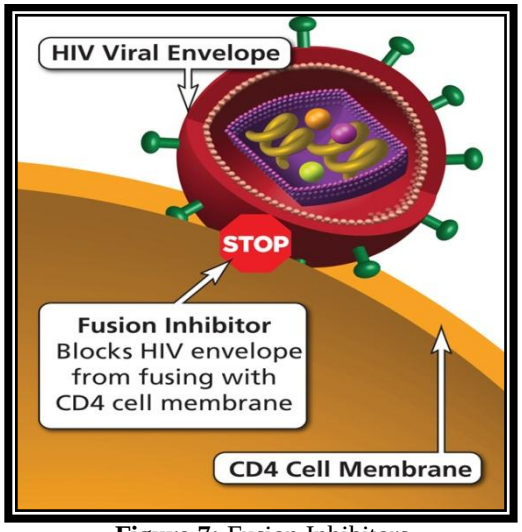


Figure 7: Fusion Inhibitors

Drug Therapy

1) Enfuvirtide

2) Mechanism of action Enfuvirtide-

- Enfuvirtide works by disrupting the HIV-1 molecular machinery at the final stage of fusion with the target cell, preventing uninfected cells from becoming infected. A biomimetic peptide, enfuvirtide was designed to mimic components of the HIV-1 fusion machinery and displace them, preventing normal fusion. Drugs that disrupt fusion of virus and target cell are termed entry inhibitors or fusion inhibitors.
- HIV binds to the host CD4+ cell receptor via the viral protein gp120; gp41, a viral transmembrane protein, and then undergoes a conformational change that assists in the fusion of the viral membrane to the host cell membrane. Enfuvirtide binds to gp41 preventing the creation of an entry pore for the capsid of the virus, keeping it out of the cell.
- Enfuvirtide is also an activator of the chemotactic factor receptor, formyl peptide receptor 1, and thereby activates phagocytes and presumably other cells bearing this receptor (see formyl peptide receptors).The physiological significance of this activation is unknown.

Uses of Enfuvirtide-

a) This drug is used with other HIV medications to help control HIV infection. It helps to decrease the amount of HIV in your body so your immune system can work better. This lowers your chance of getting HIV complications (such as new infections, cancer) and improves your quality of life.

b) Enfuvirtide is not a cure for HIV infection. To decrease your risk of spreading HIV disease to others, do all of the following:
   - Continue to take all HIV medications exactly as prescribed by your doctor,
   - Always use an effective barrier method (latex or polyurethane condoms/dental dams) during all sexual activity,
   - Do not share personal items (such as needles/ syringes, toothbrushes, and razors) that may have contacted blood or other body fluids.

Side effect Enfuvirtide

- Pain, redness, itching, bruising, hardened skin, or bumps at the injection site may occur. These types of reactions are common and may last up to 7 days. Runny nose may also occur.
- Unexplained weight loss, severe tiredness, muscle aches/weakness that doesn't go away, headaches that are severe or don't go away, joint pain, numbness/tingling of the hands/feet/arms/legs, vision changes, signs of infection (such as fever, chills, swollen lymph nodes, trouble breathing, cough, non-healing skin sores), signs of an overactive thyroid (such as irritability, nervousness, heat intolerance, fast/pounding/irregular heartbeat, bulging eyes, unusual growth in the neck/thyroid known as a goiter), signs of a certain nerve problem known as Guillain-Barre syndrome (such as trouble breathing/swallowing/moving your eyes, drooping face, paralysis, trouble speaking).
- Serious side effects, including: anxiety, numbness/ tingling/ shooting nerve pain near injection site, signs of injection site infection (such as oozing, warmth, persistent pain and redness), abdominal pain, and loss of appetite.

Dose of Enfuvirtide

100 mg BD

8) Integrase inhibitor

- Integrase inhibitors (INIs) are a class of antiretroviral drug designed to block the action of integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell.
- Since integration is a vital step in retroviral replication, blocking it can halt further spread of the virus.

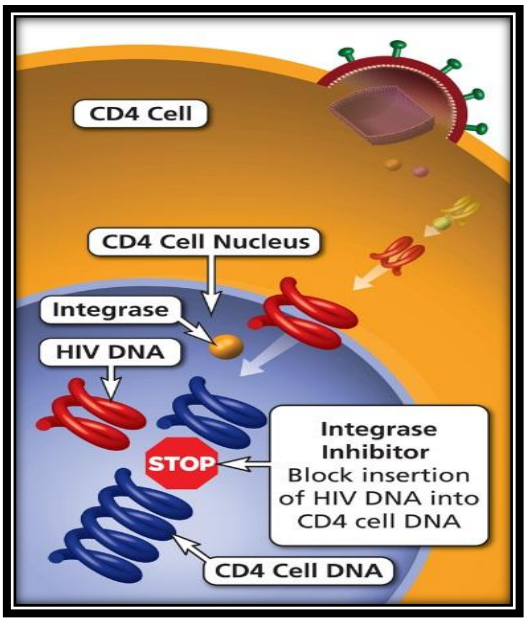


Figure 8: Integrase inhibitor

1) Dolutegravir

Mechanism of action

Dolutegravir is an HIV-1 antiviral agent. It inhibits HIV integrase by binding to the active site and blocking the strand transfer step of retroviral DNA integration in the host

cell. The strand transfer step is essential in the HIV replication cycle and results in the inhibition of viral activity.

Uses

It is used in the treatment on HIV infection.

Side effects-

- trouble sleeping (insomnia),
- tiredness,
- headache,
- allergic reactions such as rash,
- changes in liver tests,
- changes in body fat (especially in your back, neck, and trunk),
- changes in your immune system,
- depression,

Dose of Dolutegravir

- 50mg oncea daily.

2. Conclusion

The breadth and depth of the HIV-1 therapy pipeline may arguably be among the most successful for treating any single human disease, infection, or disorder as illustrated by the number of antiretroviral agents and unique drug classes available. In reviewing the history of ARV drug development, however, there are some key lessons and parallels that need to be kept in mind as we consider the development of small-molecule prevention strategies for HIV-1 and evolving treatment strategies for other viral infections, including hepatitis C virus (HCV). The road to successful HIV-1 treatment was hard, and in the early days many patients were inadequately treated with suboptimal regimens that rapidly led to failure and drug resistance. Although it is unknown whether the prevention of HIV-1 transmission will require the same number of agents, the inherent plasticity of HIV-1 would suggest erring on the side of caution and focusing early on combination products that would mitigate this risk. In the case of HCV, the breadth of genetic diversity appears to be greater than that observed in an HIV-1 infected individual. Anti-HCV drugs in the most advanced stages for approval inhibit a small number of targetsand each class appears to share significant cross resistance; when tested as single agents, the emergence of HCV drug resistance is rapid. The success of HAART should provide the benchmark for HCV drug development and a roadmap for the development of novel prevention strategies in HIV-1 to avoid potential risk to both the individual patient and the population by preventing the acquisition and transmission of drug resistance.

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