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# A REVIEW ON ANTIRETROVIRAL DRUGS

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## ABSTRACT

*Human immunodeficiency virus (HIV) infection is now recognized as a chronic illness. There are several classes approved by USFDA of antiretroviral agents that act on different stages of the HIV life-cycle. The different drugs have different mechanism of action and adverse effects. Treatment has been so successful that in many parts of the world, HIV has become a constant condition wherein movement to AIDS is progressively rare. The United States Department of Health and Human Services and the World Health Organization prescribe offering antiretroviral treatment to all patients with HIV.*

***Keywords*** *– HIV, AIDS, Antiretroviral drugs, Adverse effect, Mechanism of action.*

## 1. INTRODUCTION

Antiretroviral drugs are the drugs that active against HIV (Human immunodeficiency virus) called retrovirus. These drugs are used to improve the quality of life and delay the complications of AIDS (Acquired immunodeficiency syndrome), but do not cure the infection [1].

AIDS is a viral disease that caused by the HIV (human immune virus). A virus that is composed not DNA but of RNA. Retroviruses have an enzyme, called reverse transcriptase that gives them the one of a kind property of transcribing their RNA into DNA after entering a cell. The retroviral DNA can integrate into the chromosomal DNA of the host cell [2].

Two major form of HIV are:

- HIV-1, the most prevalent worldwide,
- HIV-2, the most common in western Africa.

The first case of acquired immunodeficiency syndrome (AIDS) were described in homosexual men in the US in 1981 [3]. Several years later in 1983 and 1984 respectively, French, and American scientist confirmed that the causative agent for AIDS was a retrovirus, HIV [4].

The protease inhibitor was introduced in first revolution in 1996, in the combination of two nucleotide analogue reverse-transcriptase inhibitors that form highly active antiretroviral therapy (HAART) and improve and diagnosis of lethal disease [5].

HIV/AIDS is an eloquent and developing public health concern for worldwide. Now a day's Approximately 25 million individual peoples are died from AIDS. In world war the total number of American causalities was raised more than 60 times and over 33

million people globally are infected and living with HIV and 2 million peoples are caused death with AIDS. Regrettably half of all who are infected with HIV acquired the infection before the age of 25 years and are killed by AIDS before turn 35 [6].

A wide array of such factors or barriers has been put forward in the literature including health system-level barriers and population-level barriers [7].

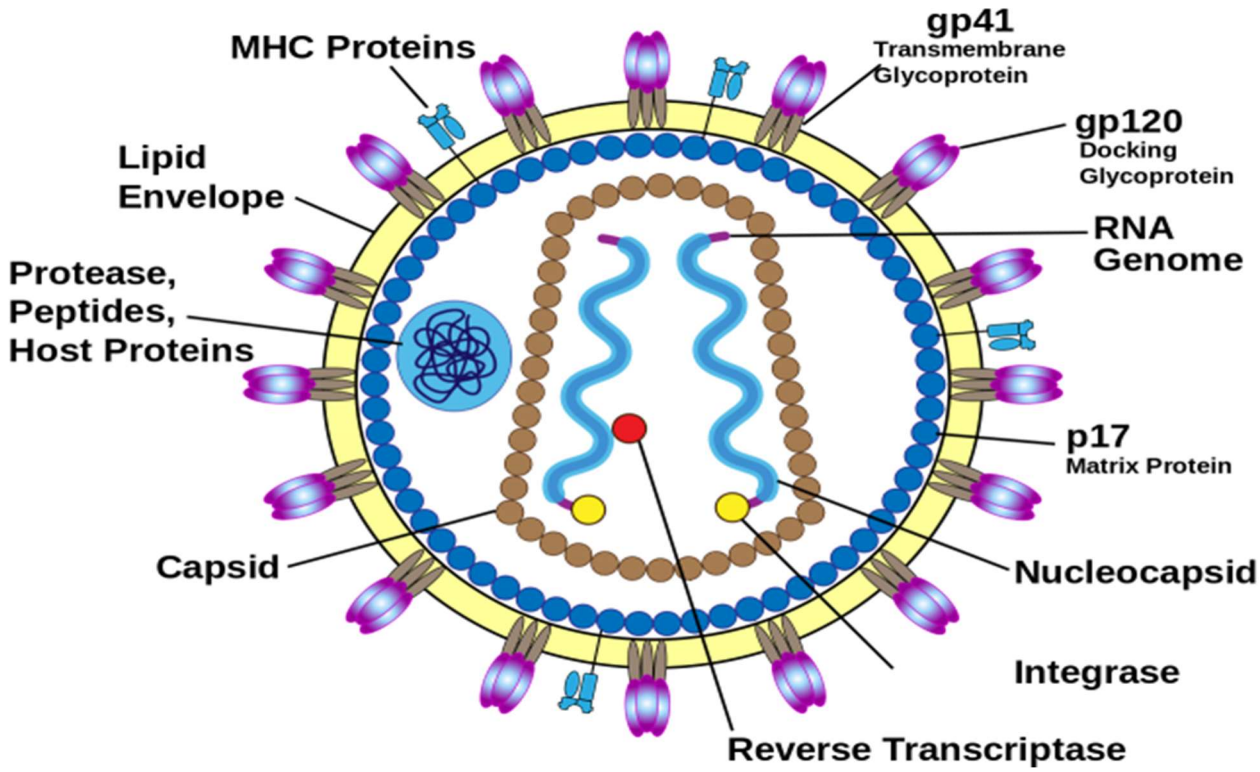


**Fig. 1: Structure of immunodeficiency virus**

**2. HOW HIV IS TRANSMITTED?**

HIV (Human immunodeficiency virus) spread from one person to another person is called HIV transmission. HIV is spread only in certain body fluids from a person who has HIV [8]. These body fluids include

- Blood
- Semen
- Pre-seminal fluid
- Vaginal fluids
- Rectal fluids
- Breast milk

HIV transmission is just possible through contact with HIV-infected body fluids. In the United States, HIV is transferred for the most important part by:

- Sharing injection drug equipment (works), such as needles, with somebody who has HIV
- Having sexual relationship with someone who has HIV without using a precaution or taking medicines to prevent or treat HIV [9].

HIV also spread from HIV infected woman to her child during pregnancy, or breastfeeding is called HIV transmission of mother-to-child.

HIV spread by hand shaking or hugging a person to another person who was infected with HIV. HIV can also spread contact with the dishes, toilet seats, or parts of door and windows used by an infected person with HIV.

HIV is not spread through the air or in water or by mosquitoes or other blood-sucking insects [8].

**3. HOW HIV IS NOT TRANSMITTED?**

Family, friends and co-workers should not fear getting infected with HIV through easygoing contact with a HIV-infected individual at home, at work, or socially. These exercises will not transmit the infection:

| | |
|---|---|
| Shaking hands,<br>Hugging or kissing<br>Coughing or sneezing<br>Using a public phone<br>Visiting a hospital | Opening a door<br>Sharing food,<br>Eating or drinking utensils<br>Using drinking fountains<br>Using toilets or showers<br>Using public swimming pools |

**4. STAGES OF HIV INFECTION**

- Without treatment with HIV prescription, HIV contamination propels in stages, deteriorating after some time.
- The three phases of HIV diseases are:

(1) Acute HIV infection,

(2) Chronic HIV infection, and

(3) Acquired immunodeficiency syndrome (AIDS).

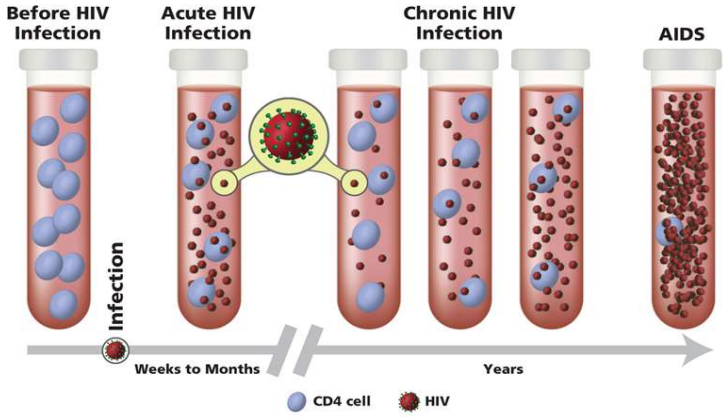


**Fig. 2: HIV Progression**

**4.1 Acute HIV Infection**

Acute HIV infection is the earliest stage of HIV infection, and it generally expands within 2 to 4 weeks after infection with HIV. During this period, flu-like symptoms are formed by some peoples such as fever, headache, rash, fatigue, sore throat, night sweats, loss of appetite and mouth ulcers. In this stage, HIV rapidly multiplies the infection and spreads into the whole body [(11)]. The virus attacks and demolishes the infection-fighting CD4 cells of the immune system. The level of HIV in the blood is very high in this stage of HIV infection, which increases the risk of HIV transmission. A person may experience significant health benefits if they start ART during this stage [10].

**4.2 Chronic HIV Infection**

The second phase of HIV infection is chronic HIV diseases also called asymptomatic HIV infection or clinical dormancy. During the chronic HIV infection, HIV multiplies continuously into the body but at very low levels. In this stage no HIV-related symptoms are formed into the peoples [11]. Without ART, chronic HIV infection usually advances to AIDS in 10 years or longer, though in some people it may advance faster [5]. Individual who is taking ART may be in this stage for several decades. While it is as yet conceivable

to transmit HIV to others during this stage, individuals who take ART exactly as prescribed and maintain an undetectable viral load have successfully no risk of transmitting HIV to a HIV-negative partner through sex [12].

**4.3 AIDS**

AIDS is the final, most serious stage of HIV infection. Since HIV has seriously harmed the immune system, the body can't fight off opportunistic diseases. People with HIV are diagnosed with AIDS if they have a CD4 count of less than 200 cells/ $mm^3$ or if they have certain opportunistic infections [13]. When an individual is diagnosed with AIDS, they can have a high popular burden and can transmit HIV to others without any problem. Without treatment, people with AIDS typically survive about 3 years [14].

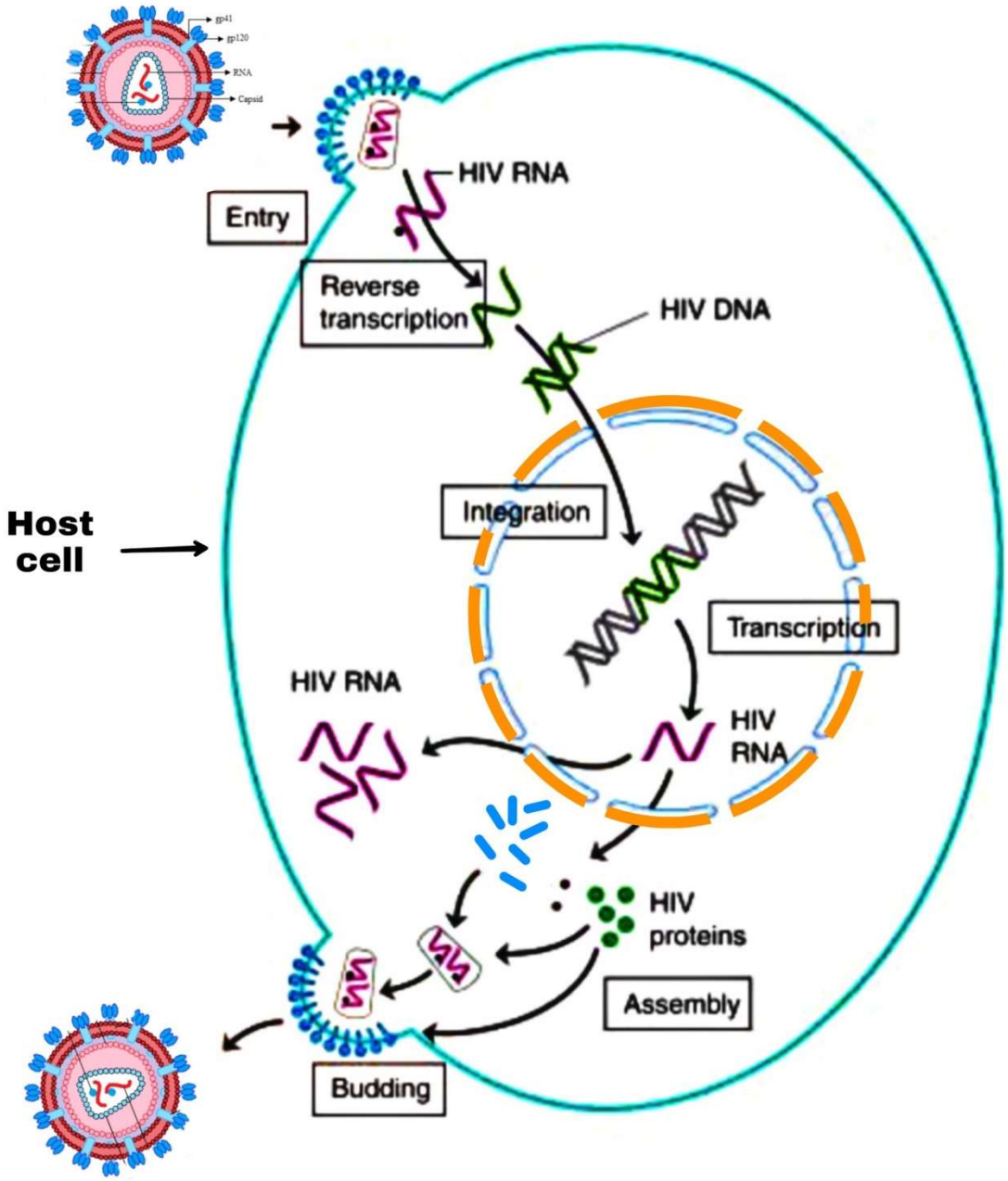


**Fig. 3: HIV Lifecycle**

**5. HIV DRUG CLASSIFICATIONS**

The list of US-FDA approved anti-HIV drugs are summarized in table-1.

**Table - 1: US-FDA approved Anti-HIV drug**

| NRTIs | NNRTIs | Protease inhibitors | Fusion inhibitors | Entry inhibitors | Integrate inhibitors |
|---|---|---|---|---|---|
| Zidovudine<br>Stavudine<br>Lamivudine<br>Tenofovir<br>Abacavir<br>Emitricitabine<br>Zalcitabine | Nevirapine<br>Delavirdine<br>Efavirenz<br>Travirine,<br>Rilpivirine<br>Doravirine<br>Etravirine | Darunavir<br>Fosamprenavir<br>Indinavir<br>Lopinavir<br>Ritonavir<br>Saquinavir<br>Tipranavir | Enfuvirtide | Enfuvirtide<br>Maraviroc | Dolutegravir<br>Elvitegravir |

**5.1 NRTIs**

Compete with natural deoxynucleotides for fuse into a developing viral DNA chain. However, NRTIs lack a 3'-hydroxyl group on the deoxyribose moiety [15]. This difference results in the incorporation of an NRTI, and the next incoming deoxynucleotide cannot form the following 5', 3' phosphodiester bond needed to extend the DNA chain. The result is a chain termination in DNA synthesis [16].

**5.2 NNRTIs**

Block reverse transcriptase (RT) by directly binding to the enzyme. Though NNRTIs do not get incorporated into the viral DNA, they inhibit the movement of protein domains of RT that are essential to carry out the DNA synthesis [17].

**5.3 Protease Inhibitors**

Bind HIV-1 protease and block proteolytic cleavage of protein precursors that are necessary for the production of viral particles [18].

**5.4 Fusion Inhibitors**

Disrupt binding, combination, and section of HIV virions into a human cell. Enfuvirtide ties to gp41 and disturbs film connection.

**5.5 Integrase Inhibitors**

Block the action of integrase, preventing the viral genome from inserting itself into the DNA of a host cell [19].

**6. MECHANISM OF ACTION**

**6.1 Lamivudine:** This deoxycytidine analogue is phosphorylated intracellularly and inhibit HIV reverse transcriptase as well as HBV DNA polymerase. It incorporates into DNA and result chain termination. Point mutation in HIV reverse transcriptase and HBV DNA give rise to rapid lamivudine resistance. However, certain lamivudine-resistance mutants become slow growing and have lower virulence [20].

**6.2 Zidovudine:** It is a structural analogue of thymidine. It is a prodrug that must be phosphorylated to its active 5-transcriptase metabolites. It inhibits the activity of HIV-1 transcriptase via DNA chain termination after incorporation of nucleotide analogue. It incorporates into viral DNA. It is also a weak inhibitor of cellular DNA polymerase α and γ [21].

**6.3 Tenofovir:** Once tenofovir is activated by a bi-phosphorylation it acts as an antiviral acyclic nucleoside phosphonate. It is a potent inhibitor of the viral reverse transcriptase with an inhibitory constant of approximately 0.022 micromolar [22].

Once activated, tenofovir acts with various components including the hinderance of viral polymerase causing chain end and the inhibition of viral synthesis. All these activities are achieved by its opposition with deoxyadenosine 5'-triphosphate in the age of new popular DNA. When tenofovir is fused in the chain, it induces a chain termination which in order inhibits viral replication. The security of tenofovir depends on its low affinity towards the cell DNA polymerase including the mitochondrial DNA polymerase gamma [21].

**6.4 Abacavir:** Abacavir is a carbocyclic synthetic nucleoside analogue and an antiviral agent. Intracellularly, abacavir is changed over by cellular enzymes to the active metabolite carbovir triphosphate, an analogue of deoxyguanosine-5'-triphosphate (dGTP). Carbovir triphosphate hinders the movement of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its fuse into viral DNA [23]. Viral DNA growth is terminated because the incorporated nucleotide lacks a 3'-OH group, which is needed to form the 5' to 3' phosphodiester linkage essential for DNA chain elongation [24].

**6.5 Indinavir:** Indinavir inhibits the HIV viral protease enzyme which prevents cleavage of the gag-pol polyprotein, resulting in noninfectious, immature viral particles [25].

**7. CONTRAINDICATIONS**

**7.1 Abacavir:** Patients who have the HLA-B*5701 allele, or with a prior hypersensitivity reaction to abacavir or with moderate or severe hepatic impairment [26]. Emtricitabine: Patients with previously demonstrated hypersensitivity to any of the components of the products. Lamivudine: Patients with a previous hypersensitivity reaction to lamivudine. Tenofovir Disoproxil Fumarate: Previous hypersensitivity and/or glomerular filtration rate (GFR) less than 50.

**7.2 Zidovudine:** Patients who have had potentially life-threatening allergic reactions (e.g., anaphylaxis, Stevens-Johnson syndrome) to any of the components of the formulations. Efavirenz: Patients with clinically significant hypersensitivity, for example, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the ingredients of this product. Coadministration of efavirenz with elbasvir and grazoprevir is contraindicated [27]. Etravirine: Hypersensitivity

**7.3 Nevirapine**: In patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment or for use as occupational and non-occupational post-exposure prophylaxis (PEP) regimens. Women with CD4 greater than 250 or men with CD4 greater than 400 due to an increased probability of hypersensitivity reaction.

**7.4 Rilpivirine:** Contraindicated for co-administration with all of the following; carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, dexamethasone, St. John's wort, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. Atazanavir: In patients with previously demonstrated clinically significant hypersensitivity, for example, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions, to any of the ingredients of formulations. When co-administered with medications that are highly dependent on CYP3A or UGT1A1 for clearance, and for patients in which elevated plasma concentrations of the interacting drugs are associated with severe and life-threatening events. When co-administered with drugs that strongly induce CYP3A4, it may lead to lower exposure and loss of efficacy of formulations [28].

**7.5 Darunavir**: Co-administration of formulation is contraindicated with drugs that are exceptionally liable to CYP3A for freedom and for which raised plasma concentrations are connected with serious and dangerous occasions [29].

**7.6 Ritonavir:** Contraindicated in patients with clinically critical hypersensitivity, for example, toxic epidermal necrolysis (TEN), or Stevens-Johnson syndrome, to ritonavir or any of its ingredients. Ritonavir is contraindicated with medications that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and life-threatening reactions [30]. It is moreover contraindicated with drugs that are remarkable CYP3A inducers, where basically decreased lopinavir plasma concentrations may compare with the potential for loss of virologic response and possible resistance and cross-resistance [31].

**7.7 Saquinavir:** Contraindicated in those with congenital long QT syndrome, those with refractory hypokalemia or hypomagnesemia, and combination with drugs that both increase saquinavir plasma concentrations and prolong the QT interval .Is also contraindicated in people with complete atrioventricular (AV) block without implanted pacemakers, or in patients who are at high risk of complete AV block [30]. Contraindicated in patients with clinically critical excessive hypersensitivity (e.g., anaphylactic reaction, Stevens-Johnson syndrome) to saquinavir, saquinavir mesylate, or any of its ingredients. Contraindicated in patients with severe hepatic impairment. It is also contraindicated with drugs that are CYP3A substrates for which increased plasma levels may result in serious or life-threatening reactions [32].

**7.8 Enfuvirtide:** Known hypersensitivity to enfuvirtide or any of its components.

**7.9 Dolutegravir:** With previous hypersensitivity reaction to dolutegravir or receiving dofetilide due to the potential for higher dofetilide plasma concentrations and the risk for serious and life-threatening events [33].

**8. TREATMENTS OPTIONS FOR HIV**

HIV infection has a very complex pathogenesis and varies substantially in different patients. Therefore, it can easily be considered as a very host - specific diseases. The specificity of pathogenesis often complicates treatment options that are currently available for HIV infection [34]. Viable administration of HIV disease is possible utilizing various combinations of available medications. This strategy for treatment is collectively known as antiretroviral therapy (ART). Standard ART is comprised of a concoction of at least three medicines (termed as "highly active antiretroviral therapy" or HAART) [35]. Effective ART frequently helps control the multiplication of HIV in infected patients and build the count of CD4 cells, consequently, prolonging the asymptomatic period of infection, slowing the movement of the disease, and also helps in reducing the risk of transmission. Figure 3 demonstrates the percentage of HIV patients under ART [36].

**9. ADVERSE EFFECTS OF ART (ANTI RETROVIRAL THERAPY)**

One of the significant difficulties that patients and doctors face with ART is the frequency of adverse drug reactions (ADR). ADR is characterized as "a response to a medication that is harmful and unintended and occurs at doses normally utilized in man for the prophylaxis, diagnosis, or treatment of disease, or for change of physiological function" [37]. ADR often persuades patients from proceeding with treatment, thus resulting in suboptimal efficacy. A genuine result of treatment discontinuation is the emergence of drug resistance, making future therapeutic interventions incapable [38].

The major adverse effects of ART can be grouped into the following categories:

1. Gastrointestinal: Nausea, diarrhea, vomiting, taste perversion, constipation, dyspepsia, abdominal pain, hepatotoxicity, and pancreatitis [39].

2. Central nervous system: Headache, vision problems, dizziness, tinnitus, insomnia, paresthesia, pain/numbness/tingling in extremities, peripheral neuropathy, somnolence, excessive sleep at night, memory problems, loss of olfactory function, and hearing impairment [39].

3. Hematological: Anemia, bilirubinemia, increased urate, and blood in the urine [40].

4. Psychological: Anxiety, confusion, depression, nightmares, elation, and delusions [40].

5. Metabolic: Abnormal fat distribution (lipodystrophy), anorexia, dyspnea, fatigue, lethargy, and weight gain [38-39].

6. Dermatological: Skin rash, facial discoloration, and purities [40].

7. Musculoskeletal: Body aches and vague chest pain [38].

8. Miscellaneous: Hypersensitive reactions, oral ulcerations, fever, and irregular menstrual cycles [38].

**9.1 Drug Abuse**

Continuous drug abuse is an important risk factor in HIV/AIDS patients' ART, non-adherence, and mortality [40]. In a study conducted on HIV-positive drug addicts in Canada, heroin and cocaine injections were reported to adversely affect adherence to ART [41]. In a different six month long longitudinal investigation, which analyzed the effect of medication use and abuse on ART among 150 HIV positive patients, it was found that intense impacts of intoxication adversely impact ART adherence. The major mechanisms by which drug abuse results in ART nonadherence include drug abuse induced neurocognitive/psychosocial impairment and psychiatric dysfunctions [42].

**9.2 Mental Disorders**

The prevalence of psychiatric disorders is reported to be very high among HIV-infected individuals [43]. In a longitudinal study investigating the mental health, substance abuse, and psychosocial predictors among HIV-positive mothers, the presence of psychiatric disorders, stressful lifestyles, suboptimal living conditions, and parenting stress were associated significantly with ART nonadherence [44]. Childhood sexual violence-induced anxiety and depression may also result in ART nonadherence [45]. Hazardous drinking is another significant precipitator of anxiety and depression among HIV patients that results in ART non adherence [46].

**9.3 Socioeconomic Status**

Socioeconomic status is unequivocally connected with HIV-related mortality in the contemporary universal healthcare system because opportunities for patients of lower socioeconomic status to get ART are small. In an examination led among HIV-positive Cambodian ladies, 80% of the individuals who discontinued ART were of low socioeconomic status. The estimated risk for low adherence in this population was reported to be five times higher for women than those in a medium or high social position [47]. Poverty-induced stress is an important aspect that has to be addressed in issues regarding ART non adherence. The quality of housing and access to food are the two most important factors that prevent the poverty-ridden population from ART adherence [48].

**9.4 Poor Literacy**

Literacy is another major factor closely associated with ART nonadherence with people of lower health literacy experiencing higher illness severity than people with better health literacy [49]. Health education has been characterized by the WHO as "the intellectual and social skills which decide the inspiration and capacity of people to gain access to, understand, and use data in manner which promote and maintain good health" [49]. Many reports suggested that the inability to comprehend medication instructions by illiterate HIV-positive patients is an important factor resulting in failure to follow accurate daily medication therapy [50].

**10. FDA-APPROVED ANTI-HIV COMBINATION AVAILABLE IN MARKET**

The US-FDA approved anti-HIV combinations available in market are as follows:

| |
|---|
| Abacavir and Lamivudine |
| Abacavir, Dolutegravir, and Lamivudine |
| Abacavir, Lamivudine, and Zidovudine |
| Atazanavir and Cobicistat |
| Bictegravir, Emtricitabine, and Tenofovir Alafenamide |
| Darunavir and Cobicistat |
| Dolutegravir and Rilpivirine |
| Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate |
| Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate |
| Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate |
| Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide Fumarate |
| Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Disoproxil Fumarate |
| Emtricitabine, Rilpivirine, and Tenofovir Alafenamide |
| Emtricitabine, Rilpivirine, and Tenofovir Disoproxil Fumarate |
| Emtricitabine and Tenofovir Alafenamide |
| Emtricitabine and Tenofovir Disoproxil Fumarate |
| Lamivudine and Tenofovir Disoproxil Fumarate |
| Lamivudine and Zidovudine |
| Lopinavir and Ritonavir |

The FDA does not approve investigational HIV drugs. Investigational drugs include those used to treat or prevent HIV and vaccines to treat or prevent HIV [51]. These drugs are only available in clinical trials. No vaccines exist yet; however, researchers are studying this possibility [52].

**11. CONCLUSION**

Recent advancement in HIV treatments has dramatically altered the nature and progression of HIV/ AIDS. HIV prevention programs have focused primarily on developing risk reduction intervention for those at high risk for becoming infected with HIV. Although there are huge number of people in United states at" social hazard" for HIV disease, transmission can happen just from individuals who are infected with the virus.

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