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Recent Pharmaceutical Interventions in The Treatment of HIV/AIDS

Melody Chola[1], Rajan Kumar[1], Rakesh Kumar[1], Manish Vyas[1], Navneet Khurana[1], Puneet Utreja[2], Neha Sharma[1,3,4,*]

[1]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India, PIN- 144 411

[2]Faculty of Pharmaceutical Sciences, PCTE Group of Institutes, Ludhiana, Punjab, India, PIN- 142 021

[3]Akal College of Pharmacy and Technical Education, GursagarMastuana Sahib, Sangrur, Punjab, India, PIN- 148 001

[4]I.K. Gujral Punjab Technical University, Kapurthala, Punjab, India, PIN- 144 603

[*]Corresponding author: c4nehagautam@gmail.com

ABSTRACT

Various researches over the past years have targeted the cure of HIV but there has not been any success. A lot of drugs are utilized for anti retro viral therapy but all of these drugs target the HIV reservoirs and suppress the viral load. Since the introduction of ART, all the drugs were administered orally which led to so many adverse effects like renal failure, hypersensitivity reactions, hepatotoxicity, diarrhea, constipation and many others in different patients. In order to overcome these adverse effects a number of pharmaceutical interventions have been introduced. This has led to better treatment and management of human immunodeficiency virus. These include discovery of a new class of drugs known as maturation inhibitors which are still in clinical study. Prophylaxis by insertion of vaginal rings in women for slow release of anti retro viral drugs is another intervention that has been improvised in ART. Besides the adverse effects, some drugs have very less bioavailability. In order to overcome these problems, the drugs were formulated as nanosystems which include liposomes, niosomes, dendrimers, solid lipid particles and many others. Recent studies have shown already existing drugs like metformin which is used to treat diabetes type 2 can be used in ART as it reduces the reservoirs of HIV. Cannabinoids can also be used to decrease inflammation in HIV patients as they are prone to chronic inflammation. Thus, use of these cannabinoids suppresses the inflammation. All these interventions have played a major role in the maintenance and treatment of HIV.

KEYWORDS

Human immunodeficiency virus, pharmaceutical intervention, prophylaxis, nanosystems, cannabinoids

Introduction

Human Immunodeficiency Virus (HIV) belongs to a class of viruses called Retro virus(Pattman et al., 2005). There are two types of HIV i.e. HIV 1 and HIV 2. There are a lot of notable differences between the two types(Kaslow et al., 2014). Type 1 is the most infectious, and commonly found worldwide while type 2 is less common, less infectious and mostly found in West Africa. HIV is responsible for the disease known as acquired immunodeficiency syndrome (AIDS) by attacking the T–lymphocyte cluster of differentiation 4 cells (CD4 cells) leading to the decrease of the T-lymphocytes which weakens the immune system. The most prevalent symptoms are lack of energy, drowsiness, malaise, nervousness, numbness, muscle aches, diarrhea, constipation, hypersensitivity reactions, dry mouth and nausea. This infection is transmitted by various methods such as blood transfusions, interaction of body fluids such as breast milk and vaginal fluids, with sexual intercourse being the most common method of transmission(Supervie et al., 2014). In recent years, there has been introduction of HIV testing kits where the testing can even be done in the comfort of your home(Tavakoli et al., 2017). Mostly HIV testing involves a blood test because the virus resides in the blood .There has not been any cure for this disease but introduction of anti-retro viral therapy (ART) drugs like lamivudine, tenofovir, zidovudine, nevirapine, dolutegravir and many others are administered for maintenance therapy which helps in the management and preventionof HIV by maintaining the viral load in low concentration in blood which also decreases the progress of HIV to AIDS. This has led to increased life expectancy in millions of infected people(Koibuchi, 2013).The drug resistance or increased side effects to the particular ART, such as kidney failure in tenofovirdisoproxilfumarate therapy(Mills et al., 2016). Withdrawal from ART may cause immediate death of patient as the patient becomes prone to all the opportunistic diseases. Recently there are propositions of development of long acting ART and vaccines that will play a major role in the curbing of HIV. A lot of pharmaceutical interventions like use of oral cannabinoids to strengthen the immune system(Costiniuk et al., 2019).

2.1 Definition

HIV is a virus that is responsible for causing AIDS. It attacks T- lymphocytes of the CD4 cells which weakens the immune system. HIV virus has been one of the leading causes of death in recent years(Melhuish and Lewthwaite, 2018).

2.2 Types of HIV

There are two types of HIV; HIV 1 and HIV 2.

Table no. 1: Difference between HIV1 and HIV 2

HIV-1	**HIV-2**	**References**
Progression is faster	Progression is slow	(Kaslow et al., 2014)
Viral load is relatively high	Viral load is low	(Gueudin et al., 2008)
Responds to fusion inhibitors and non-nucleotide reverse transcriptase inhibitors.	Resistant to fusion inhibitors and non-nucleotide reverse transcriptase inhibitors.	(Wang et al., 2017)

2.3Symptoms

HIV infection produces a number of symptoms, due to the weakening of the immune systemsuch as fever, malaise, constipation, diarrhea, hypersensitivity reactions, numbness, muscle pain, cough, mouth sores and swollen arms. The body is prone to all the opportunistic diseases as shown in the figure below;(Burger et al., 2019).

2.4 Structure of HIV

The size of mature HIV virions varies between 100–120 nm in diameter(Pattman et al., 2005).Spherical structures consisting of a lipid bilayer membrane which is enclosed in a dense cone-shaped core(Zhao et al., 2016). The core is made of two 9.8-kb long positive sense, single stranded, linear molecules which result in the synthesis of cDNAs, tRNA found in the cells. Gag polyprotein and an envelope of the virus protein containing three enzymes named reverse

transcriptase (RT), viral protease (PR), and integrase (IN) are also part of the structural components of the virus(Hope and Trono, 2000; Briggs et al., 2009).

2.5Pathophysiology

HIV penetrates in the cell through CD4 molecules. After attachment, HIV RNA and enzymes are released in host cell(Hope and Trono, 2000). To replicate, it requires the enzyme reverse transcriptase.This enzyme makes copies of viral RNA to proviral DNA and enters the nucleus of the host cells. The integration of proviral DNA into host cells is facilitated by HIV integrase enzyme. HIV proteins get assembled and then budded from the surface of the cell(Gueudin et al., 2008).The host cells that are infected by HIV develop a very short life span because once they get infected by virus, they later become producers of the virus and act like a store for them.HIV continuously replicates itself in maximum 10 million to 10 billion host cells every day(Calles et al., 2010).

2.6Transmission

HIV transmission is achieved by direct contact of body fluids such as blood, vaginal secretions, breast milk and many other or secretions from wounds or lesions that may contain the virus(Murphy et al., 1995).The high risk causes are generally sexual intercourse and anal sex, because these cause inflammation of the mucus membrane(Supervie et al., 2014).Recent studies have shown that HIV patients with low viral load, undetectable levels, has proven that they have less or no chances of transmitting HIV to their partners who may be negative (Hassan et al., 2017).Mother to child transmission is also one of the most common methods of transmission.Caesarean delivery and treatment of the child with ARVs for the first few weeks after, it is born also reduces the risk(Surjushe and Maniar, 2008). The receiver of the organ is likely to get infected by the virus (Supervie et al., 2014)

2.7 Conventional treatments of HIV

Currently, there is no cure for HIV/AIDS but there are a number of drugs that are available for treatment just to suppress the virus. This treatment is called ART(Kembaren, 2018). Antiretroviral therapy is the recommended option for treatment of HIV viral suppression and also for reduction of deaths of infected people(Brooke et al., 1990). The first drug to be discovered for this therapy early in the 1980s was Zidovudine(Mondal, 2016).In 1987, the treatment with zidovudine commenced, which led to discovery of more Nucleoside reverse transcriptase inhibitors (NRTIs) like Stavudine, Zalcitabine and Didanosine which were also used in the HIV therapy(Hassan et al., 2017).The major adverse effects of zidovudine were neutropenia,anaemia, myositis, nausea and vomiting leading to reduction in the life expectancy of patients(Mondal, 2016).In 1996, there was introduction of new class of drugs known as non-nucleoside reverse transcriptase inhibitors (NNRTIs). Nevirapine was the first drug to be approved.When given in combination with zidovudine and lamivudine in a triple therapy, it showed maximum effect by increasing the number of T-lymphocytes(Vitoria et al., 2019).

2.8Current treatment regimens

Current drugs that are available for this treatment do not completely eradicate HIV infection but prolonged treatment is improvised.Eight protease inhibitors (atazanavir, ritonavir, lopinavir, saquinavir, darunavir, fosamprenavir, tipranavir, nelfinavir) prevent the maturing of virions results in the production of non-infectious particles (Burger et al., 2019).

1. Nucleoside reverse transcriptase inhibitors (NRTIs)

They are similar to the building blocks that the virus requires in order to be able to replicate.These drugs include Abacavir, emtricitabine, tenofovir, lamivudine, and zidovudine(Koibuchi, 2013).

Mechanism of action: They inhibit HIV replication by competitive inhibition of HIV reverse transcriptase and termination of the DNA chain(Nikolenko et al., 2005).Reverse transcriptase is an enzyme (DNA polymerase) which allows HIV RNA to be transcribed into single and double stranded proviral DNA(Holec et al., 2017).

Adverse effects: The adverse effects of NRTIs includeLactic acidosis, hepatic steatosis , lipodystrophy , elevation in amylase and liver function test , rash , kidney failure , diarrhoea and many other (Mills et al., 2016).

2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

These cause disturbances in the protein that is required by the virus in order to replicate.Examples of these drugs are efavirenz, etravirine and nevirapine.

Mechanism of action: They interfere with reverse transcription by directly binding with the enzyme and disrupting its function(Nikolenko et al., 2010).

Adverse effects: Headache, nausea, dizziness , vivid dreams and insomnia(Brinkman et al., 1998).

3. Integrase inhibitors

There is a protein known as integrase which is required by the HIV in order to incorporate its genetic material into the CD4 cells.These include raltegravir and dolutegravir(Pommier et al., 2005)

Mechanism of action: The integrase enzyme incorporates viral DNA into the host genome. Integrase binds to viral DNA and joins it with host DNA,integraseinhibitors prevent the formation of covalent bonds with host DNA.This prevents incorporation of HIV into the host genome.(Garg and Ko, 2014).

Adverse effects: Headache, mood swings, bad dreams, insomnia,fatigue,dizziness, muscle pain (Lepik et al., 2018).

4. Protease inhibitors

HIV requires a protein known as protease in order to replicateeg.atazanavir, darunavir, indinavir, ritonavir(Tapp Alter, 2001).

Mechanism of action: They inhibit the action of enzyme viral protease which prevents proteolytic break down of HIV gag andpolyproteins which are important parts on the structure of the HIV virus (Scholar, 2007).

Adverse effects: Insulin resistance, high blood sugar levels , high cholesterol levels,liver problems , nausea , changes in food tastes(Naggie and Hicks, 2010).

5. Fusion inhibitors

The fusion inhibitors prevent the HIVfrom entering into the CD4 cells. These include maraviroc, enfuvirtide(Koibuchi, 2013).

Mechanism of action: A fusion inhibitor blocks the HIV envelope from combining with the host CD4 cell membrane (fusion).This results in prevention of HIV from entering the CD4 cell(Qadir and Malik, 2010).

Adverse effects: Pain , redness , itching ,nerve pain , numbness , pricking , burning sensation, paraesthesia (lasts up to 6 months)(Jing et al., 2005).

2.9Recent pharmaceutical interventions in the treatment of HIV/AIDS.

Despite not finding the cure for HIV there has been a number of pharmaceutical interventions in recent years for prevention and treatment of HIV.

2.9.1 Interventionon the maturation of HIV-1 Virus

Maturation is the last step in the lifecycle of HIV -1 virus and in this stage there are two known events that occur(Salzwedel et al., 2007).One class being protease inhibitors (PI) which inhibit the enzymatic activities of the viral protease these drugs include ritonavir, lopinavir, atazanavir, saquinavir and nelfinavir(Tapp Alter, 2001). These drugs are already in use and have been utilized in the maintenance therapy of HIV. Bevirimat is the drug from this class which was undergoing clinical development but recently it showed that some strains of HIV-1 were resistant to this drug(Bedoya et al., 2018).Despite some strains of viruses being resistant to bevirimat the information obtained like mechanism of action has led to development of new drugs like vivecon which is able to show effect in the bevirimat resistant strains(Wang et al., 2015).

2.9.2 Nanotechnology based systemsfor treatment and preventionof HIV

There has been recent advances in the drug delivery, the drugs are delivered in forms of nano particles(das neves et al., 2010).These enhance the drug delivery because decreased particle size results in an increase in bioavailability.These nanosystems are also improvised in vaginal microbicides and vaccines(Kumar et al., 2015).The main nanotechnology based systems used for HIV therapeutics are Liposomes, nanoparticles,niosomes, polymeric micelles and dendrimers.When the current anti-retroviral drugs are formulated as nano particles their

pharmacological effect is modified(Parboosing et al., 2012).By delivering the anti HIV nucleic acids to the HIV reservoirs creating a targeted drug delivery system.While delivering drugs to HIV reservoirs these exhibit minimum toxicity(Cao and Woodrow, 2019).

Mechanism of drug release: Once the nanosystem reaches the site of action the drug will be released and there will be increased drug concentration on targeted site with increased residence time which enhances the anti-viral effect of the drug. These drugs include lamivudine,stavudine,zidovudine , emtricitabine , tenofovir and many others(Grande et al., 2019).

2.9.3 Effect of metformin on the reservoir of HIV in non-diabetic patients.

Metformin is the drug that is used in treatment of diabetes type 2. There is the persistence of HIV in the long lived CD4 cells which results in the formation of major HIV stores. Among the strategies that have been under investigation, metformin is a very popularly used anti-diabetic drug that has been discovered to possess the abilities to decrease the size of the reservoirs and thereby reduction of inflammation. This changes the composition of microbes in the gut thereby reducing inflammation (Routy et al., 2019).

2.9.4 Oral Cannabinoids as an effective anti-retro viral therapy

Usually patients on anti-retro viral therapy are prone to chronic inflammation.This also plays a role in persistence of the HIV virus in the body of patient on ART.Cannabis can be taken to reduce this inflammation and also improve the disease resistance of the immune system (Costiniuk et al., 2019).Mostly HIV is associated with peripheral neuropathy. Marijuana is known to alleviate this condition.Peripheral neuropathy occurs when the exterior sheath covering the nerve cells is stripped away.The types of peripheral neuropathy associated with HIV include distal symmetric polyneuropathy which is the most common and Inflammatory demyelinating polyneuropathy. Distal symmetric neuropathy causes numbness , weakness and tingling.Inflammatory demyelinating polyneuropathy is can either be acute or chronic.In this type there is inflammation of the root of nerves and destruction of peripheral nerves (Lewis et al., 2017) .

Conclusion:

In the recent, various pharmaceuticalinvestigation have come over in the treatment of HIV/AIDS. Such as the drugs were formulated as nano systems which include liposomes, niosomes, dendrimers, solid lipid particles and many others. Recent studies have shown already existing drugs like metformin which is used to treat diabetes type 2 can be used in ART as it reduces the

reservoirs of HIV. Cannabinoids can also be used to decrease inflammation in HIV patients as they are prone to chronic inflammation. Thus, use of these cannabinoids suppresses the inflammation. All these interventions have played a major role in the maintenance and treatment of HIV.

Conflict of interest: There is no conflict of interest.

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