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Antiretroviral therapeutics with different mechanisms of action on HIV infection.

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ABSTRACT

This review is devoted to showing different approached to HIV/AIDS therapy from the point of variability of different chemical structures utilized for the therapy of HIV infection and also in newer attempts to prevent this infection. In the introductory part, the mechanism of HIV infection and life cycle of the virus in the host cell is a briefly summarized. After that, classification of anti-HIV drugs is discussed according to their mechanism of action. The main groups are the following: Nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, fusion inhibitors, integrase inhibitors, protease inhibitors, and chemokine receptor antagonists. A typical example of each of the therapeutic group is given and discussed. The representative agents are Atazanavir, Abacavir, Delavirdine, Raltegravir, Enfuvirtide and Maraviroc. Obviously, the use of these drugs is affected by various factors, such as age, HIV RNA load, CD4+ count, pregnancy, drug resistance etc. Additionally, the use of anti-HIV drugs for HIV prophylaxis is outlined briefly. Adverse side effects of anti-HIV drugs differ in severity from one patient to another and their discussion is also included.

Keywords: HIV; antiretroviral therapy; reverse transcriptase inhibitors; fusion inhibitors; integrase inhibitors; protease inhibitors; chemokine receptor antagonists.

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INTRODUCTION

Human immunodeficiency virus (HIV) is a chronic state of infection that increases the level of cytokines and inflammation in the body. Today, an estimated 35 million people have been infected with HIV globally. Every year, 2.1 million become infected with HIV and an estimated 1.5 million people die from AIDS [1]. Consequently, there is a significant increase in numbers of people infected. This prompts doctors and biomedical scientists to investigate new ways to lessen the burden of HIV infection using safer therapeutics. Significant advances have been made in antiretroviral therapy since 1987 [2] and this effort continues at present time [3]. The Middle East and North Africa region has HIV prevalence rates of 0.1 percent which is one of the lowest rates of the world. However, between 2001 and 2012, HIV infected people increased by 73 percent, the world's fastest growing HIV epidemics [1].

As a response to this situation, tremendous effort was put into developing new drugs and combinations of these drugs for the benefit of HIV patients. This development was supported by better knowledge and understanding of mechanism of HIV infections. The aim of this work is to review modern anti-HIV therapeutics through illustration of their different mechanisms of action against at different stages of HIV infection on representatives of various therapeutic subgroups.

THE GENERAL MECHANISMS OF HIV INFECTION AND SUBSEQUENT AIDS DEVELOPMENT

STRUCTURE OF HIV VIRUS

HIV is a relatively large (120 nm) RNA virus that belongs to the family of human retroviruses and the subfamily of lentiviruses. HIV is subdivided into two types, HIV-1 (HIV-1A, B, C, D, F, G, H, J, N, O subtypes) and HIV-2 (HIV-2A and B subtypes). While HIV-1 is globally more common and easier to transmit, HIV-2 is mostly found on the west coast of Africa [2].

HIV virions are formed by a viral glycoprotein-containing envelope and a matrix that encloses a capsid enveloping two copies of the single-stranded RNA and enzymes required for HIV replication (reverse transcriptase, integrase and protease) [2,4].

THE MECHANISM OF HIV INFECTION

Like all viruses, HIV replicates using the genetic material of the infected cell. The attack on the host cell proceeds after inoculation of a host with biological fluid (e.g. blood, blood products or sexual secretions) containing HIV virus, During entry, the major target for HIV binding is the CD4 receptor present on helper T lymphocytes, which activate and coordinate other cells of the immune system, and also to a co-receptor, generally the chemokine co-receptors (e.g. CXCR4 –CXC motif chemokine receptor type 4 or CD184 (cluster of differentiation 184)). This binding induces irreversible conformational changes [5]. After that transmembrane protein - glycoprotein 41 (gp41, a subunit of the envelope protein complex of retroviruses) is involved in the fusion of virus and the host cell lipid bilayer taking place within a span of several minutes. Following fusion, viral RNA is released into the host cell and is converted to complementary DNA (cDNA) by HIV viral reverse transcriptase. It was demonstrated that the HIV reverse transcriptase is prone to errors, mutations are quite common to happen [6]. These mutations increase HIV resistance to the host immune system and make it difficult to control by a host organism. The cDNA enters the cell's nucleus and then is integrated into the cell's DNA by a viral enzyme called integrase. The process continues through transcription to messenger RNA and translation to structural proteins that are needed to assemble and form new infectious HIV. The new virus buds through the membrane of the infected cell to the outside. Then, the budded virus must mature and another HIV enzyme - HIV protease - cuts structural proteins in the virus, causing them to rearrange [5,7]. Eventually, the infected cell is destroyed. This leads to production of thousands of new viral particles capable of infecting and destroying other cells. Massive viral replication occurs in the four to eight weeks immediately after HIV infection [5].

AIDS DEVELOPMENT

Within a few days or weeks, the blood and genital fluids contain a very large amount of HIV, and the number of CD4+ lymphocytes decreases (4-8 weeks after infection). When the CD4 lymphocyte drops below

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200 cells/mm^3 (200 × 10^6/L), the host become susceptible to opportunistic infections, such as *Pneumocystis jirovecii* pneumonia and tuberculosis, or malignancies, e.g. Kaposi's sarcoma and lymphoma (Appendix A). However, the period of relatively good health usually lasts from 5 to 12 years. Susceptibility to opportunistic infections defines the later stages of HIV-1 infection, known as acquired immunodeficiency syndrome (AIDS) [8].

A BASIS OF THE ANTI-HIV DRUGS USE: MECHANISMS OF ACTION

The development and production of anti-HIV medications, HIV infection became controllable chronic disease in patients who are administered these medicines. Anti-HIV drugs provide effective treatment choices. Many opportunities for effective anti-HIV1 therapeutic intervention exist within the viral life cycle. However, only six classes of anti-HIV drugs are used currently:

A) Nucleoside reverse transcriptase inhibitors,
B) non-nucleoside reverse transcriptase inhibitors,
C) fusion inhibitors,
D) integrase inhibitors,
E) protease inhibitors, and
F) chemokine receptor antagonists.

Each class is effective at a different and specific stage of viral infection during the glycoprotein CD4 (cluster of differentiation 4) targeting on the surface of T lymphocytes and other recipient cells [9].

The aim of the following information is to illustrate similarities and differences among different classes of anti-HIV therapeutics. Table 1 documents the fact that all of the selected representative antiretroviral drugs, with the exception of the fusion inhibitor Enfuvirtide, are small but complex molecules of aromatic nature containing not only nitrogen-containing heterocycles but also groups similar to peptide bonds, such as carbamate or carbamide functional group. This is important for peptide interaction. (Abacavir serves as a nucleic acid antimetabolite. Consequently, it is a nucleoside analog.)

Table 1: Summarization of the representative anti-HIV (antiretroviral) therapeutics

Group	Drug	M.W.	Type of the molecule	Mechanism of action
NRTIs	**Abacavir**	286.33	A synthetic carbocyclic	Inhibition of reverse transcriptase
			purine nucleoside analog	
NNRTIs	**Delavirdine**	456.19	A methanesulfonic acid derivative	Inhibition of reverse transcriptase
Fusion	**Enfurvirte**	4491.87	A synthetic peptide	Fusion/entry inhibitor targeting the hydrophobic
inhibitors				pocket in the HIV-1 gp41 N-terminal
Integrase	**Raltegravir**	444.42	carbamoyl, oxopyrimidin,	HIV integrase inhibitor / integrase strand transfer
inhibitors			oxadiazole and carboxamide-	inhibitor
			containing molecule	
Protease	**Atazanavir**	704.86	Carbamate	Inhibition of viral polyprotein processing
inhibitors				
Chemokine	**Maraviroc**	513.67	Azabicyclo carbamide	Interaction with chemokine receptor CCR5
receptor				
antagonists				

A. Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs represent the first class of drugs that been approved by the Food and Drug Administration (FDA) as anti-HIV therapeutics. NRTIs as such are prodrugs and require phosphorylation by cellular kinases to become active [10]. Members of this group competitively prevent HIV reverse transcriptase enzyme and act as DNA synthesis sequence terminators [11]. The viral DNA is stopped because the structural changes of

integrated nucleotide analogs. Missing functionality, i.e. missing 3'-OH group, prevents the 5' to 3' phosphodiester connection necessary for DNA sequence elongation.

HIV resistance occurs through nucleotide associated mutations that remove NRTIs from the 3' end. The FDA approved NRTIs are: Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Zalcitabine, Zidovudine, and Tenofovir disoprovil fumarate [12].

B. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTIs inhibit HIV-1 by directly binding to the enzyme - reverse transcriptase. NNRTIs blocks polymerization through allosteric regulation by changing the position of critical components within the catalytic location of the reverse transcriptase enzyme. This leads to inhibiting an essential step in viral replication [13]. Unlike NRTIs, these noncompetitive inhibitors do not inhibit the reverse transcriptase of other lentiviruses, such as simian immunodeficiency virus (SIV). Additionally, unlike NRTIs, these molecules do not require metabolic activation through phosphorylation of the 5' nucleoside hydroxyl group to form a biologically active nucleotide. The currently approved NNRTIs are Etravirine, Delavirdine, Efavirenz, and Nevirapine [12].

C. Fusion inhibitors

The fusion inhibitors stop the interaction of the two domains in the viral glycoprotein gp41 with each other. These drugs are designed to mimic one of the domains thus disturbing the intra-molecular interactions of the virus protein. They are peptides with significant antiviral activity against HIV-1. HIV mutations may occur in gp41 leading to the failure of therapy. Monotherapy with fusion inhibitors causes viral loads rebound after two weeks of therapy because of these mutations. Rational design of this type of inhibitors ultimately produced a molecule, Enfuvirtide, with potent antiviral activity in vivo [12].

D. Integrase inhibitors

These drugs block the integrase HIV enzyme by attaching themselves to the integrase-viral DNA complex making this class the only one in anti-HIV drugs that bind with two essential elements of the virus: the integrase enzyme as well as the viral DNA [14]. These inhibitors interact with the two essential magnesium metal ions in the integrase active site and also the DNA. As a result the integrase inhibitors contain two essential components which are a metal-binding pharmacophore for the active site magnesium, and a hydrophobic group for the viral DNA. This leads to preventing HIV from augmenting which can reduce the amount of HIV in the body. Mutations on the integrase active site have damaging effects on enzymatic function and viral replicative capacity. Raltegravir is an Integrase inhibitors that was tentatively FDA approved in 2007 [12, 15].

E. Protease inhibitors

HIV-1 protease is essential for viral infectivity. Its mechanism of action is based on cleaving specific polyprotein precursors during viral maturation. It was shown that cellular proteins can also be cleaved by protease. This may be a base of a viral strategy to counter host defense mechanisms. Protease inhibitors hinder the action of HIV protease through selective binding and blocking proteolytic cleavage of protein precursors essential from the production of infectious HIV particles. Consequently, the amount of viruses in the viral loads decreases because of the inhibition of protease [16]. The drugs approved by FDA are Amprenavir, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir, Simeprevir and Tipranavir [12].

F. Chemokine receptor antagonists

Antagonists of chemokine receptor CCR5 bind to the hydrophobic pockets within the trans-membrane helices of CCR5. This binding promotes a receptor conformation that is not recognized and blocks the binding to HIV-1 envelope [12]. Maraviroc and Aplaviroc have been shown to inhibit virus replication in human HIV-infected patients [17]. The compound Maraviroc was approved for therapeutic use by the FDA in 2007. CXCR4 is another chemokine receptor for HIV-1 but the development of CXCR4 antagonists fail in clinical

studies [12]. Potential resistance mechanisms for chemokine receptor antagonists include binding to CXCR4 instead of CCR5 [12].

PROPERTIES OF REPRESENTATIVE ANTI-HIV THERAPEUTICS.

(Chemical formulas and other data on properties of the representative anti-HIV therapeutic were all retrieved from PubChem database, National Center for Biotechnology Information, National Institute of Health, USA [18]. See the summarization of properties of the selected antiretroviral therapeutics in Table 1.

A. NRTIs: Abacavir

Abacavir (Fig. 1A) is a synthetic purine (guanosine) nucleoside analog with cyclopropyl substituent at the nucleoside base. The sugar moiety of natural nucleosides is replaced by 2,3-cyclopentene thus creating an artificial carbocyclic nucleoside. Abacavir requires phosphorylation of its hydroxyl group to be incorporate into viral DNA. The phosphorylated Abacavir competitively inhibits the HIV reverse transcriptase enzyme and serves as a DNA chain terminator. It is a strong reverse transcriptase inhibitor.Therapy with Abacavir leads to a decreases of HIV loads and delays or prevents the damage to the immune system. This reduces the chances of developing AIDS [19].

Abacavir was approved as an anti-HIV drug by the FDA in 1998. Is used as a component of antiretroviral therapies. When used as monotherapy, the loss of response to the therapy occurs [19].

Toxicity had been studied in animals which a group of mice and rat have been given a range of 6 to 32 times the human recommended dose of Abacavir orally for two years. The results revealed an increase in the occurrence of malignant and non-malignant tumors in the preputial gland of males and in the liver of female rats [20].

Abacavir is highly effective anti-HIV drug. However, around 5% of patients suffer from immune-related hypersensitivity reaction causing immediate interruption of the therapy. Consequently, other different therapeutic antiretroviral regimen has to be utilized. Hypersensitivity reaction in Abacavir-treated patients is associated with a specific in the structure of the leukocyte antigen B (HLA-B) gene [21].

Comprehensive toxicity data in humans are not available. The commonly reported adverse reactions of at least moderate intensity with incidence ≥ 10 % in adult HIV-1 clinical trials were nausea, headache, malaise and fatigue, nausea and vomiting, and dreams and sleep disorders. **Abacavir may cause a serious allergic reaction, lactic acidosis (accumulation of lactic acid in the blood) and consequently liver problems [20].**

B. NNRTIs: Delavirdine

Delavirdine (Fig. 1B) was approved in the USA by the Food and Drug Administration (FDA) in 1997 for the use to be used as a medication for treating HIV infection in patients above sixteen years. It structure is interesting as it includes a methanesulfonic acid functional group [22]. Drug resistance develops fast if Delavirdine is administered as a monotherapy and thus it should always be administered as part of a combination treatment. In humans, toxicity of this drug was reported as skin rash. However, animal studies among rats, mice, rabbits, dogs, and monkeys to observe the effects following the administration of high doses Delavirdine. The most significant toxicity found was necrotizing vasculitis. It happened when the serum concentrations of Delavirdine were at least 7-fold higher than the recommended dose. Other major organs that can be affected in these animals include the liver, bone marrow, kidneys, gastrointestinal tract, lymphoid tissue, lung, endocrine organs, and reproductive organs [23].

Delavirdine (and other first-generation NNRTIs - Nevirapine and Efavirenz) possesses a low genetic barrier and poor resistance profile. This stimulated the investigation of new generations of NNRTIs of this type. Some of the second-generation NNRTIs have been approved by the FDA and others are currently being investigated for their clinical use [24].

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C. Fusion inhibitors: Enfuvirtide

Enfuvirtide is an HIV-1 fusion inhibitor approved by FDA in 2003. It is indicated for combination therapy with other anti-HIV agents in patients who are on the anti-retroviral therapy for prolonged time. It is a linear 36-amino acid synthetic peptide (Fig. 1C) with the N-terminus acetylated and the C-terminus is a carbetamide [25]. Enfuvirtide targets the hydrophobic pocket in the HIV-1 gp41 (the transmembrane subunit of envelope glycoprotein) N-terminal. FDA approved by for being the first HIV fusion/entry inhibitor for treatment of HIV/AIDS patients failing to respond to other currently used antiretroviral drugs [26]. However, Enfuvirtide exhibits low anti-HIV-1 activity because of drug resistance and cross-reactivity with preexisting antibodies in HIV patients [26] and short half-life [27].

Results of long-term animal toxicity studies of Enfuvirtide are not available and data on its toxicity in the human are limited [28].

D. Integrase inhibitors: Raltegravir

Raltegravir (Fig. 1D), the first generation integrase inhibitor, is an aromatic substance containing two heterocycles in its structure [29]. It interferes with the function of integrase - the HIV enzyme integrating the viral genetic material into host chromosomes. This is a very critical step of HIV pathogenesis [29].

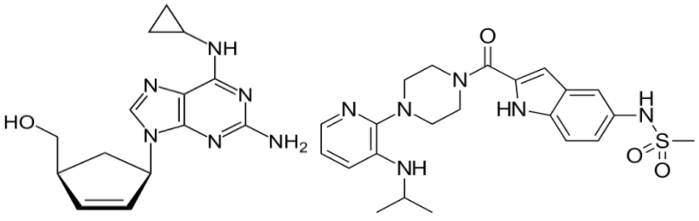
A randomized study investigating the effects of high concentrations of Raltegravir in plasma found no severe effect [30]. No evidence of mutagenicity or effect on fertility was observed in animal toxicology studies [30]. Raltegravir was recommended by FDA for combined HIV therapy in 2007. It seems to be important that this drug is active against both HIV-1 and HIV-2 [30]. Raltegravir is suitable for therapy of new HIV patients but also of patients that underwent previous antiretroviral treatment [31,32]. Raltegravir cross-resistance properties stimulated the introduction of Dolutegravir, a second generation integrase inhibitor, possessing efficacy, excellent tolerability and infrequent drug-drug interactions [33].

E. Protease inhibitors: Atazanavir

The FDA approved the Atazanavir (Fig. 1E) in 2003 to be used in therapy with other HIV medicines in both adults and children. Atazanavir is an HIV-1 protease inhibitor preventing the formation of mature virions through the strong and selective inhibition of viral polyprotein processing in HIV-1 infected cells [34,35]. (The role of HIV protease is to cleave newly synthesized polyproteins helping to create mature protein components of fully functional HIV virion [34].) Atazanavir is normally taken with Ritonavir [35]. However, recent data indicate that changing the patients with achieved virological suppression from retroviral-boosted-by-Ritonavir-therapy to Atazanavir improves safety (decrease of abnormalities in blood parameters) without a sacrifice of virological efficacy [36].

F. Chemokine receptor antagonist: Maraviroc

Maraviroc (Fig. 1F) is a prescription drug approved by the FDA in 2007 for treatments of HIV infection in adults [37]. Maraviroc as an anti-HIV drug is selective small molecule antagonist of the interaction between HIV-1 and chemokine receptor 5, CCR5. Chemokines and their receptors regulate the trafficking of leukocytes in hematopoiesis and inflammation. Consequently, they are essential for the immune integrity of the host. Maraviroc is the first clinically used CCR5 antagonist. However, the drug should be specifically used only in the patients infected with HIV strain containing CCR5 receptor [38]. It was demonstrated that the Maraviroc-containing antiretroviral therapeutic regimes are possessing high effectivity. Additionally, these therapeutic regimes are safe for R5-tropic HIV patients [39].



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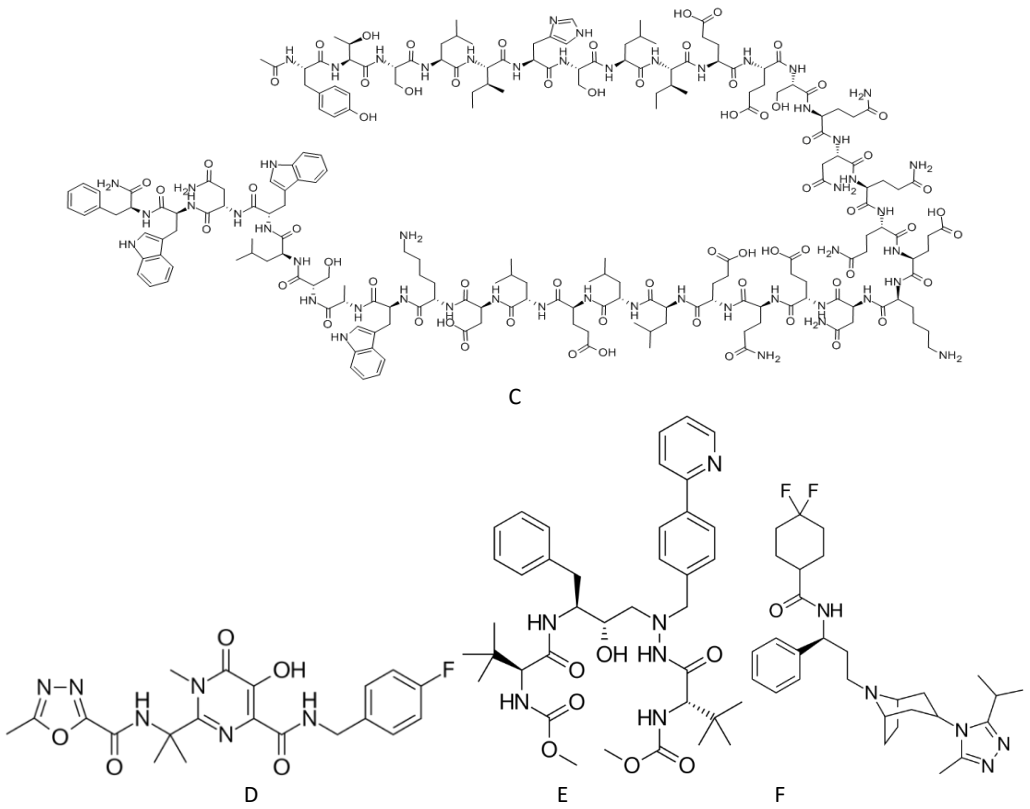

Fig 1. Chemical structures of representative anti-HIV therapeutics (also available at PubChem 2015; [18]).

A – Abacavir (NRTI); B – Delavirdine (NNRTI); C – Enfuvirtide (fusion inhibitor); D – Raltegravir (integrase inhibitor); E – Atazanavir (protease inhibitor); F – Maraviroc (chemokine receptor antagonist).

FACTORS AFFECTING THE USE OF ANTI-HIV THERAPEUTICS

There are some essential factors that need to be considered when selecting the optimal anti-HIV drug therapy. These factors include mainly characteristics of the patient, patient's comorbidities and some specific properties of the considered drugs [40].

Age is an important patient's characteristic factor that been studied to know its effect on antiretroviral drug therapy. Many pieces of information were accumulated so far. For example, Abacavir safety and effectiveness were established in HIV infected children 3 months to 13 years of age HIV [20]. Atazanavir is indicated as a combination therapy with other antiretroviral drugs in patients of 3 months of age or older with the body weight at least 10 kg. However, Atazanavir is not recommended for younger children (less than 3 months) as it may cause kernicterus (a bilirubin-induced brain dysfunction [35]. Raltegravir was assessed and found to be safe and effective in patients from 4 weeks to 18 years of age in an open-label multicenter clinical trial called IMPAACT P1066 [30]. On the other hand, HIV infected people older than 65 years were not included in clinical studies. Consequently, the effects on the use of antiretroviral therapy in this age group is not known. Besides age, HIV RNA load, CD4 cell count and patient anticipated adherence play an important role in effecting the use of antiretrovirals. It is necessary to underline the importance of adherence as a missed dose could lead to a treatment failure. When adherence is interrupted, it may lead to drug resistance and an increased viral RNA load. Also, patient comorbidity such as pregnancy or renal impairment should be considered before the start of treatment. As for pregnancy, Abacavir have shown to cause fetal malformation in animals and is classified as category C for humans. Thus, Abacavir is used in pregnant women with HIV only when benefits outweigh the risk according to the doctor [20]. In addition, Delavirdine is also classified as the category C drug because it is teratogenic in rats. In a pre-marketing clinical study in which 9 pregnant women were given Delavirdine, eight of the infants were born healthy and one infant was born HIV-positive [23]. Raltegravir is also classified as the category C drug. So far, study was conducted in pregnant patients [30]. Maraviroc [38] and Atazanavir [35] are classified as the category B drugs for the purpose of the use in

pregnancy. This means that they are used only in patients, for which benefits of antiretroviral therapy outweigh the risks. Anti-HIV drug specific potential adverse effects should be considered before starting the therapy (Table 2). Additional consideration for applying anti-HIV therapy are the dosing frequency of the anti-HIV drugs and availability of fixed-dose combination products as both of these influence the use of these drugs by a patient. Cost is an important factor in anti-HIV therapy as the therapy is for life. Impact of these drugs cost effect not only the infected HIV people but also the countries.

Table 2. Specific adverse effects of the representative drugs discussed in the review. (Adapted from references [20,23,28,30,35,38]).

Drug	Adverse Effect
Abacavir	**The most common side effects in adults:** • Bad dreams or sleep problems • Nausea and vomiting • Headache • Tiredness **The most common side effects in children:** • Fever and chills • Nausea and vomiting • Rash • Ear, nose, or throat infections
Delavirdine	**Most common side effects:** • Fatigue • Rash • Lipid abnormalities • Nausea • Diarrhea • Lipodystrophy
Enfuvirtide	**Most common side effects:** • Erythema or injected site reaction • Neutropenia • possible increased frequency of pneumonia **Less common side effects:** • Pain and numbness in feet or legs • Loss of sleep • Depression • Decreased appetite • Enlarged lymph nodes
Raltegravir	**Most common side effects:** • trouble sleeping • headache • dizziness • nausea • tiredness **Less common side effects:** • depression • kidney failure • kidney stones
Atazanavir	**Most common side effects:** • Rash • Hyperbilirubinemia • jaundice • Liver function tests elevated • PR interval prolongation
Maraviroc	**Most common side effects:** • Diarrhea, nausea • Elevations in liver function tests, • Upper respiratory tract infections, • Fatigue, dizziness, headache • Joint and muscle pain

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THE EVIDENCE OF USEFULNESS OF ANTI-HIV THERAPEUTICS AS PROPHYLACTIC AGENTS AGAINST HIV INFECTION

To decrease the risk of HIV infection, a method of treatment as prevention of HIV infection by using antiretroviral/anti-HIV drugs was developed. Anti-HIV drugs reduce the viral load in the body fluids (blood, semen, vaginal fluid and rectal fluid) to very low levels, thus reducing an individual's risk of HIV transmission [5,8]. In 2011, a study called HPTN 052 revealed that early initiation of anti-HIV drugs for the HIV-positive partner in a serodifferent couple reduced HIV transmission to the HIV-negative partner by 89% [41].

The prophylactic methods may be divided into three groups: prevention of mother-to-child transmission, pre-exposure prophylaxis and post-exposure prophylaxis.

Prevention of mother-to-child transmission

The rate of HIV transmission from the infected pregnant woman without treatment to her child is 15 to 45% [42]. Zidovudine, a NRTI, has been used to prevent HIV transmission from mother to child since the mid-1990s. Research has found that when Zidovudine is given to HIV-infected pregnant women, it reduced transmission to the child from 45 to 8%. Since then, studies devoted to treatment of HIV-positive mothers with anti-HIV drugs during pregnancy shown to reduce the risk of transmitting HIV to less than 5%. Significant level of the HIV infection transfer from a mother to her child was reported as early as 1994. The decrease in transmission of HIV infection reported was 2/3rds when antiretroviral therapy has been given to pregnant women for the period of 14 days [43]. More recent investigations report perinatal HIV transmission at 6 weeks of child's age to be 2.7%. Failure to diagnose a mother with HIV infection before delivery is the main cause of missing to administer HIV transmission prophylaxis [44]. Currently, some studies are raising concern regarding the safety of the fetuses that are exposed to anti-HIV drugs. Adherence to the therapeutic protocols by mothers represents another critically important challenge. It is critical to carefully evaluate both short- and long-term effects of antiretroviral therapy on mothers and children [45].

Pre-exposure prophylaxis (PrEP)

It is an HIV prophylactic method that uses anti HIV therapy to protect HIV-negative people from being infected during their exposure to the virus. It is targeted toward people with high risk of HIV transmission, such as homosexual men, young women and drug-abusers using injections [46]. Although it has not been documented in humans, there is some concern about the possibility that this strategy may increase the likelihood of developing HIV resistance to the drug that has been used. The researchers have found that in monkeys, to whom a protease inhibitor drug Tenofovir was administered, an occurrence of a mutation leading to an HIV drug resistance took place [47]. Adherence to the prophylactic pre-exposure regime of anti-HIV drugs reduced the risk of HIV transmission by up to 92%. Despite the fact that pre-exposure prophylaxis has potentially population-wide benefits, the majority of countries cannot afford to implement this method due to the resources constrain [46].

Post-exposure prophylaxis (PEP)

The post-exposure prophylaxis is short-term intervention, during which anti-HIV drugs are taken for a month after possible exposure to HIV. It provides the immune system with the chance to protect the organism against HIV infection and prevent HIV from becoming established there. Post-exposure is very important and useful for healthcare staff members who may have been exposed to HIV-infected fluids. Additionally, it has been recommended later to give those who may have been exposed to HIV during a single event such as sexual assault or sharing drug injecting equipment. It is important that new guidelines are being introduced with the hope of achieving improved success in the post- (and also pre-) exposure prophylaxis of HIV infection [48, 49].

There are several factors that may lead to failure of post-exposure prophylaxis. The effectiveness of the post-exposure prophylaxis may be compromised when the initiation of the prevention is delayed beyond 72 hours of exposure to HIV or when the source of the potential HIV infection is drug resistant [50].

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THE POTENTIAL ADVERSE EFFECTS OF ANTI-HIV THERAPEUTICS

Like most drugs, anti-HIV drugs can cause unwanted side effects that are often mild. However, sometimes these side effects are more serious and affect quality of life. Rarely, they can be life threatening. Because these drugs have to be taken every day for life without missing a dose, it is important to reduce the impact of side effects by treating them or switching to alternative drugs. It is well known that side effects vary from person to person and it is unpredictable how each individual will be affected. Some people take anti-HIV drugs for years with hardly any problems, while others cannot tolerate the same drugs. The most common side effects that are seen in antiretroviral drugs diarrhea, nausea and vomiting, rash, lipodystrophy and lipid abnormalities [51].

Diarrhea

Diarrhea is a side effect for many anti-HIV drugs but the incidence of diarrhea is especially high with protease inhibitors. A study has revealed that 60 % of people living with HIV complain of diarrhea [52]. Diarrhea could occur during the first few weeks of treatment only or may last for as long as the drug is taken. Also, the severity of diarrhea differs from tolerable to inconvenient and persistent. It may lead to several complications, such as dehydration, poor absorption of nutrients and drugs, weight loss and fatigue. There is no recommended drug therapy for this form of diarrhea in HIV positive patients. Therefore, to reduce the severity of the diarrhea, it is recommended to change the diet by drinking plenty of fluids and eating bananas, potatoes, fish or chicken. If it's very severe, then changing drugs may be the best option [53,54]. Advances in treating antiretroviral therapy/HIV-associated diarrhea includes a development of new antisecretory agents, i.e. Crofelemer [55].

Nausea and vomiting

Almost all anti-HIV drugs cause nausea and vomiting during the first few weeks of treatment. It is necessary to keep eating and drinking despite suffering from these side effects. Eating several small meals and avoiding spicy and greasy food, alcohol, aspirin and smoking may help to relief the nausea and vomiting. Also, anti-emetics could be taken to lessen these side effects. If the nausea and vomiting occur accompanied with additional symptoms (dizziness, thirst, fever, muscle pain, diarrhea, headache or jaundice), more serious problems, e.g. lactic acidosis or pancreatitis need to be considered. In this case, stopping the drug and changing it to an alternative antiretroviral agent seems to be the best option [54].

Rash

Rashes often appear as itchy but are usually short-lived and harmless. However, with some drugs, such as Abacavir, the rash could be very dangerous hypersensitivity reaction [54]. Any rash that occurs during the first few weeks of treatment with anti-HIV drugs should be reported immediately, as well as, if it accompanied by fever, blistering, facial swelling or aches. To relive the rash, it is advisable to avoid hot showers, humidify the air and try moisturizers or calamine lotion. Antihistamine tablets can be given but interaction with antiretroviral agents may occur. In severe cases, it is necessary to use steroids for the rash treatment [54].

Lipodystrophy

Lipodystrophy is a condition associated with long-term side effects of anti-HIV drugs. The body loses or accumulates fat that often could be disfiguring and stigmatizing. Lipodystrophy occurs more often with the use of NRTIs (such as Stavudine and Zidovudine) and protease inhibitors. The particular lipodystrophy manifestations are either losing fat on the face, arms, legs and buttocks, or gaining fat deep within the abdomen, between the shoulder blades, and on the breasts. In some cases, a mixture of fat gain and fat loss may be observed [56]. Currently, the treatment for lipodystrophy is limited and changing the diet makes no significant difference. However, weight lifting exercises may improve for the lost fat by building muscle to compensate. Switching to other anti-HIV drugs may stop the symptoms of getting worse. However, once the condition has advanced, is unlikely to lead to much improvement [54].

Lipid abnormalities

Lipid abnormalities are common side effect of antiretroviral therapy. They are more severe in the patients taking protease inhibitors and in patients with the lipodystrophy. HIV patients usually suffer from high levels of a low density lipids (LDL), low levels of high density lipids (HDL) and increased levels of cholesterol and of high levels of triglycerides in the blood. These lipid abnormalities have been associated with greater risks of cardiovascular disease, stroke and diabetes. Treating lipid abnormalities in an HIV-negative person is attempted through the lifestyle and diet changes. However, in patients with HIV dieting may jeopardize building/retaining muscle mass. Statins and fibrates are prescribed to improve lipid profiles in HIV patients [54].

NEW DEVELOPMENTS OF ANTI-RETROVIRAL THERAPY

The development of new anti-HIV drugs and new therapeutic measures depends on particular goals and on adequate resources and technology. Investigators use the rational design to produce or improve new drugs that are more effective at controlling HIV with less side effects and less resistance development. Various project concentrate on the developments of new anti-HIV drugs, non-anti-HIV drugs benefiting the HIV-infected patients, on targeting latent HIV and, in some extent, on gene therapy.

Selected new antiretroviral drugs currently in clinical trials

The majority of new drugs belong to the drug classes that are currently utilized for HIV therapy. The new drugs are being investigated with the goal of developing new agents that would be superior to the currently used medications. The effort of scientists and clinicians currently concentrates on development of new NRTIs, protease inhibitors, NNRTIs, and integrase inhibitors [54]. These new investigational molecules may change the future HIV therapies and lead to optimized HIV treatments.

An interesting representative of a new therapeutic antiretroviral agent is Festinavir (Fig. 2A), a Stavudine analogue with reduced potential toxicity [57,58]. Festinavir is also a strong inhibitor of HIV-2 [59]. Attention is also being paid to Tenofovir conjugates and prodrugs achieving higher concentrations of the active triphosphate in the blood at decreased doses [57,60].

An informative update on the development in antiretroviral drugs is periodically available in The Antiretroviral Pipeline [61].

Non-Antiretroviral Drugs and Therapies

Studies have found some complementary therapies that reduce the immune dysfunction and inflammation in people with HIV. One protein that is being investigated in HIV infected people is Interleukin-7. Interleukin-7 stimulates production and maturation of T-cells in the bone marrow. Consequently, it may increase immune function HIV-positive individuals. Clinical trials conducted in monkeys documented restoration of T-cell functions. Additionally, Interleukin-7 appeared to be well tolerated [62].

Targeting Latent HIV Reservoirs

Targeting latent HIV reservoirs is aimed to cure HIV by removing cells infected with latent, non-replicating HIV. The HIV infection has the ability to establish a subset of latent infected CD4+ T cells that are undetectable to the immune system and play a role of latent HIV reservoirs. This is a major roadblock to achieve complete viral eradication. However, histone deacetylase inhibitors (HDACIs) have the ability to induce the reactivation of latent HIV [63].

Several drugs that are being studied as latent HIV activators / HIV-1 latency reactivation agents. Vorinostat (Fig. 2B), a HDACI, is currently the most successful representative of this group of potential antiretroviral therapeutics that are under clinical investigation to eliminate latent HIV-1 reservoirs [64].

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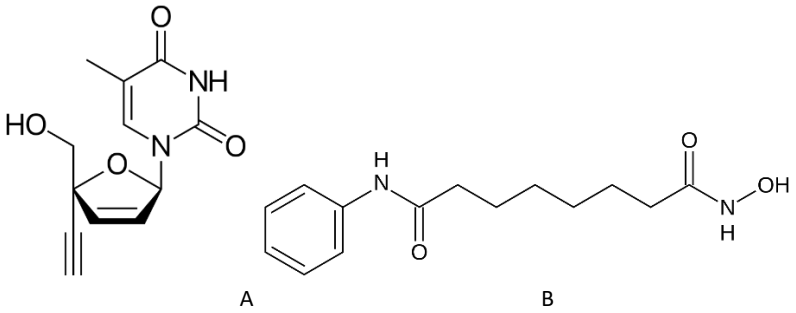

Fig 2. Chemical structure of Festinavir (4'-ethynylstavudine) and Vorinostat (suberanilohydroxamic acid).

Gene Therapy

Gene therapy is a promising, so far experimental, approach for potential HIV cure. It is currently in early stages of clinical testing. In summary, gene therapy is performed by harvesting cells from the patient's body, modifying their genetic information and then injecting them back to the patient. Strategies in gene therapy that are being investigated involve preventing immune cells from being infected, turning off HIV genes and enhancing the immune system's response to HIV.

Other rationale of introducing gene therapy as a part of anti-HIV therapy is based on the fact that about 1% of European descent population is lacking CCR5 co-receptors, which makes it resistant to HIV infection. It was found in 2014 that among six HIV-positive patients who received gene therapy without anti-HIV drugs, four patients had elevated CD4+ count. Furthermore, the HIV disappeared completely in one patient who had some T cells that were already resistant to HIV [65].

CONCLUSION

In conclusion, HIV infection mechanism and life cycle of the virus in the host cell is a complicated process. Mutations could occur during the HIV RNA translation. This makes HIV virus harder to treat and increases chances of drug resistance. HIV infection and its various complications are constantly drawing attention of many scientists, clinicians and public health specialist. Many new chemicals compounds are developed and tested for their activity on HIV virus function and on their potential to be used for the benefit of patients. Currently, six main chemical groups of antiretrovirals acting on HIV infection are clinically relevant. These are nucleoside and non-nucleoside reverse transcriptase inhibitors, fusion inhibitors, integrase inhibitors, protease inhibitors, and chemokine receptor antagonists. Their use depends on many clinical factors (age, HIV RNA load, CD4+ count, pregnancy, drug resistance etc.) and also on social situation of the patients (marriage, in-partnership, pregnancy etc.). As all of these are very important, the significant development in the research and clinical application of its results is expected for the benefit of both individual patients and society.

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