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Review Article

Latest Scientific and Pharmacological Findings in the Face of AIDS: Mini Review

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Abstract

The human immunodeficiency virus, namely HIV, weakens the immune system's resistance to off common germs, viruses, fungi, and other invaders. It's the virus that causes AIDS, acquired immune deficiency syndrome. People with HIV can get sick easier than common. AIDS can't be cured, but the medications available today help people stay healthy, live longer, and even obtain a normal life expectancy. There are two main types of the virus: HIV-1 and HIV-2. HIV-2 is most commonly found in West Africa, although places in other parts of the world are seeing it, too. HIV tests usually look for both kinds. The main goal of HIV treatment is to defeat the virus in your body. The most importance is trying to do this without causing unpleasant and unhealthy side effects. There's no cure for HIV, but treatment options are much better than they were a few decades ago. Because of medical advancements, many people with HIV now live longer, active lives with HIV. More than thirty kinds of antiretroviral drugs have been approved by the FDA to treat HIV infection. We try in this review to discuss related methods against the AIDS.

Introduction

The infection spreads from person to person when certain body fluids are shared, usually during vaginal or anal sex, or when sharing drugs you inject. It can also be passed from dirty needles from tattoos and body piercing. It can be spread through oral sex, too, although the chance is small. A mother can pass HIV to her child during birth, when the baby is exposed to her infected blood, or in her breast milk. But in some areas of the developing world, it's safer for a mom with HIV to breastfeed for a few months rather than to give a newborn formula with potentially contaminated water, especially if she is receiving treatment for HIV [1,2]. HIV doesn't live in saliva, tears, pee, or sweat, so it can't be spread by casual contact with these body fluids. HIV is not as easy to get as other infectious diseases. The virus can't survive for long outside the human body; it dies quickly when the body fluid dries up. It's not spread by animals or insects. You won't find it on public surfaces like door handles or toilet seats [3,4]. All blood products used in the United States and Western Europe today are tested for HIV. Blood banks get rid of any donated blood that tests positive, so it never gets into the public supply [5]. Someone who donates HIV-positive blood will be contacted so they can be tested by their doctor, and they won't be able to give blood again. Sub-Saharan Africa (the southern part) has the greatest number of people who are infected. The World Health Organization and the United Nations' UNAIDS office estimate that more than a third of adults are infected with HIV in some areas of Africa. The numbers of people who have HIV in Eastern Europe and in some parts of Asia are growing because of injection drug use. There are two main types of the virus: HIV-1 and HIV-2. HIV-2 is most commonly found in West Africa, although places in other parts the world are seeing it, too. HIV tests usually look for both kinds.

HIV Viral Load

Your viral load gives you an idea of how much of the HIV virus is in your body. The test measures the number of HIV copies in a milliliter of blood. The test can also help diagnose recent HIV infection in someone with inconclusive HIV antibody tests. However, in these cases, a subsequent positive HIV antibody test should be used to confirm the diagnosis. Keeping your viral load low will make complications of HIV less likely and help you live longer. It is possible if you adhere to your treatment to obtain a normal or near-normal life expectancy.

HIV viral load tests look for RNA, the part of HIV that has the recipe for reproducing itself. They add an enzyme, a kind of protein, to make more copies of the RNA. This makes it easier to measure how much HIV is in your blood sample.

Antibody Screening Tests

These tests check for a kind of protein that your body makes in response to the HIV infection, 2-8 weeks later. They're also called immunoassay or ELISA tests. They're generally very accurate, but they won't catch early infections.

CD4 Counts

The CD4 count is a test that measures how many CD4 cells you have in your blood. These are a type of white blood cell, called T-cells that move throughout your body to find and destroy bacteria, viruses, and other invading germs. Keeping your CD4 count up with an effective antiviral treatment can hold off symptoms and complications of HIV and help you live longer. In fact, studies have found that patients who adhere to regular treatments can achieve a life span similar to persons who have not been infected with HIV [6-8].

Persons with very low CD4 counts may need to take drugs to prevent specific opportunistic infections in addition to taking their ART. Once the CD4 count increases in response to ART, it may be possible to stop taking these OI medications. HIV damages your immune system because it targets CD4 cells. The virus grabs on to the surface of a cell, gets inside, and becomes a part of it. As an infected CD4 cell multiplies so it can do its job, it also makes more copies of HIV.

Those new bits of virus find and take over more CD4 cells, and the cycle continues. This leads to fewer and fewer HIV-free, working CD4 cells. HIV can destroy entire "families" of CD4 cells, and then the germs these cells fight have easy access to your body. The resulting illnesses are called opportunistic infections because they take advantage of your body's lack of defense. A normal CD4 count is from 500 to 1,400 cells per cubic millimeter of blood. CD4 counts decrease over time in persons who are not receiving antiretroviral therapy. At levels below 200 cells per cubic millimeter, patients become susceptible to a wide variety of opportunistic infections, many of which can be fatal [9].

Classes of Drugs

There are six classes of drugs, which are usually used in combination, to treat HIV infection. Use of these drugs in combination can be termed Anti-Retroviral Therapy (ART), Combination Anti-Retroviral Therapy (cART) or Highly Active Anti-Retroviral Therapy (HAART). Anti-Retroviral (ARV) drugs are broadly classified by the phase of the retrovirus life-cycle that the drug inhibits. Typical combinations include 2 NRTIs as a "backbone" along with 1 NNRTI, PI or INSTI as a base (Figure 1).

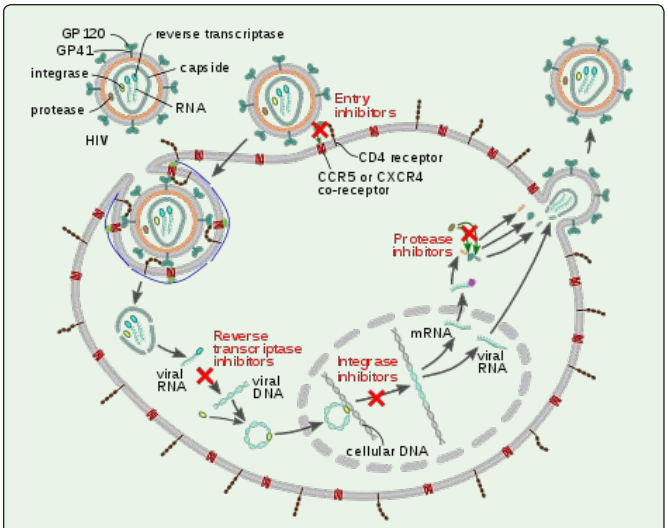

Figure 1: Schematic description of the mechanism of the four classes of currently available antiretroviral drugs against HIV.

Images and dosages of medications most commonly used to treat HIV-1 infection (not a complete list of every medication used to treat HIV):

Treatment of HIV-1 infection requires a combination of different medications, also called antiretroviral drugs

- Some of these medications are combined together into one pill
- These medications should be taken every day as prescribed, in order to control the virus
- These medications do not cure HIV-1 or AIDS
- These medications reduce but do not eliminate the risk of passing HIV-1 to others
- Not all medications are right for all people and treatment may be different for each person; talk with your doctor or other health care providers if you have questions about your treatment.

*Nucleoside Reverse Transcriptase Inhibitors (NRTIs): NRTIs block reverse transcriptase, an enzyme HIV-1 needs to make copies of itself (Figure 2).

*Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): NNRTIs bind to and alter reverse transcriptase, an enzyme HIV-1 needs to make copies of itself (Figure 3).

*Fusion Inhibitor: Fusion inhibitors block HIV-1 from entering the CD4 cells of the immune system (Figure 4).

*CCR5 Antagonists: CCR5 antagonists block CCR5, a protein on the CD4 cells that a certain type of HIV-1 needs to enter the cell.

Figure 2: Nucleoside Reverse Transcriptase Inhibitors (NRTIs).

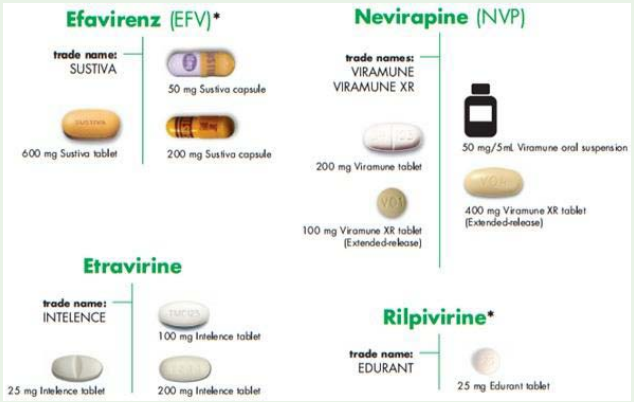

Figure 3: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs).

Protease Inhibitors

Protease inhibitors work by binding to protease. This is a protein that HIV needs to replicate in the body. When protease can't do its job, the virus can't complete the process that makes new copies. This reduces the number of viruses that can infect more cells.

Protease inhibitor drugs include:

- Tipranavir (Aptivus)
- Indinavir (Crixivan)
- Atazanavir/cobicistat (Evotaz)
- Saquinavir (Invirase)
- Lopinavir/ritonavir (Kaletra)
- Fosamprenavir (Lexiva)
- Ritonavir (Norvir)
- Darunavir/cobicistat (Prezcobix)
- Darunavir (Prezista)
- Atazanavir (Reyataz)
- Nelfinavir (Viracept)

Some protease inhibitors are only approved by the U.S. Food and Drug Administration (FDA) to treat hepatitis C. But there drugs are also sometimes effective in treating HIV. This special use of these drugs I called "off-label use." Off-label drug use means that a drug has been approved by the FDA for one purpose but it is used for another purpose that the FDA has not approved. A doctor can still use the drug for that purpose. This is because the FDA regulates the testing and approval of drugs, but not how doctors use drugs to treat their patients. So, your doctor can prescribe a drug however they think is best for your care. Doctors who are experienced at treating both HIV and hepatitis may choose to prescribe these drugs for people with HIV. These drugs include:

- Simeprevir (Olysio)
- Boceprevir (Victrelis)
- Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir (Viekira Pak)

Figure 4: Fusion Inhibitor.

Several studies have aimed to use autologous or allogeneic HSC transplantation in association with antiretroviral therapy as a strategy to eradicate HIV in seropositive patients diagnosed with leukemia and/or lymphomas (Table 1).

Gene Therapy

The apparent cure of the Berlin patient after receiving HSCT from a CCR5Δ32 homozygous donor and the impossibility of applying this protocol in a large scale has inspired attempts to generate HIV resistant cells through gene therapy. One of the most promising gene therapy strategies against HIV infection aims to disrupt the CCR5 gene by expressing an engineered Zinc-Finger Nuclease (ZFN). Evidence that ZFN could inactivate CCR5 in primary human CD4þ T cells and in CD34þ hematopoietic stem cells limiting HIV replication was first obtained in mouse models [10,11].

Innovative Approaches to Eliminate HIV Reservoirs

Several experimental and proof-of-concept studies aim to interfere with cell cycle and survival of HIV infected cells to facilitate their elimination or avoid their persistence by homeostatic proliferation. Rapamycin is an immunosuppresor that blocks the Mammalian Target of Rapamycin (mTOR), a protein kinase that control cell cycle, proliferation and survival, and plays a critical role in the differentiation of T cells. Rapamycin has been shown to be able to block HIV infection in vitro by decreasing the expression of CCR5, and also interferes with the synthesis of HIV transcripts [12].

Figure 5: CCR5 Antagonists.

Table 1: Hematopoietic stem cell transplantation in HIV positive patients.

Study Reference	Patients			Diagnosis	Graft Type	Strategy against HIV infection	Effect on HIV Persistence	Clinical Outcome
	N	Gender	Age					
Holland et al. (1989)	1	M	41	NHL	Allogenic (bone marrow)	High-dose zidovudine for 2 weeks before transplantation	No detectable HIV RNA and DNA at day 32 after transplantation and at autopsy	Death 47 days after transplantation
Contu et al. (1993)	1	F	25	NA	Allogenic (bone marrow)	Zidovudine, IFN-alpha 2 and anti-HIV-1-specific T cell clones	No detectable HIV RNA at day 30 after transplantation and at autopsy	Death 10 months after transplantation
Sora et al. (2002)	1	F	33	AML	Allogeneic (bone marrow)	cART before and after transplantation, with interruptions due to side-effects	No detectable HIV RNA on cART from day 210 after transplantation	Alive after 42 months of follow up
Gabarre et al. (2004)	14	M/F	27-53	BL, HL, NHL	Autologous	cART before and after transplantation	No detectable HIV RNA on cART in three patients who survived	Five patients were alive
Resino et al. (2007)	4	NA	31-58	BL,HL,NHL	Autologous	cART before and after transplantation	On cART No detectable HIV RNA after transplantation (two patients). viral load rebound (two patients) Detectable HIV DNA at month 12 after transplantation for all patients	The four patients were alive after 12 months of follow up
Avettand-Fenoel et al. (2007)	1	M	17	BL,AML	Allogeneic (bone marrow)	cART before and after transplantation, with interruptions due to side-effects	Undetectable RNA and DNA on cART. Detectable HIV RNA and DNA at day 16 after TI	Death 191 days after transplantation
Hutter et al. (2009)	1	M	40	AML	Allogeneic (bone marrow)	Donor homozygous for CCR5Δ32	No cART. No trace of HIV after 6 years of follow-up.	Alive after 6 years of follow up. Considered the first case of AIDS cure
Simonelli et al. (2010)	24	M/F	<45(n=15) ≥45 (n=9)	HL, NHL	Autologous	cART before and after transplantation, with interruptions due to side-effects (n=8)	On cART Detectable HIV RNA and DNA after transplantation. HIV DNA significantly lowers at month 24 than those at base line	Alive, immunologic characteristic comparable to HIV negative patients
Cillo et al. (2013)	10	M	24-60	BL, HL, NHL	Autologous	cART before and after transplantation, with interruptions due to side-effects (n=3)	On cART. Detectable HIV RNA (9/10 patients) and DNA (10/10 patients) after transplantation	Alive with undetectable VL by conventional methods, but with detectable proviral DNA
Henrich et al. (2013)	2	M	NI	HL	Allogeneic (bone marrow)	cART before and after transplantation	Undetectable HIV RNA on cART, detectable after TI. Detectable HIV DNA early after transplantation and undetectable in long term follow-up	Alive 5 and 3 years after transplantation, but viremia rebounded after TI
University of Minnesota (not published)	1	M	12	ALL	Allogeneic (cord blood)	Donor homozygous for CCR5Δ32 deletion	No detectable HIV after treatment discontinuation	Died 2 months after transplantation by a severe graft-versus-host disease

ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; BL: Burkitt Lymphoma; BM: Bone Marrow; F: Female; HL: Hodgkin Lymphoma; M: Male; NHL: Non-Hodgkin Lymphoma; NA: Not Available; PBMC: Peripheral Blood Mononuclear Cells; PCR: Polymerase Chain Reaction; TI: Treatment Interruption; VL: Viral Load

Conclusion

Thirty years after the identification of HIV, a cure for HIV infection is still to be achieved. Advances of Combined Antiretroviral Therapy (cART) in recent years have transformed HIV infection into a chronic disease when treatment is available. However, in spite of the favorable outcomes provided by the newer therapies, cART is not curative and patients are at risk of developing HIV-associated disorders. Moreover, universal access to antiretroviral treatment is restricted by financial obstacles. This review discusses the most recent strategies that have been developed in the search for an HIV cure and to improve life quality of people living with HIV. HIV remission will require efficient host responses to control infected cells and to prevent harmful HIV-related inflammation. These areas of research need to be explore in parallel to strategies targeting the reservoirs. In view of the problems inherent in the treatment and care for patients with a chronic disease that might persist for several decades, a global effort to identify a cure is now underway.

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