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REVIEW ARTICLE

Recent Advances In Antiretroviral Therapy

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ABSTRACT

Despite significant progress in the study of human immunodeficiency virus (HIV) infection over the past few years, it still remains a leading cause of death throughout the world. The field of antiretrovirals is dramatically growing. 25 antiretroviral drugs have been approved by the US-FDA till date. The development of newer antiretrovirals has dramatically altered the progression of the disease and has improved the quality of life in many HIV-infected patients. Over the last two years, three novel antiretroviral drugs, maraviroc (CCR5 antagonist), raltegravir (integrase inhibitor) and etravirine (a second generation non nucleoside reverse transcriptase inhibitor) have been approved by the FDA and several others are in the pipeline. This review discusses the pharmacology of the three novel antiretroviral agents. Drugs which are currently in the pipeline and the latest HIV treatment guidelines have also been addressed.

Key Words: Newer antiretrovirals, maraviroc, raltegravir, etravirine, pipeline drugs.

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Introduction

The United States center for disease control and prevention (CDC) defines Acquired Immunodeficiency Syndrome (AIDS) as any HIV-infected individual with a CD4+ T cell count of <200 cells/mm^3, regardless of the presense of symptoms or opportunistic infections. The history of AIDS dates back to 1981 when the first case was described in the United States. In 1983-84, French and American scientists confirmed the causative agent to be a retrovirus, the human immunodeficiency virus (HIV)[1]. Today, 25 years after the isolation of HIV, more than 33 million individuals are infected and are living with HIV all over the world. In 2007 itself, 2.7 million individuals became newly infected and 2 million died of HIV globall [2].

Zidovudine, the first effective antiretroviral for the treatment of HIV infection, was approved in 1987, 3 years after HIV was isolated [3]. The field of antiretrovirals is dramatically growing. Currently, 25 antiretrovirals belonging to 5 different classes have been approved by the FDA and are available for use in the US [Table/Fig 1].

(Table/Fig 1) US-FDA Approved Antiretrovirals

NRTIs	NNRTIs	PIs	Entry inhibitors	Integrase inhibitor
Zidovudine (AZT). Lamivudine (3TC). Stavudine (d4T). Didanosine (ddI). Abacavir (ABC). Emtricitabine (ETC). Zalcitabine (DDC). Tenofovir (TDF).	Nevirapine (NVP). Efavirenz (EFV). Delaviridine (DLV). Etravirine.	Saquinavir (SQV). Indinavir (IDV). Ritonavir (RTV). Nelfinavir (NFV). Atazanavir (ATV). Amprenavir (APV). Fosamprenavir (FPV). Tipranavir (TPV). Darunavir. Lopinavir (LPV/r).	**Fusion inhibitor**: Enfuvirtide (T-20). **CCR5 antagonist:** Maraviroc.	Raltegravir.

(Table/Fig 2) HAART regimen

	Dual NRTI	NNRTI	PI
Preferred	Tenofovir + emtricitabine	Efavirenz	Atazanavir + Ritonavir. Darunavir + Ritonavir. Fosamprenavir + ritonavir
Alternative	Zidovudine + lamivudine. Abacavir + lamivudine. Didanosine + lamivudine.	Nevirapine	Atazanavir (unboosted). Saquinavir + Ritonavir. Fosamprenavir (unboosted). Fosamprenavir + ritonavir.

HIV treatment options:

Nucleoside Reverse Transcriptase Inhibitors (Nrtis) [3],[4]

These drugs require intracellular phosphorylation by host cell kinase enzymes to active triphosphate form, which then competitively inhibits the reverse transcriptase enzyme, thereby inhibiting the conversion of viral RNA to proviral DNA (reverse transcription). They are also incorporated in the growing viral DNA by reverse transcriptase and terminate chain elongation as they lack the 3-OH group. Toxicity is mainly due to the partial inhibition of human DNA polymerase (which is a mitochondrial enzyme) and includes anaemia, granulocytopaenia, myopathy, peripheral neuropathy, and pancreatitis. Lactic acidosis, hepatomegaly and hepatic steatosis is a rare but potentially fatal complication associated with most NRTIs. They generally do not have clinically significant drug interactions as they are not substrates for, nor induce/inhibit hepatic CYP450 enzymes.

Non-Nucleoside Reverse Transcriptase Inhibitors (Nnrtis) [3],[4]

NNRTIs are non-competitive inhibitors that directly bind to the HIV-1 reverse transcriptase and induce a conformational change, resulting in the inactivation of the enzyme. Unlike NRTIs, they do not require intracellular phosphorylation for their action. They induce enzymes as well as are substrates for hepatic CYP450 enzymes. Pharmacokinetic drug interactions are thus an important consideration with the use of NNRTIs.

Rashes occur frequently with all NNRTIs, but are usually mild and self limiting. Rare cases of Stevens-Johnson syndrome have been reported.

Protease Inhibitors (Pis) [3],[4]

Protease inhibitors competitively inhibit the action of the protease enzyme and interferes with its cleaving function, resulting in the production of immature, non-infectious virus particles, thus preventing further rounds of infection. The most common side effects associated with their use are GI intolerance: nausea, vomiting and diarrhoea. Headache, dizziness, limb and facial tingling, numbness and rashes also occur. Lipodystrophy or a syndrome of the redistribution of body fat that includes abdominal obesity, buffalo hump and wasting of limbs and face has been observed. Raised triglycerides and cholesterol, insulin resistance and worsening of DM can occur. All PIs are substrates for CYP3A4 and different PIs either inhibit or induce specific CYP isoenzymes to a different extent. Drug interactions with them are common and are often unpredictable.

Fusion Inhibitor: Enfuvirtide [3],[4]

It is an HIV-derived synthetic peptide that binds to the HIV-1 envelope and prevents the fusion of viral and cellular membranes, thereby blocking the entry of the virus into the cell. Local injection site reactions like pain, erythema and induration at the site of infection are most prominent adverse effects. Some patients develop nodules and cysts, while 4-5% patients discontinue therapy due to adverse effects. It is available only for parenteral use.

Recent Advances:

Two new classes of drugs, the CCR5 antagonist and the integrase inhibitor and a next generation NNRTI, have been recently approved by the FDA. The drugs in these classes are maraviroc, raltegravir and etravirine. These newer drugs are valuable options for use in patients with resistant strains of HIV.

Maraviroc

Maraviroc, the first agent in a novel class of antiretrovirals known as entry inhibitors, was granted accelerated approval by the FDA on August 6, 2007. It is approved for use in combination with other antiretroviral agents for the treatment of CCR5-tropic HIV-1 (R5 virus), in the treatment of experienced adults with the evidence of viral replication or against HIV-1 strains which are resistant to multiple antiretrovirals [5]. The CCR5 tropism test should be carried out prior to starting maraviroc therapy.

Mechanism Of Action

Entry of HIV-1 into the host cell is an essential step in the life cycle of HIV. This process requires the attachment of the virus to both, the CD4 receptor and a chemokine receptor which serves as a co-receptor. HIV utilizes two different chemokine receptors for entry, the CCR5 and the CXCR4 receptors. While the CCR5-tropic variant of the virus is common in earlier HIV infections, viruses which are adapted to use the CXCR4 receptor gradually become dominant as the HIV infection progresses. Maraviroc prevents HIV infection of the host cells by selectively binding to and blocking the chemokine receptor CCR5 [5],[6]. As such, CXCR4-tropic and dual-tropic HIV-1 entry is not inhibited by maraviroc.

Clinical Trials

In two phase III clinical studies which enrolled triple-class, treatment-experienced patients who experienced failure on their current antiretroviral regimens with detectable viraemia with only CCR5-tropic (R5) viral strains, Maraviroc, as compared with placebo, resulted in a significantly greater suppression of HIV-1 and greater increases in CD4 cell counts at 48 weeks when added to optimized background therapy [7].The efficacy of maraviroc in the treatment of naive patients and against CXCR4-tropic or mixed/dual-tropic viruses has not been established [5].

Pharmacokinetics

Maraviroc is rapidly absorbed orally and the absolute bioavailability ranges from 23% at a 100 mg dose to 33% at a 300 mg dose. It is approximately 76% plasma protein bound. Maraviroc is metabolized primarily by CPY3A4 and is also a substrate for P-glycoprotein (Pgp). It does not significantly influence the activity of major drug metabolizing enzymes. Its elimination occurs both in faeces (76%) and urine (20%), with a terminal half-life of 14-18 hours [5],[8],[9],[10].

Adverse Effects

It is well tolerated at clinically relevant doses, with most adverse events being mild or moderate and includes cough, upper respiratory tract infection, fever, muscle and joint pain, sleep disturbances, abdominal pain and dizziness due to postural hypotension (dose limiting side effect). The serious adverse effects reported are myocardial ischaemia and hepatitis, with the elevation of liver enzymes [5],[11].

Drug Interactions

Maraviroc being a CYP3A4 as well as a p-glycoprotein (Pgp) substrate may require dosage adjustments when administered with CYP- or Pgp-modulators. CYP3A/Pgp inhibitors such as ketoconazole, lopinavir/ritonavir, ritonavir, saquinavir and atazanavir increase maraviroc concentrations: dose reduction upto 50% may be required. CYP3A/Pgp inducers such as carbamazepine, phenytoin, phenobarbital, rifampin and efavirenz decrease maraviroc plasma concentrations: doubling the dose appears to compensate for induction.[5,10,12] Tipranavir/ritonavir, a CPY3A inhibitor but a Pgp inducer, does not affect maraviroc pharmacokinetics [5]. Maraviroc has no clinically relevant interactions with the CYP3A4 substrate midazolam, the NRTIs zidovudine and lamivudine, or the oral contraceptive steroids [13].

Dosage

It is available as 150 and 300 mg film coated tablets. The recommended dose is 300 mg twice daily, but the required dose adjustment when used with CYP3A4/Pgp modulators [5].

Raltegravir

Raltegravir is the first in a novel class of antiretroviral drugs known as integrase inhibitors. It was approved by the FDA in October 2007 for use in combination with other antiretroviral agents to treat HIV-1 infection in treatment-experienced adult patients who had an evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral regimens [14,[15]

Mechanism Of Action

Integrase is an enzyme which is essential for HIV-1 replication. It catalyses the insertion of HIV-1 DNA into the DNA of the human genome, making it possible for the infected cell to make new copies of HIV. Raltegravir specifically inhibits the final step in integration,

that is the strand transfer of viral DNA to the host cell DNA, thus blocking the ability of HIV to replicate [14],[15],[16],[17].

Clinical Trials
In Phase III clinical studies which enrolled triple-class, treatment-experienced patients who experienced failure on their current antiretroviral regimens with detectable viraemia, raltegravir plus OBT provided significantly better viral suppression than OBT alone for at last 48 weeks [18].

Pharmacokinetics
Raltegravir is rapidly absorbed orally. The absolute bioavailability of raltegravir is approximately 32%. Raltegravir is approximately 83% bound to human plasma protein. The apparent terminal half-life of raltegravir is approximately 9 hours. It is primarily metabolized via UGT1A1-mediated glucuronidation and excreted in both faeces (51%) and urine (32%). No dose adjustment is necessary in patients with mild to moderate hepatic or severe renal impairment [14],[17].

Adverse Effects
Data regarding the safety of raltegravir is primarily obtained from the phase 2 studies (study 004 and 005) and the phase 3 (BENCHMRK) studies. Raltegravir was generally safe and well tolerated and was found to have a safety profile similar to that of placebo at all doses studied. There were no dose related toxicities. The most common adverse effects reported so far include diarrhoea, nausea, headache, nasopharyngitis and insomnia. Laboratory abnormalities include mild elevations in serum AST/ALT and creatinine phosphokinase (CPK). However, these are usually transient and do not require drug withdrawal [14],[15],[19].

Drug Interactions
Raltegravir is neither a substrate for cytochromes p450 enzymes, nor does it inhibit or induce cytochrome P450 enzymes. As such, interactions with other antiretrovirals like PIs and NNRTIs which are metabolized by the CYP450 system, are unlikely [14].However, strong inducers/inhibitors of UGT1A1 may affect the plasma concentrations of raltegravir. Caution is advocated while using raltegravir with potent inducers of UGT1A1 like Rifampin or with inhibitors like atazanavir[17].

Dosage
It is recommended in a dose of 400 mg orally, twice daily. No dose adjustment of raltegravir is required when it is co -administered with other antiretrovirals [14].

Etravirine
NNRTIs are potent inhibitors of HIV-1. However, the currently available agents which have been associated with the rapid development of resistance and cross-resistance within the class is extensive. Etravirine is a next generation NNRTI which has been approved by the US-FDA in January 2009 for use in combination with other antiretrovirals, for treatment-experienced adults with HIV strains which are resistant to existing NNRTIs [20],[21],[22].

Clinical Trials
Etravirine has demonstrated significant activity against the wild-type strains of HIV-1, as well as strains which are resistant to currently available NNRTIs. Further, the potential of HIV-1 developing resistance to etravirine appears to be lower than for first generation NNRTIs [23].In phase III trials (DUET I and II) in treatment experienced adult patients infected with HIV-1 resistant to NNRTI, patients receiving etravirine plus background therapy achieved a significantly greater reduction in viral load and a greater mean increase in CD4+ cell counts at 24 weeks than in patients receiving placebo plus BT [21],[23],[24],[25].

Adverse Effects
Etravirine is generally well tolerated and the adverse effects are mostly of mild to moderate severity, with a similar incidence to that of a placebo (except rash). The most frequently reported adverse effects were nausea and rash [21],[22],[24],[25]. Other less common adverse events of etravirine include abdominal pain, fatigue, peripheral neuropathy, headache and hypertension. Rare cases of Stevens-Johnson syndrome have been reported with etravirine.

Drug Interactions
The dose adjustment of etravirine and/or other drugs is necessary while co-administration with drugs that are extensively metabolized by or those which induce/inhibit CYP3A, CYP2C9 and CYP2C19. Etravirine may inhibit the metabolism of certain anticoagulants (warfarin); antifungals (fluconazole); and benzodiazepines (diazepam), resulting in a clinically significant rise in plasma concentrations and toxicity [21].Etravirine is an inducer of CYP3A4 and hence, may result in altered plasma concentrations of CYP3A4 substrates if co-administered. It interacts differently with different PIs resulting in increased concentrations of some (amprenavir and nelfinavir), while decreasing the concentrations of others (atazanavir and indinavir). Etravirine concentrations may also be altered by different PIs. Etravirine should therefore not be administered with any unboosted PI or with boosted tipranavir, fosamprenavir, or atazanavir. It may be administered at normal doses with boosted darunavir and saquinavir and with caution with lopinavir/ritonavir.

Dosage
It is available as tablets containing Etravirine 100 mg. The recommended dose is 200 mg twice daily after meals.

Pipeline Drugs
NRTI: Apricitabine (ACT) [26].
ACT is currently under phase III clinical trials and has shown some activity against HIV strains which are resistant to other NRTIs. Resistance to apricitabine develops slowly as compared to other NRTIs such as lamivudine. In a phase IIb trial in drug-resistant HIV patients, ACT showed a greater reduction in the HIV viral load than any other NRTI in development. It is being studied as a first choice, second regimen drug for the treatment of HIV infection in patients who have failed the treatment with lamivudine. It has been well tolerated in phase II trials, the most adverse effects being mild and which includes headache, nasal congestion and myalgia. Apricitabine does not induce or inhibit any of the major CYP450 isoenzymes and hence, does not appear to have significant interactions with drugs which are metabolized by the hepatic CYP pathway.

NNRTIs: Rilpivirine [27]
Rilpivirine is being studied in Phase IIb trials for the treatment of HIV infection in treatment-naive patients as well as treatment-experienced patients with drug-resistant HIV. It is a well known high genetic barrier against the development of resistance. In phase IIa and ongoing phase IIb studies, it has been found to be as effective as efavirenz. It may offer the advantages of once daily dosing in treatment naïve patients as well as that of having fewer side effects. Unlike efavirenz, it does not appear to cause central nervous system effects such as anxiety, sleep disturbance and depression. In trials conducted so far, it has not displayed any teratogenicity unlike other NNRTIs that are contraindicated in pregnancy.

Integrase Inhibitor: Elvitegravir[28]
It is being studied in Phase II trials for the treatment of HIV-1 infection in treatment - naive and treatment - experienced patients. It requires a small dose of the drug, ritonavir to boost its effectiveness. Such a combination of tablets may be suitable for once-daily dosing. It has been found to have a favourable safety profile, with the most common side effect in phase II studies being headache. No serious adverse events or discontinuations resulting from adverse events occurred in these studies. It displays additive to highly synergistic antiviral activity in vitro, with most of the NRTIs and PIs and does not appear to have any clinically significant drug interactions when used in combination with other antiretrovirals.

CCR5 Antagonist: Vicriviroc [29]
It is a novel, orally active entry and fusion inhibitor that holds promise for use in treatment experienced HIV patients infected with the CCR5 tropic virus which is resistant to enfuvirtide and other antiretrovirals. It has been well tolerated in phase II and ongoing phase III studies with most adverse effects being mild to moderate. The most common adverse events were nausea, headache, fatigue, pharyngitis and abdominal pain. It may be suitable for once daily dosing.

Maturation Inhibitor: Bevirimat [30]
This first-in-its-class maturation inhibitor is being evaluated as once-daily monotherapy for activity against HIV-1 in patients who are resistant to available treatments. Maturation is a late stage in viral reproduction, involving the processing of the Gag protein which is necessary for further infection of human cells. Bevirimat targets this late step in viral reproduction, resulting in the release of noninfectious viral particles and the termination of viral replication.

HIV Treatment Guidelines:[31],[32]
In 2008, the department of Health and Human Sciences (USA) published its latest recommendations for the treatment of HIV infection in adults:

Initiating Treatment: When To Start?

The eradication of HIV is still not being possible with the currently available antiretroviral regimens. The primary goal of antiretroviral therapy is to increase disease free survival by suppressing viral replication as much as possible and for as long as possible and the preservation of immunological functions.

The best time to initiate antiretroviral therapy still remains uncertain and debatable. Several authorities have framed and updated treatment guidelines from time to time. According to the current guidelines, treatment initiation is recommended in the following cases:

1. All cases of symptomatic HIV disease.
2. In asymptomatic cases, treatment has to be initiated before the CD4 cell count decreases to < 350 cells/mm^3.
3. In symptomatic cases with a CD4 cell count of >350 cells/mm^3, the treatment decision should be individualized. The patient's readiness for initiation and adherence to therapy, individual risk of drug interactions, toxicity and the cost should be considered before starting treatment. The following are indications for initiating antiretroviral therapy irrespective of the CD4 cell count:
   a. Rapid decline in the CD4 cell count (>100/µl per year).
   b. Plasma HIV-1 RNA levels >100 000 copies/ml.
   c. Risk factors for cardiovascular and other non-AIDS diseases and
   d. Special cases such as pregnancy, HIV-associated nephropathy and co-infection with hepatitis B.

What To Start: Initial Treatment Options.

Monotherapy, as was used initially for the treatment of HIV, is no longer recommended as it is associated with the rapid development of resistance. With newer insights into the pathogenesis of the HIV infection and the availability of several new and potent antiretrovirals belonging to different classes, a combination of at least 3 or more drugs known as highly active antiretroviral therapy (HAART) is now the preferred initial treatment. HAART has been found to be highly effective in suppressing HIV replication, reducing mortality and improving survival among HIV infected patients.

According to the current guidelines, patients who are naive to antiretroviral therapy should be started on the HAART regimen that contains either:

- 2 NRTIs + 1 NNRTI. Or
- 2 NRTIs + 1 PI (preferably with ritonavir boosting)

Conclusion

The development of newer antiretrovirals and advances in the management of HIV infection have dramatically altered the progression of the disease and improved the quality of life in many HIV infected individuals. However, despite the advances, HIV management still remains a difficult task because several problems like long term toxicities of antiretrovirals, drug interactions, development or resistance limit the effectiveness of HAART and pose major challenges in the management of HIV infection.

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