

Current Chemotherapy of HIV

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Abstract

Since the identification of HIV is the causing agent of AIDS in early 1980s, great efforts have been devoted to develop therapies to treat HIV infection. To date 23 anti-HIV drugs, inhibiting four key stages of virus replication cycle, have been introduced to market. Due to the efficacious HAART regimens, HIV treatment strategies move toward the long-term management of a chronic infection. Despite current achievement of anti-HIV, long-term treatment success still face new challenges.

Introduction

The global AIDS/HIV pandemic is proving to be one of the most important issues of our time. Since the advent of the AIDS epidemic, more than 22 million people worldwide have died from the disease. In 2004, 3.1 million men, women and children have died. Currently, more than 40 million people are living with HIV/AIDS, the majority in sub-Saharan Africa.¹ It is predicted that approximately 68 million people will die of AIDS-related causes between 2000 and 2020 if prevention and treatment efforts are not “drastically expanded”. The epidemic continues to spread rapidly in Africa, Asia, the Caribbean and Eastern Europe, and infection rates in Asia and East Europe, especially in Russia and Ukraine, are in rise.

FDA Approved Antiviral Therapies of HIV

Since the discovery in 1984 of HIV, the virus causing AIDS, the development of drugs to treat HIV infection has been a priority. In principle, all the stages of the HIV replicative cycle (attachment, fusion, uncoating, reverse transcription, integration, replication, transcription, translation, maturation and release) could be envisaged as targets for chemo-therapeutic intervention. Numerous compounds have been described to interfere, albeit with varying specificity, with one or another stage of the viral replicative cycle. Currently licensed HIV inhibitors are targeted at the HIV-associated fusion, reverse transcriptase (RT) or protease.

Fusion Inhibitor (FI)

Fusion of viral envelop with the cellular plasma protein is crucial for HIV to release its content into and infect CD4+ T-cells. HIV envelop glycoprotein gp41 plays an important role in this process.² Fusion inhibitors (FIs) prevent the entry of the virus into CD4+ T-cells.

Enfuvirtide (ENF) is the first fusion inhibitor approved for clinical use. It specifically inhibits the action of the HIV envelope glycoprotein gp41.³ Two heptad repeat (HR) sequences, HR1 and HR2, are contained with gp41. In the fusogenic conformation of gp41, HR1 and HR2 interact with each other to facilitate the membrane fusion. Enfuvirtide is a 36 amino acid synthetic peptide

Table 1. Market Fusion Inhibitor

Brand Name	Generic	Company	Year approved	Daily Dosing
Fuzon	Enfuvirtide (T-20)	Trimeris	2003	1x90 mg 2x/day (Injection)

derived from HR2, which targets the HR1 domain and blocks gp41-mediated fusion of HIV-1 to the host cell. The safety and efficacy of chronically administered ENF has been demonstrated in clinical trials. It has to be administered twice daily by subcutaneous injection.

HIV RT Inhibitor

HIV reverse transcriptase (RT) is essential for replication of the HIV.⁴ RT carries out the conversion of the RNA genome of the virus into a linear double-stranded DNA that is subsequently integrated into host cell chromosomes. The necessity of RT in viral replication virtually guarantees that this enzyme will remain at the forefront of the antiviral drug therapies in the battle against HIV.⁵ RT inhibitors generally fall into two structural classes: nucleoside or nucleotide RT inhibitor (NRTI) and non-nucleoside RT inhibitor (NNRTI). The NRTIs interact with the substrate (dNTP) binding site of the enzyme, and, when incorporated, they terminate DNA chain elongation. The NNRTIs are a chemically diverse group of compounds that bind to allosteric site of the RT and noncompetitively inhibit DNA polymerization.

Nucleoside RT Inhibitors (NRTIs)

There are eight marketed nucleoside reverse transcriptase inhibitors (NRTIs). AZT is the first chemotherapy approved for the treatment of HIV. Since the introduction, NRTIs have been and remain to be the cornerstone of therapy against HIV infection and AIDS.

NRTIs are analogs of natural nucleoside that require phosphorylation by cellular kinases to convert them into nucleoside triphosphates. In the phosphate form, they compete with deoxyribonucleoside triphosphate (dNTP) substrates. Unlike the dNTPs, these nucleoside analogs do not possess a 3'-hydroxyl group for further chain elongation. When incorporated into replicate DNA, they cause termination of growing DNA chain, resulting in inhibition of HIV replication.

Table 2. Market NRTIs

Brand Name	Generic	Company	Year approved	Daily Dosing
Retrovir	zidovudine (AZT)	GSK	1987	1x300 mg 2x/day
Videx/ Videx EC	didanosine (ddI)	BMS	1991	2x100 mg 2x/day 1x400 mg 1x/day
Hivid	zalcitabine (AZT)	Roche	1992	1x0.75 mg 3x/day
Zerit	stavudine (d4T)	BMS	1994	1x300 mg 2x/day
Epivir	lamivudine (3TC)	GSK	1995	1x150 mg 2x/day
Ziagen	Abacavir (ABC)	GSK	1998	1x300 mg 2x/day
Viread	Tenofovir (TDF)	Gilead	2002	1x300 mg 1x/day
Emtriva	emtricitabine (FTC)	Gilead	2003	1x200 mg 1x/day

Non-Nucleoside RT Inhibitors (NNRTIs)

NNRTIs are selective inhibitors of the RT enzyme of HIV-1. They do not inhibit the RT enzyme of HIV-2 or human cellular DNA polymerase. The NNRTIs act non-competitively by interacting with a specific site on the RT that is near to but distinct from the active site where the nucleoside inhibitors bind.⁶ Studies have shown that the NNRTIs bind to the enzyme-template-primer complexes and adversely influence the enzyme's polymerizing activity.⁷ Binding of an NNRTI to the pocket significantly reduces RT's conformational flexibility required for its catalytic activity, and therefore interferes with its ability to complete converting the viral RNA genome into proviral DNA. More than 30 structurally different classes of NNRTIs have now been discovered and currently three are approved for clinical use (Table 3).⁸

Table 3. Market NNRTIs

Brand Name	Generic	Company	Year approved	Daily Dosing
Viramune	nevirapine	BI	1996	1x200 mg 2x/day
Rescriptor	delavirdine	Pfizer	1997	2x200 mg 3x/day
Sustiva	efavirenz	BMS	1998	1x600 mg 1x/day

Protease Inhibitors (PIs)

The HIV protease is responsible for the cleavage of the gag and gag-pol precursor polyproteins to the structural proteins and functional proteins to assemble a mature and infective virus. Protease inhibitors act through inhibition of the HIV protease and interfere with this late stage of the viral replication cycle and prevent formation of infectious virus particles.⁹ The introduction of the HIV PIs has drastically improved the treatment for HIV patients and helped to significantly reduce HIV-related mortality.¹⁰ However, their relatively less than optimal pharmacokinetic profiles requiring high bill burden and inconvenient dosing schedules hinder their wide spread usage. Recently, "boosted" PI – co-administration of PI with ritonavir demonstrated to improve human pharmacokinetics, and widely accepted as standard practice.

Table 4. Market PIs

Brand Name	Generic	Company	Year approved	Daily Dosing
Fortovase (Invirase)	saquinavir	Roche	1995	6x200 mg (3x200 mg) 3x/day
Novir	ritonavir	Abbott	1996	6x100 mg 2x/day
Crixivan	indinavir	Merck	1996	2x400mg 3x/day
Viracept	nelfinavir	Pfizer	1997	5x250 mg or 2x625 mg 2x/day
Agenerase	amprenavir	GSK	1999	8x150mg 2x/day
Kelatra	lopinavir/ritonavir	Abbott	2000	3x(133.3/33.3) mg 2x/day
Reyataz	atazanavir	BMS	2003	2x200 mg 1x/day
Lexiva	fosamprenavir	GSK	2003	2x600 mg 2x/day
Aptivus	tipnavir	BI	2005	2x250 mg 2x/day

HIV Treatment Strategy

Highly Active Antiviral Therapy (HAART) and Fixed-dose Combination (FDC)

For HIV treatment, monotherapy is not recommended, combination therapy - two or more drugs from different classes are typically used. The current approach to treating HIV infection is a regimen of highly active antiretroviral therapy (HAART) with the goal of suppressing plasma viral replication for as long as possible. Combination regimens usually consist of three drugs: usually two NRTIs plus either an NNRTI or a boosted PI. In unusual circumstances, three NRTIs are used together. A major barrier in the treatment of HIV is the development of viral resistance, which occurs due to selection of mutant strains. Emergence of viral resistance is associated with treatment failure. Adherence of patients to the treatment regimens is essential to minimize the emergence of resistance. Planning a long-term HAART strategy requires to consider chances for development of specific drug-resistance mutations, the pattern and thresholds for development of these drug-specific mutations and the potential for cross-resistance with other drugs of the same class. Along with drug resistance, an equally important issue affecting HIV therapy is that of drug safety and tolerability. Combination antiretroviral regimens need to be maximally suppressive but should also have favorable toxicity profiles to ensure they are taken safely, over prolonged periods of time. Safety and tolerability issues are directly related to regimen adherence.

An important approach to addressing the management of HIV/AIDS is the development of fixed-dose combinations (FDCs) of individual components administered together to simplify treatment regimens, improve patient adherence, and prevent the development of drug resistance.

Table 5. Market FDC of HIV Therapy

Brand Name	Generic	Company	Year approved	Daily Dosing
Combivir	zidovudine + epivir	GSK	1997	1x(300+150) mg 2x/day
Trizivir	zidovudine + epivir+abacavir	GSK	2001	1x(300+150+300) mg 2x/day
Truvada	tenofovir+emtricitabine	Gilead	2004	1x(300+200) mg 1x/day
Epzicom	epivir+abacavir	GSK	2004	1x(300+600) mg 1x/day

Department of Health and Human Service (DHHS) guidelines, updated on April 7, 2005, give recommendations¹¹ for first-line treatment based on efficacy, side effects pill burden and potential drug-drug interactions.

NNRTI-based Regimens (2NRTI+NNRTI):

Preferred regimens:

efavirenz + (zidovudine or tenofovir) + (lamivudine or emtricitabine)

Alternative regimens:

efavirenz + (didanosine or abacavir or stavudine) + (lamivudine or emtricitabine) *or* Nevirapine-base regimens

PI-base Regimens (2NRTI + 1 or 2 PIs):

Preferred regimens:

lopinavir/ritonavir + zidovudine + (lamivudine or emtricitabine)

Alternative regimens:

atazanavir, fosamprenavir, fosamprenavir/ritonavir, indinavir/ritonavir, nelfinavir, or saquinavir/ritonavir + (zidovudine or stavudine or tenofovir or abacavir or didanosine) + (lamivudine or emtricitabine) *or* lopinavir/ritonavir + (abacavir or stavudine or tenofovir or didanosine) + (lamivudine or emtricitabine)

There are no absolute rules when to start antiviral drugs, but in general most clinicians will start treatment of asymptomatic patients who have a CD4+ T-cell count under 350 cells/mm³ or plasma HIV RNA(viral load) greater than 100,000 copies/mL. CD4 counts and viral load are measured every few months to monitor treatment effectiveness. There are numerous factors used to determine a "suitable regimen" for patient including CD4 count, viral load, clinical status, side effects, compliance, and the patient's need.

Mother to Child Transmission

HIV can be transmitted from an infected mother to her newborn child. Without treatment, about 20% of babies of infected mothers get HIV. For prevention of Mother to Child (MTC) transmission, several antiviral drugs demonstrated efficacy. AZT greatly reduces transmission of HIV from the mother to her child. It is given to HIV-positive pregnant women from the 4th month of pregnancy until their baby is born, and to the newborn baby for 6 weeks. Even if the mother does not take antiviral medications until she is in labor, two methods cut transmission by almost half. 1) AZT and 3TC during labor, and for both mother and child for one week after the birth. 2) One dose of nevirapine during labor, and one dose for the newborn, 2 to 3 days after birth. Combining nevirapine and AZT during labor and delivery reduces transmission to only 2%. However, resistance to nevirapine can develop in up to 40% of women who take the single dose.

As HIV treatment strategies move toward the long-term management of a chronic infection, treatment issues such as convenience, safety and tolerability become even more important. Optimal adherence to HAART is one of the most formidable challenges to long-term treatment success. In addition, HIV has so far proved to be intractable to the vaccine approach, the search for new antiviral must continue.

The challenge facing anti-retroviral drug research now and beyond is the discovery and development of new agents that address the above mentioned issues, either through improvements in existing drug classes or by the discovery of agents targeting new mechanisms of action.

(Endnotes)

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