

ANTIRETROVIRAL DRUGS IN INDIA

Current status, issues and challenges

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"We can't afford to lose any more community leaders without providing access to life saving antiretrovirals. We have no excuse for not providing antiretrovirals in India as we manufacture them in various brands and proudly export them to the whole world." - The Indian Network of Positive People, Chennai, Tamil Nadu

BACKGROUND

In the 26 years since HIV was first discovered in humans and identified as a communicable, viral infection, several medications have been formulated and put into use. The onset of full-blown AIDS after HIV infection can be delayed, not completely avoided. With no effective vaccine against the infection as yet -- antiretroviral drugs (ARVs) that can lower the viral load in the infected person, help in improving the quality of life and prolonging its span.

ARVs are by nature potent drugs that can cause several side effects, something that affects the ability of patients to tolerate these drugs over the long-term (for they must be consumed life-long). Suffering too many side effects, patients often become defaulters of the punishing and expensive drug regimen, thus encouraging the creation of drug resistance. Director of the National Aids Research Institute, Pune, Ramesh Paranjape, says in India, despite the low usage of the drugs, signs of ARV resistance in the HIV virus are emerging.

The Indian government, through the National AIDS Control Organization (NACO), New Delhi, is providing free-ARV first line drugs across selected centres in the country and from 2008 onward free second line drugs are being provided (initially at only two centres).

BASIC FACTS ABOUT ARVs

For some years from the time HIV/AIDS was discovered, patients were only given drugs to treat the many opportunistic infections (OIs) brought on by HIV's gradual assault on the immune system. Anti-HIV medication or ARVs were a late 1980s breakthrough - the first time that drugs could be actually used to reduce the ability of the virus to replicate and spread (i.e. slow down disease progression), and also to try and resuscitate the immune system. The decision of when to start a patient on ARVs is often an individual, case-based one, but technically, patients showing CD4 counts below 200 per milli-cubic meter are eligible for ARVs.

ARVs belong to five different classes of drugs . The first are nucleoside reverse transcriptase inhibitors, the oldest known are ARVs such as AZT and abacavir. These act by disrupting the process of transcription (conversion of viral RNA to DNA so as to take charge of the human cell it infects). The second class of ARVs is non-nucleoside reverse transcriptase inhibitors (the commonly used nevirapine is from this class of drugs). They act by targeting the chemical that converts the viral RNA into DNA. Protease inhibitors such as indinavir and lopinavir affect the formation of new HIV particles. The fourth class of drugs is nucleotide analogues that interfere with some key enzymes required for viral replication of HIV. Tenofovir is an example of this class. The last and the most recently discovered class of ARVs are entry inhibitors - and as the name suggests they block the very entry of HIV into a CD4 - Helper T cell.

When a patient begins to consume ARVs, the basic idea is to ensure that there is a reduction in the viral load within the body and an increase in the CD 4 cell count. From the initial practice of using single drugs

or two drugs, the last several years have seen the advent of combination drug therapy that can be efficient in suppressing HIV for many years. Once on effective ARV treatment, a person's life span can be doubled from what it would be without ARVs. The use of ARVs the world over has slowly shown impact in overall AIDS-related mortality figures.

Combination ARV therapy (or Highly Active Antiretroviral Therapy (HAART)) was discovered in the mid- to late-1990s when it was found that using three or more ARV drugs in a combination, with a protease inhibitor thrown in, was much more effective than using them singly or in twos. This way, drugs show their effect for a longer time. This kind of usage of mixed drugs is also helpful in delaying the development of drug resistance in the virus. It must be noted, though, that several patients are unable to tolerate combination therapy.

SIDE EFFECTS and DRUG RESISTANCE

ARVs are known to have several side effects, but as it is with most other drugs, the range and intensity of side effects vary from individual to individual. Some side effects of ARVs are easier to cope with, such as fever, headache and diarrhoea. Other, more chronic and troublesome side-effects - pancreatitis, peripheral neuropathy and skin rashes -can even lead a patient to defaulting on the drug regimen.

Defaulting on a life-long regimen creates drug resistance. Drug resistance can be the result of mutations within HIV that make the virus resistant to mainline drugs and, while a certain degree of mutation is natural, it is a situation exacerbated by those who default on their drug regimen. As a result ARVs are available as first and second line of treatment regimens.

GENERIC DRUGS AND REDUCTION OF COSTS

In 2000 there was a dramatic reduction in the cost of the otherwise expensive drugs due to the manufacturing of generic drug, often by Indian pharmaceutical companies. Expert analyses show that the cost of ARVs has dropped to less than a dollar a day (not exactly cheap by Indian standards, but nevertheless cheaper than what ARVs were costing till not so long ago). There was a time when ARVs were not even available in India, and they could cost up to \$ 20,000 per person annually in the developed countries, where they were available. With generic versions from Indian and Brazilian pharmaceutical firms, the cost has come down drastically.

India has had the advantage of having companies like Cipla and Ranbaxy and it is their innovative manufacturing and marketing that allowed for building access to drugs for AIDS.

THE CHALLENGES AHEAD

The network of Integrated Counseling and Testing Centers has been strengthened in several states, but this needs to be done across the country, so as to ensure patients' early entry into ARV regimens. Counselling is also essential to counter any complacency that may set in within civil society regarding the need to protect oneself from HIV because of a growing availability and positive impact of ARVs.

One overarching and ongoing challenge is the stigma and discrimination that is part and parcel of this epidemic. It must be understood that any amount of progress and betterment within the sector of HIV/AIDS treatment will be futile without a lessening of social discrimination against patients of HIV/AIDS besides their immediate families and communities.

WHAT DRUGS ARE AVAILABLE?

There are three general types of antiretroviral drugs that are currently available by prescription (Table 1) or through pharmaceutical companies (expanded access programs) or clinical trials. Antiretroviral drug categories include:

Nucleoside reverse transcriptase inhibitors (NRTIs)

This group, which has been studied the most, includes **zidovudine** (AZT), **didanosine** (ddI), **zalcitabine** (ddC), **stavudine** (d4T), **lamivudine** (3TC), and **abacavir** (ABC, Ziagen). Tenofovir (Viread) is a recently approved nucleoside agent. These drugs act by blocking a step in the reproduction of HIV called reverse transcription. This step is necessary for HIV to be prepared for incorporation into the genetic material of cells. All of these agents are available by prescription.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

This group includes nevirapine, delavirdine and efavirenz. Non-nucleoside agents also block HIV reverse transcription, but they do so in a different way than nucleoside drugs.

Protease inhibitors (PIs)

This group includes **saquinavir**, **ritonavir**, **indinavir**, **nelfinavir**, **amprenavir** and **lopinavir/ritonavir** (KALETRA), many of which are available by prescription in India. These drugs work by blocking the action of protease, a protein made by HIV, which the virus must have to reproduce and infect new cells. Protease inhibitors are the most active group of anti-HIV drugs discovered to date.

First line drugs:

- Stavudine + Lamivudine + Nevirapine
- Stavudine + Lamivudine + Efavirenz
- Zidovudine + Lamivudine + Nevirapine
- Zidovudine + Lamivudine + Efavirenz

Second line drugs:

- Tenofovir + Lamivudine(oremetricitabine) + Lopinavir/Ritonavir + Zidovudine

ANTIRETROVIRAL DRUGS AVAILABLE IN INDIA

Nucleoside Reverse Transcriptase Inhibitor (NRTI)	Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	Protease Inhibitor (PI)
Zidovudine (AZT)*	Nevirapine (NVP)*	Indinavir (IDV)*
Lamivudine (3TC)*	Efavirenz (EFV)*	
Stavudine (d4T)*		Nelfinavir (NFV)*
	Delavirdine (DLV)	Saquinavir (SQV)*
Didanosine (ddI)*		Ritonavir (RTV)*
Zalcitabine (ddC)*		Amprenavir (APV)*
Abacavir (ABC)*		Lopinavir (LPV)*
Tenofovir (TFV)*		Atazanavir (ATV)*
Emtricitabine (FTC)		Foseamprenavir

* Available in India Available under National Program

POST EXPOSURE PROPHYLAXIS

The following drugs are used for post exposure prophylaxis and are supported by the Government of India

Zidovudine - 300 mg. twice daily for 4 weeks
Lamivudine - 150 mg. twice daily for a period of 4 weeks

In Combination

Indinavir - 800 mg. thrice daily or any Protease Inhibitor (only when indicated as part of expanded regime)

Fusion Inhibitor	Enfuvirtide (T-20)
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Cost of Therapy reduced from Rs 30000/- in 1998 to Rs 1000/- per month in 2006

No of pills from 32 to 1 or 2 per day

The National AIDS Control Organisation (NACO) has set up 126 ART centres across the country. It plans to have 250 centres in government hospitals in the country with provision of ART for 300,000 patients by 2011-12.

For a complete list of Public Hospitals in India that provide Antiretroviral Therapy visit the following website:

<http://www.nacoonline.org/upload/Documents/List%20of%20127%20ART%20centres%20with%20addresses.pdf>