

ANTI-RETROVIRAL DRUGS IN INDIA

Anti-retroviral Drugs In India Current Status, Issues And Challenges

By Pallava Bagla and Subhadra Menon

“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 22 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—anti-retroviral 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 still expensive for most Indians. Several nations across the world are trying to create systems and devise policies that can allow people free or subsidised access to these drugs. But these policies have obviously been easier to craft than to implement on the ground. While ingenious methods have been thought out and put into action to overcome the exorbitant costs of these drugs, the recent enforcement of the global Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement has forced countries like India to amend their patent laws.

The cost of ARVs is not the only challenge. 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 has, through the National AIDS Control Organization (NACO), New Delhi, been trying to streamline a free-ARV rollout across selected centres in the country since the middle of 2004. It aims at reaching 25,000 patients by the end of 2005. NACO’s is an ambitious plan and one fraught with challenges—of fair access to the needy, infrastructural issues, immature management of medication and trying to keep pace with an ever-growing need. It is also a plan made difficult in its implementation by sheer numbers. Despite heated debates and strident protests over how many Indians actually suffer from HIV infection or AIDS, numbers are an integral part of this plan. There are estimates that in the coming 15–20 years, there will be anywhere between 200,000 to 490,000 Indians reaching out to the health sector for HIV/AIDS related services, care, treatment and support.¹ According to the World Health Organisation (2004) there are at least 600,000 Indians who currently need ARVs as treatment for HIV/AIDS.

¹ Over, M, Heywood, P. et. al. HIV/AIDS Treatment and Prevention in India: Modeling the Cost and Consequences. The World Bank, 2004

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.² 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 must be a reduction in the viral load within the body and an increase in the CD 4 cell count. Infectiousness is highest soon after infection when an HIV-positive person shows a rapid growth in blood viral load. In most generalised cases, there is an average of 10 years between infection and death—it takes roughly five years from infection to the first showing of Opportunistic Infections and then another five years to full-blown AIDS (OIs and cancers) and finally, death. 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 world over has slowly shown impact, in overall AIDS-related mortality figures.

Combination ARV therapy 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. Highly Active Antiretroviral Therapy (HAART) is another name for combination therapy. 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 for diseases, the range and intensity of side effects varies from individual to individual. Some side effects of ARVs are easy to cope with, such as fever, headache and diarrhoea. There are the more chronic and troublesome side-effects—pancreatitis, peripheral neuropathy and skin rashes—that can even lead a patient to defaulting on the drug regimen.

² Barnes, Tracey, 2003. A Rough Guide to HIV. How's That Publishing Ltd, Great Britain.

This letting go of the consumption of drugs in what is a life-long regimen is creating drug resistance in HIV. 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 drug regimen defaulters. Therefore ARVs are available as first and second line of treatment regimens.

GENERIC DRUGS AND REDUCTION OF COSTS

Playing a big role in enhancing access to ARVs was the generic drugs manufacture initiated by Indian pharma companies in 2000, resulting in a dramatic reduction in the cost of the otherwise expensive drugs. Expert analyses are showing 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 upto \$ 20,000 per person annually in the developed countries where they were available. With generic versions from Indian and Brazilian pharma firms, the cost has come down to \$240 per person per year, to less than a dollar a day per person.³ Today, an average Indian may spend roughly Rs 1000.00 to Rs 1200.00 a month on ARVs, if it is the first line of drugs being used for treatment.

Moving to the second line is a costly option. The cost of second line goes up anywhere between four to six times over the first line of drugs, sometimes even up to 12 times, and according to WHO most second line drugs are still under patent, making access to them an issue in India. Often, within three to five years of treatment with first line ARVs, patients start to show resistance and required second-line therapy. In the richer countries of the world, where access and affordability are minor issues, several people are switching to the second and third line of ARV treatment when the first line of drugs ceases to be effective.

The new TRIPS compliant patents regime in India is expected to have lasting impact on the issue of access, especially to the second line and third line of ARVs. 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. Domestic manufacture of generic versions of ARVs in India will certainly be affected by the new regime, although it may be early days to actually evaluate the quantum of this impact.

THE CHALLENGES AHEAD

There are several challenges before India—for one it needs a rational policy for ARV usage and administration. This policy has to unfold under the realisation that ARVs are not a total cure, are expensive, and have a complex method of action that makes their administration a complicated and often bothersome issue. ARVs are administered in India in what is called “an unstructured method”, one that does not conform either to WHO or NACO guidelines.

There is also the challenge of being able to assess the positive and negative effects of growing ARV use—a lower viral load in community would be a clear positive while greater drug resistance would be a negative. With more and more people on ARVs it is hoped there will be positive impact on the number of new infections arising in the community. Interestingly, the availability of ARVs is also known to strengthen prevention efforts.

There is a need to build much stronger networks for Voluntary Counselling and Testing (VCT) 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.

³ Over, M, Heywood, P. et.al. HIV/AIDS Treatment and Prevention in India: Modelling the Cost and Consequences. The World Bank, 2004.

It would be vital, once having accepted the need to stay abreast with the best of treatment options for HIV, for India to keep pace with the latest research on drug resistance by targeting a wider range of mechanisms within HIV replication as possible ways for anti-HIV medication to act.

One overarching challenge that HIV/AIDS faces 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.

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(Key words: CD4—T Helper Cells; Viral Load; Combination Therapy; “3 by 5” Initiative; Drug Resistance)

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DRUGS AVAILABLE IN INDIA

1. Reverse transcriptase inhibitors

i. Nucleoside analogue

- AZT (azidothymidine, zidovudine) - 100 mg. each tablet
- DDC (zalcitadine) - 75 mg. Tablet each
- Stavudine - 100 mg. Tablet each
- Lamivudine - 150 mg. Tablet each

ii. Non-nucleoside analogue

- Nevirapine - 200 mg. Tablet each

2. Protease inhibitors

i. Saquinavir

ii. Ritonavir

iii. Indinavir

(VI) Post exposure prophylaxis

The following drugs are only used for post exposure prophylaxis and 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
- Indinavir - 800mg. Thrice daily (only when indicated as part of expanded regime)

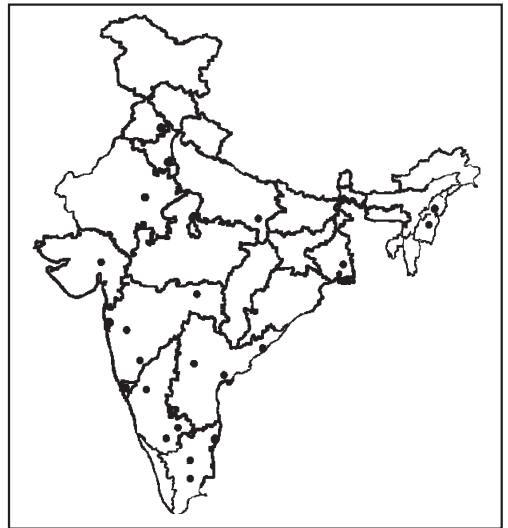
SOURCE: National AIDS Control Organization (NACO), 2004

For a complete list of the US Federal Drug Administration’s (FDA) approved anti-retroviral drugs, please see page 46.

Public Hospitals in India That Provide Antiretroviral Therapy, 2004–05

At the start of the ARV rollout in mid 2004, drugs were made available at the following centres:

1. Sir JJ Hospital, Mumbai, Maharashtra
2. Institute of Thoracic Medicine and Chest Diseases, Tambaram, Chennai
3. Regional Institute of Medical Sciences (RIMS), Imphal, Manipur
4. Bangalore Medical College Hospital, Bangalore, Karnataka
5. Osmania Medical College Hospital, Hyderabad, Andhra Pradesh
6. Ram Manohar Lohia (RML) Hospital, New Delhi
7. LNJP Hospital, New Delhi
8. District Naga Hospital, Kohima, Nagaland



According to NACO, these eight centers have achieved “an adherence rate of 96.1% among people who have been placed on treatment.” The first drug procurements were made by WHO.

During 2004-05, this list was expanded to include 17 more hospitals. It is expected that the total 25 hospitals will meet the government target of providing ART to 25,000 patients. These hospitals are:

1. Madras Medical College, Chennai, Tamil Nadu
2. District Hospital, Nammakal, Tamil Nadu
3. Government Medical College, Madurai, Tamil Nadu
4. Government Medical College, Vizag, Andhra Pradesh
5. Government Medical College, Guntur, Andhra Pradesh
6. Government Medical College, Sangli, Maharashtra
7. B J Medical College, Pune, Maharashtra
8. Government Medical College, Nagpur, Maharashtra
9. Karnataka Medical College, Hubli, Karnataka
10. Mysore Medical College, Mysore, Karnataka
11. Jawaharlal Nehru Hospital, Imphal, Manipur
12. Government Medical College, Ahmedabad, Gujarat
13. Government Medical College, Panaji, Goa
14. PGIMER, Chandigarh, Punjab
15. Calcutta Medical College, Kolkatta
16. SMS Hospital, Jaipur, Rajasthan
17. Banaras Institute of Medical Sciences, Varanasi

Source: The Government’s Stance (NACO Annual Report, 2002–2004)