# Anti-retroviral therapy in India: some cautions

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Highly active antiretroviral therapy (HAART) has changed the profile of the HIV epidemic in the developed world. Many of these countries have reported a dramatic decline in AIDS-related morbidity and mortality after the introduction of HAART into routine clinical practice (1). For the first time since its discovery, AIDS is now considered to be a chronic, manageable illness rather than a fatal disease.

This remarkable success of HAART cannot be attributed to the availability of drugs alone. Many of these countries had a proper infrastructure in place to ensure the rational use of antiretroviral drugs. This meant quality assured labs for monitoring response to therapy (viral load, CD4/CD8 counts), trained physicians, facilities for monitoring toxicity, regular clinical follow up and psychosocial support to reinforce adherence, and an infrastructure for the proper storage and dispensing of drugs. Additionally, national guidelines based on local studies have helped physicians attain uniformity in the use of these drugs. Without these systems in place, benefits from therapy would have been limited.

However, these enormous advances in HIV medicine have not been of much benefit to the developing world, where 90 per cent of HIV infected individuals reside (2). One of the important reasons has been the high price of antiretroviral drugs. Many of these countries would exhaust the whole of their health budgets if they decide to provide HIV-infected individuals with antiretroviral therapy.

Over the last few years there has been an intensive international lobbying for improving access to antiretroviral drugs for the developing world, particularly Africa. Issues such as compulsory licensing, differential pricing and parallel importing have been intensively scrutinised and debated. Pilot programmes have been launched in five African countries to assess the feasibility of introducing and integrating provision of antiretroviral therapy into the health care system (3).

The generic manufacture of drugs has been an important factor in the dramatic price reductions of many drugs in India. This has made possible for even the poor to get access to these drugs. Hence generic manufacturing of antiretroviral drugs would seem to be an important mechanism for reduction of prices. The first generic antiretroviral drug, Azidothymidine (AZT), was introduced in India in 1994. Subsequently, generic companies and multinationals alike (who own patents on these drugs) have introduced other drugs. Of late, many companies entered the antiretroviral market, considering it a lucrative market. However, not all drugs are available and there is a price war going on for the limited number of drugs (AZT, 3TC, D4T, NVP, IDV, DDI) available in India. Internationally, 16 antiretroviral drugs have been approved for the treatment of HIV infection.

There many concerns which pharmaceutical companies, the medical community and patients must address to ensure the proper use of antiretroviral drugs.

Initiating antiretroviral therapy for HIV-infected patients entails a life-long commitment to take these drugs. A single regime (usually including three drugs) will not be useful throughout the life span of the patient. In the real world, almost 60-70 per cent of people fail first-line regimes over a period of two to three years. One of the important factors in the failure of regimes is lack of adherence to therapy. When this happens, second- and third-line regimes (different drug combinations) need to be initiated for the patient to ensure durable benefit. Second- and third-line regimes are even more costly than first-line drugs, and even more difficult to adhere to. It is important to tell patients that the first-line regimes may eventually fail, and they may need to invest more for further treatment to ensure durable success. Unfortunately, information about drug failure is not promoted by companies or discussed by treating physicians, leading to the belief that the first-line, cheaper regime will be useful for a lifetime.

Physicians offering their patients ARV therapy face an important ethical question: Would it be proper to offer and initiate first-line regime when they believe the patients may not be able to afford the later regimes? This is the same ethical dilemma that they faced a few years ago regarding dual versus triple therapy.

Another important factor in ensuring the rational use of drugs is the availability of standard guidelines for their use. Internationally, three organisations, the Health and Human Services (HHS) USA, International AIDS Society (IAS) and British HIV Association (BHIVA) issue guidelines for HIV treatment on a regular basis. However, most of these guidelines have been developed from research carried out in the West. Some African countries and Brazil have developed their own guidelines to ensure uniformity in use. In India, uniform guidelines relevant for our population are not available. Though international guidelines are used, the limitations of applying them to the Indian population need to be acknowledged and addressed.

Training physicians in the prescription of antiretroviral therapy is extremely crucial to ensure the rational use of these drugs. Since information about HIV treatment is constantly evolving, frequent updating is necessary. Only a few, sporadic efforts have been made in this direction. Companies need to do more to correctly educate physicians about antiretroviral use. This would involve imparting technical knowledge and also discussing attitudinal and communication issues, particularly the importance of developing a good rapport with the patient. Additionally, a system of continuing medical education credits needs to be established.

Rifampicin used for treatment of tuberculosis, the

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commonest opportunistic infection for AIDS patients, interacts with protease and non-nucleoside reverse transcriptase inhibitors. It reduces the plasma levels of these antiretroviral drugs leading to development of resistance. Physicians need to be aware of this interaction when they plan to offer antiretroviral therapy for HIV-infected patients with tuberculosis.

The saddest part about antiretroviral therapy in India is the unavailability of paediatric formulation of these drugs. Neither protease inhibitor nor non-nucleoside reverse transcriptase inhibitor formulations are available. This essentially means that children cannot be given a three-drug regime. Neither can nevirapine be given to a neonate born to an HIV-positive mother to reduce the chances of acquiring HIV infection. Pharmaceutical companies have probably neglected this need because the market for paediatric formulations is still very small.

Two important surrogate markers, the plasma viral load and the CD4 counts, are used for initiating and monitoring response to therapy. These tests have to be carried out at frequent intervals and are costly. This cost has to be added to the cost of therapy, but nobody talks about this during drug promotions. Additionally, facilities for performing these tests are available only at a few centres. Often drug therapy is initiated without doing any of these tests, which is hazardous. It is like managing diabetes without monitoring blood sugar levels. There is also a lot of variability in the test reports from various centres. Uniform quality assurance programmes need to be established and laboratories need to be accredited.

Adherence is critical for the long-term success of antiretroviral therapy. Patients need a lot of encouragement and support to achieve more than 90 per cent adherence to their regimes. Mechanisms to ensure it need to be built up both by companies and treating physicians. It would be useful to manufacture a fixed dose combination of these drugs (such as three drugs in a single tablet), to make life easier for the patient. Another strategy would be to dispense drugs in monthly packs and not sell them in loose strips. Education and support by physicians, coupled with a commitment by patients to continue despite side effects and inconvenience, has become a critical component of successful treatment.

Hence, there many factors in addition to drug availability which determine the success of antiretroviral therapy. In the absence of addressing these background factors, reducing the prices and improving access will only contribute to more abuse than rational use. Irrational use may lead to the emergence of a multi-drug resistant HIV epidemic in the future. Moreover, these drugs will be rendered ineffective when used in pregnant women with the resistant virus to prevent their babies from getting infected.

Pharmaceutical companies' aggressive promotion of antiretroviral use will render their own products ineffective in future. Amazingly, they are not far sighted enough to observe that short-term gains can produce long-term losses. We have yet not learned from our experience of abusing antibiotics.

In conclusion, at present we are still not ready to implement chronic chemotherapy for HIV infection, even if the drugs are provided at a low cost. Moreover, the complexity of antiretroviral chemotherapy, requiring expertise and costly high technology laboratory capabilities, raises daunting challenges.

**References:**

1. The CASCADE Collaboration. Survival after introduction of HAART in people with known duration of HIV-1 infection. *Lancet* 2000; 335: 1158-1159.

2. Joint United Nations Program on AIDS and World Health Organization. *AIDS Epidemic Update: Dec 2000.*UNAIDS, Geneva, 2000.

3. Forsythe SS, et. al. The affordability of antiretroviral therapy in developing countries: what policy makers need to know. *AIDS* 1998; 12(Suppl 2): S11-S18.