

I am a physician involved in HIV/AIDS care at a large tertiary referral hospital. We find that a substantial number of patients are willing to take the new three-drug combinations in spite of the expense. Except for ZDV all these drugs have to be procured from the underground market.

infected individuals in the world are taking some form of anti-retroviral therapy. One of the major reasons for this is the poor access to these drugs at affordable prices in many regions, particularly in developing nations.

Accessibility and affordability of anti-retrovirals has in fact demonstrated the

HIV-infected individuals. When companies invest millions of dollars in drug development it is not surprising that the market prices of many of these drugs are prohibitive.

Such high costs lead to an unequal access to the drugs, making them affordable to only a handful of rich people. To improve accessibility, pharmaceutical companies have launched numerous programmes in the US, like the expanded access programme and the compassionate use programme.

When drugs are being developed at such a rapid pace it is imperative that they should rapidly be available to patients. However, drug approval has always been a tedious process. Considering the life-threatening nature of HIV infection, the US Food and Drugs Administration has developed a system of 'accelerated approval' of anti-retrovirals. By this procedure anti-retrovirals showing efficacy in improving surrogate markers (viral load and CD4 counts) are granted (relatively speedy) approval; the companies still need to subsequently conduct clinical endpoint studies to receive 'traditional approval'. In this way useful drugs are not withheld from widespread use and can benefit more patients.

In India drug approval depends on whether the molecule is old or new. Though small clinical trials need to be conducted locally for final registration of the drug, such a procedure may be bypassed for HIV drugs to avoid wasting time. However I do believe trials need to be conducted at least to assess short-term toxicities in Indian patients before a drug is launched in India.

Saquinavir - hard gel formulation (HGF, Invirase), manufactured by Roche, recently launched in India, was one of the first protease inhibitors to be approved by the US FDA. In one of the largest clinical trials involving saquinavir, SV 14604 demonstrated significant virological and immunological benefits to patients taking AZT/DDC/Saquinavir HGF.

Antiretrovirals in India

As AIDS drugs become available in developing countries, we may be getting obsolete drugs at exorbitant prices

Sanjay Pujari

Recently Roche registered its protease inhibitor Saquinavir in India, raising a number of questions about anti-retrovirals launched in developing countries: the relative costs of these drugs, the possibility that anti-retrovirals no longer popular in the West are being dumped in the developing world, and the responsibilities of the government, private industry and the community.

Over the last few years the management of HIV-infected individuals has undergone a sea change. For the first time in the history of the HIV epidemic, a reduction in the number of AIDS-related deaths has been reported in the United States. A significant contribution to the decline in death rates has been made by the use of combination anti-retroviral drugs and the advent of a new class of agents - the protease inhibitors.

Using protease inhibitors in combination with two nucleoside analog reverse transcriptase inhibitors has demonstrated dramatic and sustained improvements in virological and immunological markers. In addition, in clinical endpoint studies, such combinations have been shown to delay the progression to AIDS-defining events, and improve survival.

However, translating these scientific advances into practice has not been easy. UNAIDS estimates that only six per cent of the total number of HIV-

ever-widening gap between the developed and developing world. HIV/AIDS has always raised ethical issues. Until now these were primarily of avoiding discrimination and ostracism, respecting confidentiality, and ensuing voluntary testing and counseling. However, with the advent of combination therapies, the issue of equity and justice in relation to treatment access needs to be addressed urgently.

Equity in drug pricing: Price is at the centre of the question. Though many developed nations have paid attention to distributive justice once drug prices have been fixed, there has been little consideration of the ethics of pricing itself. For the first time in the history of drug pricing it may be stated that we need to look beyond the market's control for determining the "right", let alone the "fair", price of drugs.

In the developed world there will be no need to debate these issues, as all those in need will receive treatment. However, unless positive action (to ration treatments) is taken, the ability to pay is likely to determine access in many settings. Governments also need to negotiate with third-party payers such as insurance companies or international donors to improve access to these drugs.

It must be acknowledged that pharmaceutical companies have contributed to improving the quality of life and, to some extent, increasing survival of

Bioavailability: Since it was the first protease inhibitor to be approved it was widely used in the US initially. Subsequently as new protease inhibitors were developed it was realised that saquinavir was the weakest of its class. The major reason for this was its poor oral bioavailability. Only four per cent of the drug was absorbed by the body.

Another important issue was that dose-ranging studies saquinavir-hgf were never conducted, which could have defined a maximum tolerated dose. A trial in which higher doses of the drug was tested demonstrated that the current recommended dose of 1800 mg/day was suboptimal. In this trial patients taking higher doses of saquinavir hgf viz. 3600 mg/day and 7200 mg/day showed a larger and sustained decline in viral load and also demonstrated delayed development of genotypic resistance.

In summary, the current formulation of saquinavir is less potent because of its bioavailability. This led to saquinavir being described as an alternative protease inhibitor by the recent Health and Human Services (HHS) guidelines, endorsed later on by the International AIDS Society - USA panel guidelines.

Naturally, any three-drug combination which includes saquinavir-hgf would be considered only as an alternative regime.

To make saquinavir more bioavailable Roche has now developed a soft gel formulation (Fortovase). This formulation is 10 times more effective than the current hard gel formulation. Naturally in combination studies it produced a dramatic improvement in the viral load, and in one study was more effective than a combination containing indinavir.

Roche has applied for Indian FDA approval which is expected by the end of this year. The recommended dose of the soft gel formulation is 3600 mg/d, twice the dose of the poorly absorbed hard gel formulation. The very fact that Roche developed a soft gel formulation of saquinavir indicates it acknowledges the drawbacks of the hard gel formula-

tion.

Another issue is what has been projected as an advantage of saquinavir, its resistance pattern. It was believed that the resistance pattern of saquinavir was different from that of other protease inhibitors, allowing it to be used as a first-line drug; if and when it failed the patient could be shifted to other protease inhibitors, which would still be useful.

Drug resistance: However, we now know that saquinavir often produces mutations which causes cross-resistance to other protease inhibitors. This suggestion has been further validated in a clinical trial where the expected fall of viral load was not attained when patients who appeared to have failed

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saquinavir were shifted to indinavir (ACTG 333). As a result, the trial was terminated prematurely.

And when do patients develop resistance to anti-retroviral drugs? Either when these are taken as monotherapy or when their dose is suboptimal. Here then one can easily understand the link between suboptimal dosing and development of early class resistance with saquinavir.

Considering this background, it is no surprise that the saquinavir-hgf formulation is not prescribed very frequently in combinations. This would mean the sales of this drug are slated to fall in the West (particularly after the HHS guidelines). Already in the US the drug is used only as a second-line therapy. So why is such a drug being launched in India now?

If the soft gel formulation is going to be marketed in the near future why not wait for the more potent drug, rather than dumping a second line formula-

tion? Have dose-ranging studies amongst Indian patients been carried out? If they have, for how long has the drug been studied? The public needs to have access to these India-based studies.

Piramal Health Care is marketing the saquinavir - hgf formulation in India. The price fixed is around Rs 19,000 — beyond the reach of the majority of Indian patients. It is preposterous that the least potent protease inhibitor is priced so high. There is no doubt that a significant part of the price goes towards customs duties and other taxes, which the government should seriously think of waiving.

Initially the drug was made available for a lower price (Rs 7,000 for a month's supply) for some patients. Piramal has argued that it was providing the drug through its Compassionate Use programme. We are not aware of any such programme. Nor was a single patient told that he was receiving the drugs on a compassionate basis 'and that prices were slated to rise after registration. If such a warning had been issued the number of patients taking the drugs would have dramatically dropped.

Patients already taking the drug who are now unable to afford the raised cost would have to stop the drugs, leading to subsequent resistance, thus limiting their future options.

Thus, the registration of the first protease inhibitor and its subsequent pricing should be viewed in the larger context of the future approval of other anti-retrovirals. Policies, particularly regarding pricing, such as waiving of customs duties, should be developed before drug registration so that uniformity in pricing is achieved.

Advocacy groups working with people living with HIV/AIDS need to be part of the approval process. A helping, not confrontational, attitude will help bring the benefits of the current and future drugs to HIV-infected individuals in India.