of therapy now is to lower viral load as much as possible for as long as possible." From the data shown in Emini's presentation (and several others), it is clear that this goal is attainable. Although "HIV can't be eradicated with these drugs" it may be possible to "make everyone [who is] infected a long-term nonprogressor," according to John Phair of the Northwestern University Medical School in Chicago. Another benefit of the viral load assay is the possibility of quickly testing future compounds for their antiviral activity *in vivo*. Such studies will "do away with waiting years for clinical end points [progression to AIDS or death]," says Phair, thus allowing promising drugs to be brought to the market more quickly.

Perhaps the more important question, however, is not which drugs to use, but rather *when* to start treatment?

Despite the optimism, there are problems with the new compounds. None of them is a "magic bullet": the ability of the virus to mutate rapidly allows the emergence of drug-resistant strains, though perhaps not as quickly as seen with other AIDS drugs. Furthermore, resistance to one protease inhibitor may lead into resistance to the others, a significant problem for those unlucky enough to be carrying such resistant strains. The current compounds are not well-absorbed, which means they must be taken at high doses. And because they are difficult to manufacture, they are expensive. Saquinavir costs an estimated US$5,800 a year at its currently approved dose, and the other protease inhibitors are expected to be similarly priced, although Merck and Abbott have both agreed to meet with patient advocacy groups to discuss the cost of the drug and buyer's assistance programs before setting a price.

With the seeming abundance of new drugs and combinations with existing antiviral drugs, which is the best treatment? There is no direct answer to that, but it seems clear that the Abbott and Merck protease inhibitors, once approved, will be the choice of most clinicians (in combination with existing antivirals like AZT), at least until other drugs prove themselves.

Perhaps the more important question, however, is not which drugs to use, but rather *when* to start treatment? Until now, most decisions about therapy have been based on a patient's $CD4^+$ T cell count which, in combination with the toxicity of available AIDS drugs, has led to delays in treatment until the infected person had progressed substantially (and irreversibly). But because the volume of virus in a patient predicts $CD4^+$ cell decline by as much as two years. Some clinicians are suggesting that antiviral treatment should begin only when viral load is "high" (generally considered to be more than 10^5 viral RNA copies per milliliter of blood).

Others disagree. "Even 10,000 [viral copies] is really unacceptable," says David Ho, who has advocated an HIV treatment strategy of "hit it early and hit it hard." This makes intuitive sense, because if the virus is prevented from replicating rapidly in the earliest stages of infection, the chances of resistant strains arising by mutation are significantly lower. However, the cost and difficulty of taking the current drug cocktail indefinitely, especially without knowing the long-term effects, is considerable (the *Wall Street Journal* estimates the triple combination of indinavir, AZT, and 3TC at more than $12,000 a year). New data make it clear that going off the protease inhibitors even transiently allows the virus to rebound rapidly. Studies are either planned or under way to consider the effects of and optimal dose for early intervention.

Patients live longest if they have an AIDS specialist for a doctor

Finally, it is essential that physicians be educated in the use of the protease inhibitors and the interpretation of viral load testing. The importance of this was underscored by a report released at the conference showing a direct correlation between the length of life of an AIDS patient and the experience of his or her doctor in treating the disease: the less experienced the physician, the sooner the death of the patient.

Although they sound cautionary notes, even activists are gladdened by the good news coming out of the conference. "Of course we'll want to wait and see how long these good effects [of the protease inhibitors] will last," says Jules Levin, director of the National AIDS Treatment Action Project in New York, and a tireless proponent of protease inhibitors. "But I am pretty excited."

FINTAN R. STEELE

Japan tries to reduce prescription drug use

More than a quarter of the ¥23,800 billion (US$238 billion) that Japan's public medical insurers spent in 1994 went for prescription drugs and injections, according to a recent survey by the Ministry of Health and Welfare. Despite a significant fall of 2.3% from the previous year to 27.2%, Japan still spends a higher proportion on medicine than any other major industrial nation.

The fall, however, brings the figure to its lowest level since 1987, when the current system for analyzing medical expenditure was set up by the Ministry of Health and Welfare. The ministry, which is in a constant battle to halt Japan's escalating medical costs (*Nature Medicine* 1, 985; 1995), reduced the official National Health Insurance (NHI) average drug price by 6.6% in 1994. It plans to reduce it a further 8.5 percent from April, at the start of the new financial year to try to relieve some of the strain Japan's rapidly greying society is putting on the medical insurance system.

Japanese hospitals and clinics purchase drugs directly from pharmaceutical companies and wholesalers at a price that is on average 10 percent below the official rate, set by the ministry. Hospitals and clinics are able to bolster their income by claiming the full official rate from Japan's public medical insurers. This, industry observers believe, has encouraged Japanese physicians to overprescribe drugs.

The ministry has, however, been trying to encourage the separation of the roles of prescribing and dispensing drugs. According to the survey, which was based on information from 9,000 hospitals throughout Japan, the number of prescriptions filled at pharmacies outside the clinic or hospital where the original prescription was made increased by 3.6 percent in 1994. But the vast majority, 83 percent of prescriptions, are still dispensed on site.

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