nature medicine
VOLUME 3 • NUMBER 5 • MAY 1997

Sealing the fate of HIV

An eclectic group of articles in this issue give us pause to consider again the direction of HIV research and whether this direction is likely to meet the long-term needs of the community. It has only been relatively recently that the less sensationalist HIV researchers have even dared ask the question "can HIV be eradicated from an infected person?" With the advent of promising new drugs of the reverse transcriptase and protease inhibiting variety, and their combination into protocols that are commonly referred to as "triple therapy", researchers have seen patients' blood levels of the virus reduced to below detection thresholds. It was reasonable for the community to be excited, and excited they were. Early 1996 saw reports from the Third Annual Conference on Retroviruses and Opportunistic Infections, claiming that for the first time it was possible to consider AIDS a treatable disease, and drew promises from the FDA that New Drug Applications for a new line of protease inhibitors would be rushed through on a fast track in light of their early promise and potential. To be fair, much of this reporting reflected on the fact that for the first time there were drugs that could definitively lower blood plasma levels of the virus and that with this lowering was a reasonable expectation for prolonged survival for AIDS patients — and assuredly this was welcome news for desperate patients and their doctors.

However, even in some of those early and enthusiastic reports of antiviral drug development, it was quietly noted that coming off the drugs allowed viremia to rebound, and virologists were murmuring that such drugs were not a long-term answer. On page 483 of this issue, Giuseppe Pantaleo reiterates much of this, mentioning as yet unpublished results showing that even after a full year of triple therapy and even in infected patients in whom virus can no longer be detected in the blood, stopping antiviral therapy allows viremia to rebound to former heights within just two to four weeks. Pantaleo notes that although these have to be considered preliminary observations, they do not bode well, and suggests that the only long-term solution to infection is a combined antiviral and immune-based approach to keeping the virus at bay — permanently.

That is not to say that triple therapy has no part to play. All evidence to date suggests that lower viremia translates into longer life expectancy. However, intensive and costly treatment protocols are called for and at best this approach may prolong life only for the duration of the treatment. As yet, there are no data on the consequences of very long term treatment, and from the global perspective, this therapy can only help a minority of patients with access to advanced medical care. Should there be any doubt over the likely continuing impact of HIV in developing countries, on page 553, Daniel Low-Beer and colleagues present empirical evidence to show what a dramatic effect HIV infection can have on local populations in the developing world, with infants being particularly hard hit and grave consequences for population structure and demographics.

The solution is to avoid the necessity of treating the infection by preventing it in the first place, and although topical microbicides may have a role to play as will other antiviral approaches to reduce mother-infant transmission, a vaccine is the only real answer. In the late 1980s, development of an HIV vaccine was all the rage and prompted forecasts of great dividends for the companies working on such vaccines. But early (and continuing) difficulties identifying an appropriate viral protein on which to base a vaccine and understandable concerns with the safety of any live attenuated HIV vaccine coupled with doubts surrounding the effectiveness of other vaccine constructs, meant that the excitement was short lived. Antiviral drugs showed more promise and soon took center stage. But progress on vaccines has been made. Although it is unlikely that the unaided human immune system can fend off infection entirely, evidence from studies of long-term nonprogressors shows that some patients produce both humoral and cellular immune reactions that are at least partially effective and suggests that an efficacious vaccine will need to generate very robust responses from both arms of the immune system. Such a double-edged response against HIV and SIV has been provoked in animal studies, although protection has eluded the field to date. On page 526, Jean Boyer and colleagues describe the results from using a DNA-based anti-HIV-1 vaccine in chimpanzees. They show that despite variable immune responses, both vaccinated animals challenged with HIV-1 remained infection-free for nearly a year (the duration of the experiment).

Although it remains unclear just how effective triple therapy is, it seems unlikely that it will be appropriate for a worldwide offensive and may even be too limited for long-term use in those developed countries that can afford it. More attention must turn to the question of long-term immune-based therapies to treat infection and to vaccines to prevent it — not such an attractive proposition from the point of view of corporate profits, but a much healthier outlook for the planet.