

Gay Men's Health Crisis

A Long March, in Unknown Territory, to an Uncertain End

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In this special double issue, Treatment Issues presents the results of its second survey of physicians' practices. Our first survey, conducted in the spring of 1996 just as the first crop of potent antiviral agents was entering the market, revealed a wide range of improvisations by physicians. Doctors answered the classic treatment questions of who, what and when in a variety of ways. They favored different combinations, some containing two drugs, some three, and introduced them at different stages of disease. Viral load tests were also a novelty, and physicians expressed considerable disagreement, confusion even, as to how low viral loads need or could be pushed.

Has another 18 months of experience clarified treatment strategy? The first thing that the medical community has realized is that 18 months of maximally suppressing HIV does not eradicate the virus. There remains a small pool of infected cells that could serve as a source of resurgent infection should treatment be terminated. Physicians have also observed rebounds in viral loads in many people who remain on therapy that is not fully suppressive therapy. And a few people on treatment have rebounded although their viral loads are below 50 copies/ml the new ultrasensitive assay's limit of quantification.

The factors behind treatment failure remain nebulous to survey respondents. They related an enormous range of estimates about how commonly HIV bounces back during treatment -- from a small percentage of patients to virtually 100%. This difference may reflect the difference in patient populations that the respondents see. Doctors with more advanced or more treatment-experienced patients obviously will observe earlier and more frequent treatment failure.

Because of their experience, the doctors in our survey are deeply concerned that patients be able to completely cooperate with the complicated dosing schedules of triple combination therapy. There is also heightened realization that doctors and patients in the past wasted drugs by exposing HIV to them one after another in sequential therapies that did not completely block HIV replication. The result has been up and down swings in viral load accompanied by the emergence of ever more drug-resistant HIV. Because of drug resistance, as well as intolerance, many individuals are running out of treatment options despite the availability of 11 marketed and four experimental anti-HIV drugs (see pages 18-25 for a review of the new agents).

The worry about exhausting available drug options causes wide divergence about when to introduce and switch treatments. Most doctors now favor starting out with a three-drug combination including a protease inhibitor (or perhaps a nonnucleoside reverse transcriptase inhibitor for those with low viral loads). A minority of respondents still prescribes two drug combinations in patients with lower viral

load. Their favorite two-drug combination is mainly d4T/ddI because of these drugs' presumed reduced vulnerability to the evolution of drug resistance. They hope to reserve the potent but vulnerable drugs like 3TC and the protease inhibitors for a time when untreated viral load would be massive and there is no effective therapy without including these agents.

Similarly, although everyone in the survey now uses viral load to monitor patient progress, some still allow measurable viral loads of a few thousand copies per ml in patients, as opposed to insisting on regimens that reduce viral loads to unquantifiable levels by the standard PCR (which measures down to 400 copies/ml). They report that their patients can be clinically and immunologically stable despite such levels of HIV. But most survey respondents fear that such patients will have progressively greater viral loads and eventually decline clinically. A few are now using the ultrasensitive test to track their patients' progression, although they have yet to understand the further significance of driving viral load past 400 copies/ml to below 50 copies/ml.

A very hopeful sign is that respondents reported a greatly reduced level of opportunistic infections, except for candidiasis. About half are recommending that some of their patients reduce the number of medicines that they are taking as opportunistic infection prophylaxis. This reduction balances off some of the increased pill burden and toxicity encountered with the new potent anti-HIV regimens.

A Note on Treatment Guidelines There are now in the U.S. two sets of quasi-official treatment guidelines and one set of treatment "principles" in wide circulation. The International AIDS Society-USA updated "recommendations" were published in The Journal of the American Medical Association on June 25, 1997 (pages 1962-9). The final version of the Public Health Services' "guidelines" were issued November 5, and the National Institutes of Health's "principles" are still available only as a draft issued last July. These latter two have not been published but are available at several sites on the World Wide Web (for example, www.cdcnac.org or www.hivatis.org).

All three advise more aggressive therapy than would have been the case in the past. According to these documents, anti-HIV drugs should be at least offered if patients' viral loads exceed modest levels. Triple drug combinations, usually with protease inhibitors, are the treatments of choice. These documents also recommend changing therapies in the case of rising viral loads. The exact details differ in each of the three, with the IAS-USA advice being the most aggressive and the NIH principles the least specific, but all promote the goal of maximum viral suppression.

The respondents in our survey, some of whom participated in the drafting of one or another of these documents, have clearly been influenced by these recommendations. Many argue however that such efforts at guiding doctors are still speculative due to the lack of sufficient research into the outcome of long-term management of HIV infection.

The big question then remains where does highly suppressive therapy ultimately lead -- viral breakthrough, eradication (at least for a few), or prolonged reduction of HIV to tolerable levels. And whatever therapy's theoretical potential, will the build-up of drug toxicities become a limiting factor in managing HIV over the years? We have accumulated much new experience in treating HIV infection since Treatment Issues' first survey. But clearly we have years to go before the many uncertainties and doubts can be definitively settled.

[See the topic on aegis.org](http://aegis.org)