Absorbing Drama

Drug-level tests may be key in preventing treatment failure.

March 1, 1998 By Bernard Bihari, MD

Laboratory analyses of blood and other medical measurements, which help health practitioners make diagnoses and detect toxic effects of medication, can also help people with HIV track their health. In this issue, ***Bernard Bihari, MD****, a Manhattan clinician and researcher who has treated thousands of PWAs, discusses the results of a recent drug-level test performed on* POZ *founder Sean O. Strub.*

Sean's viral load has remained consistently undetectable for more than a year, a lab result that goes hand in hand with his overall continued well-being. However, recent reports of drug failure in a large percentage of people after a year or more of highly active antiretroviral therapy (HAART) have heightened interest in determining the possible causes of such failure. If we can learn where the problem lies, we may be able to give PWAs a much better chance for drug effectiveness that lasts years.

I have long felt that individual differences in protease inhibitor absorption are responsible for much of the drugs' variable effectiveness, both initially and down the line. For this reason, I ordered a drug absorption test -- now easy to obtain but so far rarely prescribed -- to see how well the Crixivan (indinavir) Sean is taking is actually getting into his body. Before commenting on Sean's results, it's important to discuss the context in which we're looking at this absorption issue.

First, we know that the initial drop in viral load differs greatly among individuals. It is estimated that in 15 percent to 20 percent of patients who begin HAART, the drugs are unable to reduce viral loads to undetectable levels -- and in some, even the best combos yield little if any improvement. In an era when the dramatic antiretroviral and clinical benefits of HAART have raised hopes about making HIV infection a manageable disease, this initial failure seems particularly cruel.

Even in those in whom the combos work well initially, there is often later failure. In multiple studies of PWAs treated with HAART, there have been alarmingly high rates of viral breakthrough over time. Even in some people whose viral loads have been kept undetectable for as long as a year, HIV levels eventually begin to rebound.

Since dropping the viral load to an undetectable level and then keeping it there ad infinitum has become the Holy Grail of HIV care, these findings are disturbing. Discovering all the reasons for

both the initial lack of sufficient antiretroviral power to make HIV undetectable as well as the causes of viral breakthroughs is crucial.

Nonadherence to difficult drug regimens clearly explains some treatment failures. In my private practice -- where frank, nonjudgmental discussions about adherence-related issues take up a lot of appointment time -- it appears that approximately 5 percent of patients on protease inhibitors have serious problems sticking to the regimen, particularly with the rigorous rules governing Crixivan use. The nonadherence rate may be somewhat higher in the populations so far studied, but is not, I believe, high enough to explain the dramatic failure rates found in PWAs for whom adherence is known to be a life-or-death issue.

So if failure to take the drugs correctly is an inadequate explanation for drug failure, then we must look at the possibility that they may not be getting into the body very well. It doesn't matter how perfectly you take drugs if they're not being absorbed after you swallow them. And research points to the possibility of wide variability in absorption.

In a 19-person study by Boeringer Ingleheim, manufacturer of nevirapine, assessing the effect of adding its drug to Crixivan, all patients were initially given the standard Crixivan dose of 800 mg every eight hours for 28 days. The most striking finding was not the 27 percent drop in Crixivan blood levels when nevirapine was added but rather the 300 percent variation between patients in Crixivan blood levels before nevirapine was initiated. Whether low or high initially, drug blood levels were generally consistent, remaining at the same level in each patient throughout the study.

The importance of this is clear. It is only by stopping viral replication completely that we prevent the virus from developing the mutations that can prevent the drugs used against it from working. Since there is a minimum therapeutic anti-HIV blood level for each antiretroviral, some of the people whose blood levels remain low are likely to have inadequate power to fully suppress HIV. These patients are likely to develop viral resistance to the protease inhibitors within a few months. Others may have intermediate blood levels that yield initial suppression of viral replication but eventually allow slow development of resistance. And the lucky PWAs who achieve optimal levels may be the only ones for whom the drugs will keep on working.

Because of concern that I might not be achieving adequate drug blood levels in my patients, I have begun testing Crixivan levels; Sean was the first to get the test. Blood was drawn one hour after his morning Crixivan dose. The drug level result, 15.46 uM (micromoles), is on the high end of the laboratory's reference range for peak Crixivan levels (listed as Cmax) of 8.20 to 16.66 (referred to on the chart as 12.62uM +/- 4.04uM). This range refers to the blood levels known to effectively suppress HIV. The effective levels of all antiretrovirals have been established in the clinical trials that led to their approval, although the use of drug blood-level tests for treatment decision-making hasn't been validated by researchers.

Sean is taking 800 mg of Crixivan every eight hours along with standard doses of delavirdine and d4T. Delavirdine tends to raise Crixivan blood levels, which may partly account for Sean's high-

normal finding. It’s also possible that genetic factors, which greatly influence drug absorption, play a role here. Since Sean is doing quite well on this regimen, I would maintain the present Crixivan dosage, despite his somewhat high blood level.

Out of the 30 patients for whom I have so far obtained Crixivan blood levels, five have required dosage increases in order to reach an effective level. And two patients had to be switched to other drugs when even a high dose of 1,600 mg of Crixivan, three times per day, failed to put them within the effective range. So, to date, obtaining drug levels has pointed to the need for drug changes in almost one out of four patients.

The lesson may be that we need to consider strongly each individual’s absorption capacity and make drug level-dictated dose adjustments where necessary. This should not be surprising. We have decades of experience using the results of blood level tests to adjust the doses of drugs used to treat such conditions as epilepsy, congestive heart failure, manic-depressive illness and abnormal heart rhythms. The general experience is that doses of these drugs must be adjusted over at least a 300 percent range to achieve standard therapeutic blood levels in each individual.

It will also be important to devote more attention to drug absorption -- and ways to improve it. I am interested in the possibility of increasing absorption by using L-glutamine, an amino acid required for the turnover of small-intestine cells and the maintenance of their absorptive capacity. Preliminary research indicates that glutamine may be in short supply in many PWAs, a factor that might contribute to drug malabsorption. (For further information on the glutamine needs of PWAs, see “Those Darned Free Radicals,” *POZ,* August 1997.)

I would encourage people with HIV to request that their physicians monitor blood levels of antiretrovirals. Although the lab used for Sean’s test only does Crixivan levels, Specialty Laboratories (800.421.7110) now offers tests -- costing about $160 each -- that measure most such drugs (not only protease inhibitors, but also non-nucleoside reverse-transcriptase inhibitors [NNRTIs] and nucleoside analogues).

I strongly urge drug manufacturers, the Food and Drug Administration, the National Institutes of Health and the U.S. Public Health Service to include drug blood level monitoring -- and appropriate dosage adjustment -- as an essential element of the standard of care for people with HIV. There should also be a loud call for insurance reimbursement for the tests. Studies to determine relationships between blood levels and viral breakthroughs will be crucial in the development of such standards, as we refine the use of our ever-improving armamentarium in the treatment of HIV infection.

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