Viral load: To treat or not to treat?

Many physicians are using a new laboratory assay to determine therapeutic approaches for their HIV-infected patients, without FDA approval.

A major difficulty in designing clinical trials of anti-HIV drugs and in planning therapeutic strategies for HIV-infected individuals is the lack of universally valid clinical end-points (except for death) or immunological landmarks (except, perhaps, the number of CD4+ T cells). But a relatively new laboratory measurement is rapidly becoming the marker of choice, both for physicians in private practice and for researchers seeking new antiviral drugs. And the US Food and Drug Administration (FDA) is in the awkward position of being unable to offer concrete guidelines on the proper use of the new test for either, because no formal application for its approval has yet been made.

This new procedure, known to the *cognoscenti* as a 'viral load assay', was a major topic of discussion at a joint FDA- and National Task Force on AIDS Drug Development-sponsored meeting held 6–8 September on the campus of the US National Institutes of Health (NIH). The central thrust of the gathering of AIDS experts was to identify and suggest remedies for the supernumerary problems plaguing AIDS-related clinical trials. Of particular interest to the FDA, however, was gathering a consensus from researchers on the use of the viral load assay as a surrogate marker, both in research settings (testing new antiviral drugs) and in clinical settings (prognosis and monitoring disease progression). The FDA also used the occasion publicly to encourage companies with assays in development, most notably the branched DNA assay from Chiron (Emeryville, California) (see figure) and the PCR-based viral load assay from Roche (Nutley, New Jersey) to hasten submitting applications for clinical use approval. Representatives from both companies state that applications will be submitted "very soon".

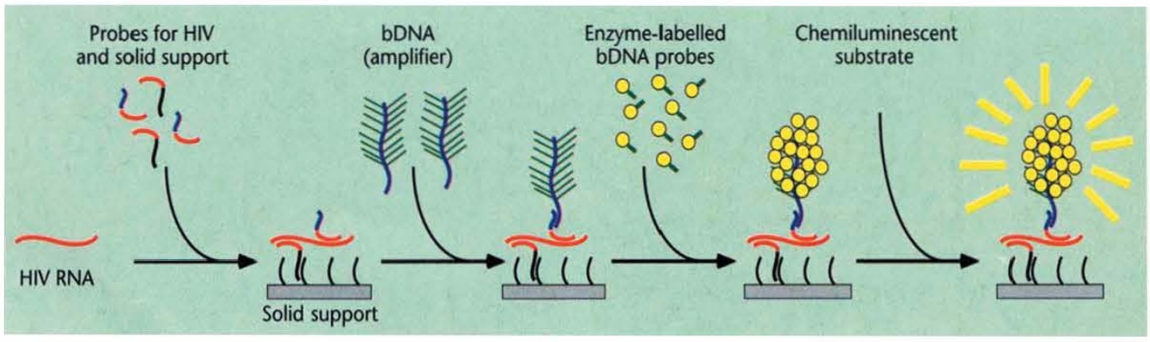
Although researchers generally believe that viral load measurements are, or will be, useful, they also have significant concerns. For example, several meeting participants pointed out that, despite its short-hand name, a 'viral load' test is more properly only a measurement of the amount of HIV viral RNA in the plasma, and thus only part of the total amount of virus carried by an infected person. Furthermore, the test "doesn't measure infectious virus, but is rather a surrogate for virus replication," said John Modlin of Dartmouth Medical School, Hanover, New Hampshire, and acting chairman of the FDA antiviral drugs advisory committee. Modlin also said that despite a growing number of studies, the interrelations between virus replication, infectious virus, the number of CD4+ cells and disease progression is unclear. However, both he and other committee members agreed that viral load studies to date have shown enough correlation with clinical prognosis to warrant future FDA approval of the quantification techniques.

Despite the lack of FDA approval — and guidance for proper use — the technique is gaining wide clinical acceptance by individual physicians as a tool for monitoring their patient's disease progression. And not always wisely. "The test is being widely used now to make therapeutic decisions, and we need to rein in the abuses," says Fred Valentine of the New York University Medical Center and member of the FDA advisory committee. Valentine and others point out that immune activation against other agents, even something as simple as cold sores, can transiently increase HIV viral load, leading to poor decisions. "They [the physicians] get one measurement, and then change their patient's therapies based on what they believe is a high viral load," says Valentine. He adds that doctors and patients have to be educated as to the proper use and meaning of viral load results, a sentiment that was echoed at the meeting by several scientists who felt that educational requirements should be part of any future FDA approval of the technique.

Another danger inherent in the rush to embrace the new test is overemphasizing viral load at the expense of other important factors discovered over the fifteen years of the epidemic. "We're making viral load too much of a stand-alone issue," says Robert Schooley of the University of Colorado and member of the the National Task Force on AIDS Drug Development. "To make clinical decisions about treatment we also need CD4+ cell counts, how the patient is feeling and the patient's willingness to undergo aggressive treatment — in addition to viral load."

Whether viral load will ultimately turn out to be the long-sought valid marker for evaluating the efficacy of antiviral therapies is unknown, pending the design and completion of studies aimed at determining what viral replication levels in the plasma really mean in terms of disease progression or treatment efficacy. It is a task that is difficult at best, though ultimately necessary for issuing rational guidelines for use, and for preventing bad therapeutic decisions based on incomplete or misleading data.

FINTAN R. STEELE



The branch DNA (bDNA) technique, one of several tests used to determine viral load. (Based on information provided by Chiron.)