Predictive Value of Viral Load Testing Questioned

September 30, 2006 By Tim Horn

September 30, 2006 (AIDSmeds)—While the value of viral load testing is pretty much undisputed with respect to monitoring HIV-positive people while on treatment, a recent study by a nationwide team of HIV researchers strongly challenges conventional thinking about viral load as a measure of disease progression in those who aren't yet on therapy and questions the value of using viral load to determine when treatment should be started. The study, published in the September 27th issue of the *Journal of the American Medical Association (JAMA)*, indicates that viral load is much less reliable as a tool for determining the rate at which an HIV-positive person will lose CD4 (T4) cells than previously thought.

Ten years ago, a monumental paper published in *Science* by John Mellors, MD, of the University of Pittsburgh and his colleagues, concluded that an HIV-positive patient's viral load is an excellent predictor of how quickly he or she will progress to AIDS if the infection is left untreated. Soon after these findings were published, HIV experts and healthcare providers all over the world embraced the idea of using viral load, in conjunction with CD4 cell counts, to monitor their patients' health and to figure out when to initiate treatment.

A simple analogy is often used to illustrate how viral load and CD4 count testing are supposed to work together. Viral load and CD4 cell counts are like a train rushing along a set of railroad tracks. Up ahead is a cliff. This cliff represents AIDS. The CD4 cell count tells us how far the train is from the cliff, whereas the viral load tells us how fast we are moving towards it.

The new research, headed by Benigno Rodríguez, MD, and Michael Lederman, MD, of Case Western Reserve University in Cleveland, doesn't debate the decade-old research concluding that average viral loads may predict average CD4 cell count declines in large cohorts of patients. What Dr. Rodríquez's group argues is that viral load is a relatively poor predictor of disease progression in individual patients. Based on the observed variability in viral loads and disease progression rates seen in individual patients, they say, depletion of CD4 cells is not solely driven by high HIV replication in the body.

"The results of this nationwide study may have profound implications in our understanding of how HIV causes disease and in our approach to the management of HIV-infected patients," says Dr.

Rodriguez. “We hope that this study will provide impetus for a more thorough understanding of the mechanisms of HIV-induced damage to the immune system and for the design of strategies to block those mechanisms.”

In the study, Dr. Rodríguez and his colleagues report the results of analyses involving two large cohorts of 2,800 HIV-positive people who were not receiving treatment for HIV. The first cohort consisted of patients enrolled in one of four sites of the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), the San Francisco Men’s Health Study (SFMHS), and the Research in Access to Care for the Homeless Cohort (REACH). The second cohort, which the investigators used to validate their findings in the first group, included participants in the Multicenter AIDS Cohort Study (MACS) – the same group of patients that was used by Dr. Mellors’ group back in 1996.

As expected, there was significant variation in the rate of CD4 cell loss within the cohort. Dr. Rodríguez’s group then tried to determine if this CD4 cell loss could be accounted for on the basis of each patient’s first recorded viral load measurement, in an attempt to reproduce more closely the situation that a healthcare provider would encounter in the “real world,” where a patient presents with an initial set of laboratory results and the doctor must try to predict how quickly that person’s CD4 cell count will reach the danger level at which treatment for HIV becomes most critical.

Using sophisticated statistical models, the researchers found that only 4% to 6% of an individual patient’s CD4 cell loss rate was explained by his or her initial viral load. Moreover, the results were remarkably similar when the analyses were reproduced separately in each of the two cohorts, and changed only minimally when the investigators considered the possible effect of errors in the measurement of the CD4 cell count and the viral load.

These results, Dr. Rodríguez says, are at odds with current thinking that the rate of CD4 cell loss in a given HIV-positive person can be accurately predicted by his or her viral load.

In a September 29th *Science* news article by Jon Cohen regarding the *JAMA* report, Dr. Mellors said that he doesn’t buy the conclusion of the study. “We don’t agree with the paper at all,” he was quoted as saying. “[Viral load] is the most powerful predictor of time to AIDS and death.” Dr. Mellors suggested that the JAMA paper’s results may reflect that CD4 measurements vary a great deal in different labs. Dr. Mellors also said that viral loads should continue to play an essential role in determining when to start people on treatment.

Dr. Rodríguez’s group is sticking to its guns and concludes that CD4 cell loss in HIV-positive people cannot be thought of as a mere consequence of the amount of virus circulating in the blood. These new findings, they say, hint at more complex scenarios of disease progression, and point to the possibility of indirect processes through which HIV can induce damage to the immune system.

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