A Load Off His Mind

Sean Strub's viral load becomes undetectable and his CD4s balloon-but...

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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. Donald Abrams, MD, is assistant director of the University of California at San Francisco AIDS Program, San Francisco General Hospital. He has been treating and researching AIDS for 15 years. Abrams analyzes the viral load and CD4 count of POZ *founder Sean O. Strub.*

Sean must be quite elated with his most recent lab results. After months of combination therapy with a protease, his CD4 count has risen markedly, to 77, and his HIV viral load is now below the limit of detection of the test used to measure it. What's even more important-he feels well with increased energy and an improvement in his Kaposi's sarcoma, to the point where he can take longer breaks between chemotherapy treatments. Sean's scenario is now shared by many PWAs, delighting their physicians as well as those embarking on the new therapies.

CD4 counts and viral-load measures are considered *surrogate markers* of a PWA's health. The term originated with clinical drug trials, where surrogate markers are used to avoid waiting for clinically meaningful end points-symptoms, full-blown diseases or death. The theory is that changes in a surrogate marker brought about by therapy will mirror later changes in endpoints.

But if suppression of the virus is somethign to shoot for (and now some people even talk about its eradication), why is viral load considered a *surrogate* marker of a drug's effect and not an *actual* marker? Because we don't yet know if our chosen surrogate is really predictive of our main desire: Prolonging the life of the patient. We often hear the new mantra-"It's the virus, stupid"-but I think that's short-sighted. It really is the *patient* that should be our main concern. There was a drug recently evaluated that was extremely potent against hepatitis B virus. It virtually eliminated the virus from the bloodstream of people who had been chronic carriers for years. Unfortunately, the drug was very toxic and although the hepatitis B disappeared, several of the patients died from damaged livers. The medical literature is full of cases where a so-called surrogate marker of a disease moved in a positive direction in response to a therapy, but the patient had an overall negative outcome.

What about CD4 counts? Now that we can measure viral load, some would say there's little need to follow CD4 counts anymore. The CD4 lymphocyte is still the critical target of HIV infection. As

the immune-system building-block cells die off due to HIV infection, the body's ability to fight off the specific AIDS-defining infections declines in a way that has become relatively predictable during the past 15 years of utilizing the tool. Studies now show that baseline viral-load levels can also be used to predict overall survival-but it has not been clearly demonstrated that viral-load levels are as useful as the CD4 count in predicting the prospects for developing specific opportunistic infections. Rather than cast aside CD4 counts for clinically monitoring patients, most physicians are utilizing both tests together. Dr. John Coffin, a noted retrovirologist, has made this analogy: If a PWA is like a train heading toward a downed bridge (disease progression or death), the CD4 count tells you how far the patient is from the bridge and the viral-load level tells how fast the train is moving.

Sean's lab values strongly suggest that not only has he put the brakes on, he's also backtracked farther from the bridge. His CD4 count-listed as *absolute* CD4-has jumped from one cell in 1995 to 25 after six weeks on indinavir (Crixivan) and d4T (Zerit) and has not tripled to 77 since adding delavirdine (Resciptor) in August. A few weeks before this measure, Sean received a CD4 count of 93, done by a different lab. At first glance, the new count may seem like a decline, but the two numbers are virtually the same, especially considering the widely found variations between labs. (This is why it's advisable to stick with one lab to really follow the status of one's CD4 counts).

So if the train is moving away from the bridge, can we jettison some of the preventive therapies taken to avoid opportunistic infections? For example, at a CD4 count of 77, some might say Sean is no longer at risk to develop disseminated *Mycobacterium avium* complex (MAC) infection. Does he need to stay on his azithromycin (Zithromax)? If his CD4 count continues to rise to above 200, can he discontinue his prophylaxis against *Pneumocystis carinii* pneumonia? We don't precisely know yet, but most physicians would say once your CD4 cell count has dropped to a point where a particular prophylaxis has been deemed necessary, it's probably best to remain on it. Clifford Lane, MD, an immunologist at the Nation Institutes of Health, uses the scrabble-tile analogy. He compares CD4 lymphocytes to scrabble tiles turned face down in the box. All of them look alike with the blank sides up, but when you look underneath, you not that each has specific information. HIV goes through the scrabble box and selectively removes the tiles on at a time. Current antiretroviral drugs allow us to multiply the tiles remaining in the box, but not add back tiles (and their functions) that have already been deleted. So, once all the Z's have been removed, we can multiply the remaining tiles one hundred-fold, but we'll still be unable to spell *zebra*. We can spell *big white horse with black stripes*, but not *zebra*. It's not just a question of the number of the CD4 lymphocytes, but their function, or "repertoire," as well. Depsite his impressive CD4-cell rise, Sean is best advised to remain on his prophylaxis treatments.

Note Sean's viral load is listed two ways, both of which express the quantity of the virus' genetic material (RNA) in the bloodstream: One is *HIV-1 RNA Quant PCR*, the absolute amount, which for Sean is *less than 400* (copies/millimeter); the other is *HIV-1 RNA by PCR* (log 10), the same measurement expressed in terms of *logs* (logarithms-factors of 10), which for Sean is *less than 2.6* Either way, the virus is *not detected* by this assay (test). That seems pretty hard to beat! Has it been eradicated? Is Sean now free of HIV? Note that 400 copies (or 500 for the branched DNA [bDNA] test, a roughly comparable measure of HIV RNA) is the lowest number of virus particles

that currently available tests can count. More sophisticated tests are being used in research settings that can detect down to 20 or 25 copies of HIV per mL of blood. So someone whose viral load is reported as below the level of detection today could actually have 399 copies/mL tomorrow or whenever the next generation of test is released.

More fundamentally, standard viral-load tests tell us only the amount of virus in the *plasma* (bloodstream). This is but a small fraction of the total body HIV load, with significant amounts of virus being harbored in the lymph system. Researchers are currently investigating levels of HIV that remain in the lymph nodes and tonsils in people who achieve “undetectable” levels in the blood to see how the values correlate. In most cases reported so far, much higher levels of virus can be found remaining in these tissues despite marked declines in plasma HIV viral loads in response to treatment. So we don’t yet know if the plasma viral load really reflects what’s happening to total-body viral load.

For now, the goal of driving the HIV viral load below the level of detection is achievable for many people, especially those on the potent protease inhibitors. As the drugs have only been widely available by prescription for just about a year, the duration of their potency and the real clinical meaning of having HIV RNA loads driven below the level of detection of the assay remains to be seen. One thing’s for sure-having an “undetectable” viral load certainly does not mean that an individual is no longer able to transmit HIV to others! For now, an ounce of prevention is still worth a pound of cure.
