.38 Caliber

Make way for the new CD cell on the block. Sean had better get down for the count

February 1, 1998 By Janis Giorgi, PhD

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, Janis Giorgi, PhD, professor of medicine at UCLA Medical School, a principal investigator in the decade-old Multicenter AIDS Cohort Study and a pioneer of new immune-system measurements, discusses the results of recent tests performed on POZ *founder Sean O. Strub.*

With the use of HAART (highly active antiretroviral therapy; most recently Crixivan, d4T and delavirdine), Sean's CD4-cell numbers have shown a slow but sustained increase, going from a low of one cell two years ago to more than 300 now. His viral load has been undetectable for about a year. Overall, these findings bode well for Sean's continued good health, but it's important to study the changes in his cells closely in order to fine-tune our understanding of what's happening to his immune system. We can do this both by a close assessment of changes in standard cell measures, and by the use of newer measurements of certain cell subsets.

Although Sean's current CD4 count of 351 looks significantly higher than the July 1997 count of 223, it's important to note that his CD4 percentage (listed as **helper**, 12%) is identical to what it was then. This means that the increase in the CD4 count is simply a result of the overall increase in the numbers of total **lymphocytes** (a category of white blood cells that includes T-cells such as CD4s and CD8s) in Sean's circulation. The fact that the percentage of CD4 cells now and a few months ago is almost the same indicates that Sean's recovery of CD4 cells is not continuing at the same rate it did for the first year of HAART. This is typical since people who initiate HAART usually have some increase in CD4 numbers and percentages that continues for several months to a year. Thereafter, the values usually level off and there is no further increase despite continued therapy. Why such a plateau would be reached and why each individual seems to level off at a particular CD4 cell number is unknown.

In order to gain more specific knowledge about the types of CD4 and CD8 cells that are present in Sean's immune system—and the implications for disease progression—we measured several subsets of these cells using new tests developed in our lab. One of the most exciting results is the low quantity of **cd38 on cd8**—a protein found on the surface of CD8 cells. An elevated CD38 level indicates that the CD8 cells are activated. This means they are preoccupied with trying to fight off HIV infection and are therefore unable to respond properly to other immune challenges.

An elevated CD38 level appears to be an extremely strong marker that HIV disease will progress. In fact, although this hasn't yet been validated by large studies and thus hasn't been adopted for clinical use, our research at UCLA indicates that the marker has even more predictive value than elevated viral load. Because of this, the CD38 test may become an important tool for treatment decision making. For example, fairly high CD4 levels with intermediate viral load, accompanied by high CD38 levels, indicates that it may be beneficial to start treatment earlier than would be indicated by the other two markers alone. And it appears that the predictive value of CD38 holds whether or not the person is on antiretroviral therapy.

Sean's CD38 reading of 2,938 is slightly above the normal range, but it is in the range of values for HIV positive people categorized as "intermediate" for disease progression risk. (The four categories are: Less than 2,500 = low risk of progression; 2,500–3,999 = intermediate risk; 4,000–7,000 = high risk; and more than 7,000 = very high risk.)

Another pleasing test result from the analysis of his T-cell subsets is how many **naive cd4** cells Sean has. Naive cells are immune cells that have not yet been exposed, activated and committed to responding to any particular microbe such as HIV. Because naive cells typically decline with HIV infection—leaving the body less able to respond to new infections—it is very desirable to have high levels of these cells. Until beginning HAART in late 1995, Sean experienced severe CD4-cell loss. Although they weren't measured back then, it is likely that Sean had very low levels of naive T-cells at that time. Now, although the overall number of Sean's CD4 cells is still well below normal, 41 percent of them are naive cells—very good news, indeed, since this reading is near the high end of the **reference range**.

Since this is the first time these tests have been performed on Sean, we don't know if the favorable-looking profile evolved at the same time that his CD4 cells first rebounded, or has been gradually improving over time. In general, a substantial degree of reversal of immune activation, measured as a decrease in CD38 expression, seems to occur within a few months after viral load is suppressed to an undetectable level. Although Sean is already in the intermediate category here, indicating a relatively low risk of disease progression, a further decrease of his CD38 level would certainly be desirable. Our research shows that long-term nonprogressors with undetectable viral loads average only 500 molecules of CD38. The immune activation measured by CD38 expression is probably the immune response of the host to viral replication, and the still somewhat elevated level in Sean suggests that viral replication is occurring in the tissues, even though no virus is detected in the plasma.

On the other hand, the naive CD4-cell levels have rebounded to essentially normal levels, and there is no evidence that a further increase in percentage would be beneficial. However, a further increase in Sean's **naive cd8** cell levels, now only 15 percent, would be a good sign. This may well occur as activation is further reversed, since activation and naive T-cell levels are inversely related to one another.

What has brought about these improvements in Sean's immune system? Probably just the decrease in the level of replicating virus. Perhaps his use of Neupogen (G-CSF, a white-blood-cell

booster he took from 1995 to 1996 while on KS chemotherapy with Daunoxome) has played an indirect role, since CD4s and CD8s are particular types of white blood cells. In bone marrow transplantation, where the immune system is virtually wiped out by chemotherapy or radiation, the new bone marrow takes several months to years to produce a lymphocyte subset profile that approaches normal levels. Something analogous seems to occur in people like Sean with severely advanced HIV disease who are given antiretrovirals that successfully suppress viral replication. Once the virus is held in check for a while, the immune-system damage seems to reverse itself very gradually. The naive-cell rebound, impressive in Sean's case, is probably a good marker of that recovery.

For those who might be interested in obtaining similar cell subset tests, a warning: Although done with flow cytometry, the same technique used to measure the basic CD4- and CD8-cell counts, these cell subset measurements are not standard clinical laboratory tests. They are primarily used in research labs that are trying to understand the basis of the immune deficiency caused by HIV infection. Although some commercial labs offer the tests (for under $100), neither the test methods nor the values for the reference ranges have been standardized. Until this occurs, be aware that any interpretation of such lab results could be inaccurate or misleading.

Meanwhile, more controlled clinical trials are needed to better understand what duration of viral suppression will be required to allow immune reconstitution—and which drug combinations may work best to accomplish this. Additional studies are also needed to determine whether lymphocyte subset profiles like the one Sean has now mean that the cells will be able to function in protection against opportunistic infections like MAC and PCP.

Can Sean stop taking some of his prophylactic medications now that his immune subset profile looks so much better than it did a few years ago? That's probably not a good idea yet. It's unknown whether the cells will be able to function as well as those Sean had before he developed advanced disease, even though the numbers have increased. In addition, the balance between the antiretroviral drugs, HIV replication, other opportunistic infections in Sean's environment and his immune system may still be a little fragile. So it's probably best to wait until the CD4 percentage at least doubles and the CD38 level drops further before he even considers reducing medication.

Sean, like many others now in this position, needs to keep in mind that the CDC definition of AIDS includes people with CD4 percentages below 14. However, overall, there are promising signs in his immune profile that justify cautious optimism for both slowed disease progression and gradual restoration of immune function.
