Treatment Interruptus

November 1, 2001 By Richard Jefferys

A leading STI researcher gives Rich Jefferys the scoop on the good (hydroxyurea increases CD4s during drug breaks), the bad (most drug holidayers won't contain viral load) and the experimental (Dermavir, a therapeutic vaccine). The STI score? Promises and limitations in a tie.

Several years ago, Franco Lori, MD, and Julianna Lisziewicz, PhD, codirectors of Georgetown University's Research Institute for Genetic and Human Therapy (RIGHT), stunned colleagues with the case of a 29-year-old Berliner with HIV whose viral load did not rebound when he quit taking HAART. (His virus remains undetectable to this day.) Compelled by the implications of this fact, Lori and Lisziewicz immediately immersed themselves in the matter of how structured treatment interruptions (STIs) might not only spare HIVers some of the toxicity of antiretrovirals but also actually help the immune system fight back against HIV -- and keep the virus suppressed. Their research has also focused on Dermavir, a therapeutic vaccine candidate that may "teach" HIVers' immune systems to mount an anti-HIV response. Richard Jefferys recently talked with Lisziewicz about RIGHT's new buzz and the promise it holds for treatment.

Give us an update on what you've presented recently.

At the International AIDS Society conference last July, we reported the results of our STI study in which patients did three weeks on and three weeks off meds for six months. We compared two regimens -- hydroxyurea (Hydrea, or HU), ddI (Videx), and d4T (Zerit) vs. indinavir (Crixivan), ddI and d4T. Patients' viral loads rebounded during every interruption, but when therapy was restarted, the virus was always inhibited again. One thing we observed, though, is very important: During the STI, the rebound rate using HU or Crixivan was basically the same, but in the Crixivan group, the CD4 count bounced up and down similar to the viral load, while in the HU group, we saw a constant *increase* of CD4 count with no oscillation. This was very surprising because without an STI, HU does not increase CD4s.

Did you see changes in HIV-specific immune responses?

We're analyzing that data now. So far, it looks like a treatment interruption that actually induces a new "set point" [suppresses viral load level to a sustained new low] may work only in patients treated early in infection -- and especially before complete seroconversion. And based on Bruce Walker's and other data coming out, we cannot even say that every single person treated *before* seroconversion will be able to stop therapy and control viral load. Unfortunately, we *can* say that most of the patients starting later than this very narrow window -- and that's the vast majority -- probably will not be able to control viral load when we only do an STI but don't induce immune

responses in some other kind of way.

Is there still a role for plain STIs, which cut down therapy time to reduce toxicity and cost, and to give patients a break?

Yes, definitely. Mark Dybul, with Anthony Fauci's group, is trying a one week on, one week off STI schedule in which he's showing that viral load is *not* rebounding and toxicity is decreased. So I think it is still very encouraging that we can do STIs and the patients are not only not harmed but also they are still controlling the viral load rebound when they go back on HAART. Of course, the STI has to be very carefully administered in order to avoid a very high viral load rebound, which then might harm the immune system. But a small viral load rebound may be more tolerable than a lot of toxicity.

What's up with your studies of the experimental therapeutic vaccine Dermavir?

We designed Dermavir after we saw that the Berlin Patient only had T cell-mediated immune responses but no antibody responses at all. We asked ourselves how we could induce such T cell-mediated responses in other patients. Can we put DNA, the genetic code that makes mimics of HIV proteins, into dendritic cells (DC) -- the cells that present pieces of virus to T cells in order to kick-start the immune response? Can these DCs then go to the lymph nodes, express the genes, and induce a T cell-mediated immune response? We have encouraging data from animal studies and hope to start human trials soon. We're putting all of our energy into this -- we just can't sleep on it when patients might benefit.
