

[National AIDS Treatment Advocacy Project](#)

Report From the 3rd Int'l. Congress on Drug Therapy in HIV Infection November 5

Oy mate!! This is Jules Levin reporting from my hotel room at this conference in Birmingham, England. The meeting appears to be a mini-antiretroviral conference for doctors and activists from Europe and Australia.. The food is horrible here; every thing is deep-fried; and, the hotel is lousy; when I get back to New York, god knows what my triglycerides and cholesterol might be. At least I can understand the language and watch TV; although, the TV game and interview shows are a little quirky.

It is Tuesday, the third day of the conference which will last through Thursday. I'll briefly address some highlights and I hope to write a more elaborate report upon returning to NYC. I just finished an interview with Dr. Joep Lange, which I hope to be able to prepare for this web site soon after returning to NYC. Dr. Lange, of the University of Amsterdam, is widely considered a revered and knowledgeable AIDS researcher worldwide; and, in our interview he expressed his well defined opinions on when to start therapy, what to start with, and also on clinical endpoint studies.

Follow-up reports will review data presented and other developments: ritonavir/saquinavir combination protease; ritonavir+AZT/3TC, immediate vs. delayed nucleosides; ritonavir for pediatrics--6 mos to 18 years; update on nelfinavir resistance; nelfinavir+d4T/ddI--pilot study; ritonavir+AZT/ddC--updated 72 weeks data; indinavir, or ritonavir in advanced AIDS; high-dose saquinavir in sero-converters, small open label study; initial lymph node data from ritonavir/AZT/3TC study; nevirapine plasma and lymph tissue RNA data; 1592U89--600 mg tid data; clinical endpoints.

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Darwinian Evolution: resistance will take over and bite you.

Today, at the Merck symposium it was made clear by leading AIDS researchers (Dr. Doug Richman, Dr. Emilio Emini and Dr. Joep Lange) that the optimal approach to therapy, in their opinions, is to treat an individual with a potent 3-drug combination therapy as soon as possible in the stage of disease with the goal of rendering viral load below "detectability". Unless of course, if you might be like one of those individuals in Australia who were infected with a nef-deleted strain of virus; in which case, you may

not progress and Dr. Lange said he would not treat such an individual early and hard. Except, I'm not sure how easy it would be to determine if one has a nef-deleted virus.

The decision to treat early and hard as described above is conditioned on the patient being compliant. If a patient is not compliant, it is there feeling that this person, regardless of which stage of disease they may be at, might be better off delaying this therapy. If the patient is not compliant and resistance develops, you can never reverse it and they may be precluded from maximal or possibly any benefit from current and future protease inhibitors. The fate of Darwinian evolution is that once resistance (mutation) begins it is very difficult to stop it. The strongest virus, resistant mutation in this case, will survive.

So, if an individual is willing and able to be compliant, these scientists recommend potent 3 drug therapy as soon as possible. Dr. Lange said he would try and put himself in the shoes of the patient, if he/she presented with detectable RNA (even 100 copies), he would initiate potent 3-drug therapy. Some individuals are using 4 drugs; a 4-drug combination of ritonavir/saquinavir/AZT/3TC is being studied now.

How low does an individual need to lower their viral load?? In most of the protease inhibitor studies to date, investigators have measured viral load as low as the currently available commercial tests will permit: Roche's PCR measures to 200, and Chiron's bDNA measures to 500. Using double nucleoside therapy, some individuals have been able to render viral load to undetectable: below 200 or 500 copies/ml. Is that low enough? Today, Dr. Doug Richman said that individuals who've lowered their viral load to below 200 or 500 may be able to rebound more easily than if they were below 20. He and others here said the goal should be to go down to 20 or 0 copies/ml.

At 200 or 500 copies, there still is viral replication which can lead to resistance and the rebound of viral load. The goal of therapy, as maintained by these researchers at this conference, is to stop viral replication and to reach as many as possible sites of "sanctuary" for the virus: the brain, CSF, the gut, lymph nodes, etc.

If you accept their thinking, merely being under 200 or 500 may not be adequate. You will have to lower viral load to as close to zero as you can get. Although it is not yet commercially available Roche has a PCR test that measures as low as 20 copies and Chiron has a test that measures as low as 40 copies. Currently, Merck is examining stored blood samples of individuals from the AZT/3TC/indinavir study (trial # 035). The purpose is to determine if those individuals whose viral load was rendered "undetectable" in 035 (lower limit of test used in the study was 500) may also be as low as 20 copies. However, the consistency of the results from this test can be variable.

Other AIDS researchers are not convinced that it is necessary to reduce viral load that low. Dr. Robert Coombs, an AIDS researcher from the University of Washington at Seattle, contends that it may be acceptable or preferable to maintain an individual's viral load at 5 to 10,000 or maybe even 20,000. Dr. Coombs maintains, we don't know whether this approach would be equal to or superior to the approach of hitting hard and early, but that we need to conduct a study to address the question. Dr. Coombs suggests the reasons for considering this approach include: (1) multi-drug protease inhibitor therapy is very

expensive; some individuals may not be able to access it in the current economic climate; (2) it is difficult to comply with all the requirements for taking a protease inhibitor; if one is not compliant because they are not yet sick and don't feel the necessity to be strictly compliant, or they just are not able to or willing to be compliant, resistance could develop and severely hamper or even ruin future benefit from protease inhibitors; (3) considering the potential of cross-resistance, you could save the protease inhibitor option for the future.

What about viral reservoirs? Now that we are able to lower viral load in circulating blood to such low levels, the focus of concern is suppressing virus in other compartments: brain, lymph nodes, CSF, etc. Research is addressing this issue. The question was raised here: whether or not you need to have a neuro-protective drug in your therapy regimen? It is possible that it may not matter whether or not a therapy regimen contains a drug that adequately crosses the blood brain barrier. It is believed that virus trafficks between peripheral circulation and the brain; it is possible that therapy affects virus that may travel from the brain to peripheral circulation through the CSF, which may in turn travel back to brain. However, until we have more conclusive data regarding this, it was recommended that using a drug that adequately penetrates the brain is advisable: AZT, d4T and nevirapine penetrate the CSF.

If you are AZT resistant, it is uncertain whether or not you may be able to still retain neurological benefit from AZT. It appears as though the currently available protease inhibitors do not penetrate the brain well enough. Although, both d4T and nevirapine appear to appreciably enter the CSF, we do not yet have data in humans, for these two drugs, measuring the actual benefit neurologically.

Longer-term viral load suppression. Merck announced that in January they will present data going out to 80 weeks for some phase II study patients (from trials #s 020 and 021) taking indinavir and for a few patients who are out to 96 weeks. Generally, those individuals who were "undetectable" at about 1 year are still undetectable (the lower limit of detection was 200 copies/RNA). Some of these were individuals who initiated treatment with indinavir monotherapy and added nucleosides later.

Protease inhibitor cross-resistance. The difference of opinion between Merck and Roche remains a controversy. Roche still maintains, as they have previously, that the potential for cross-resistance to indinavir after treatment with saquinavir does exist but is not extensive (13-22%). Merck refutes this. They maintain the potential for cross-resistance to indinavir subsequent to saquinavir treatment is significantly greater. Data from both Merck and Roche are often based on information from a small number of individuals (see the report from the NIH Panel to Define Principles of Therapy of HIV Infection).

IL-2. Dr. Cliff Lane, of the NIH discussed IL-2 therapy. It appears doubtful that IL-2 restores depleted naive CD4. He claims that the increase in naive CD4 resulting from any therapy (IL-2 or antiretroviral) appears to be proportional to the amount you had prior to therapy. This appears a little unclear. Dr. Mario Roederer says (see Surrogate Marker meeting report to come) he believes CD4 increases from antiretroviral or IL-2 therapy result from redistribution of CD4 stuck in lymph nodes, not from newly produced CD4,

and that naive CD4 are not generated from therapy. Lane and Roederer agree tha memory cells are increased from therapy.

Lane said, IL-2 is capable of increasing CD4 cells for individuals above and below 200 CD4. This data from the NIH study of indinavir and IL-2 was reported by Dr. Judy Falloon at ICAAC (see NATAP ICAAC Report). Previously, without accompanying indinavir therapy, IL-2 only produced increased CD4 for individuals with over 200 CD4.

A study evaluating the longer-term clinical benefits of IL-2 therapy is necessary to truly assess the merit of this treatment. As well, we need continuing research of IL-2 in combination with protease inhibitor therapy.

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