Photo : Favraux (Louis

HAART break hotel

Chemotherapy of AIDS

Gordon Conference

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This year 105 people attended the 1999 Chemotherapy of AIDS Conference, with 40% coming from industry. Compared to the 1997 conference, this one was more subdued.

In 1997, virtually every presenter of new nucleoside analog inhibitors of reverse transcriptase characterized the compounds as DNA-chain terminators. This year not a single presenter mentioned the phrase DNA-chain terminators. Experimental controls were as absent as they were two years ago.

From my perspective the 4.5 day conference was largely a protracted yawn. However, William Cameron's talk Thursday morning made the entire trip worth while.

Cameron is on the faculty of the University of Ottawa. He is clearly an expert in designing and evaluating clinical trials. He told me that he consults for Canada's FDA.

While it was evident that Cameron fully accepts the HIV hypothesis of AIDS, nevertheless, he completely demolished the viral load surrogate marker as a substitute for morbidity and mortality end points in clinical trials. He said that people don't die of HIV viremia. He also stressed that viral load is ASSUMED to reflect quantitative effects. There was no basis for this assumption. I should point out that over the previous four days virtually every talk and poster (excluding mine of course) relied exclusively on viral load measurements to determine the effectiveness or failure of anti-HIV drug therapies.

Cameron illustrated with specific examples how easy it is to "engineer" a desired outcome in clinical trials using viral load surrogate endpoints. In order to guarantee a therapeutic effect one needs only to recruit relatively healthy patients and observe them only for a short period of time. This method works even for drugs that have no therapeutic benefit and are actually harmful to the patients. The explanation he gave (I couldn't have said it better myself) was that healthy people tolerate toxic drugs better than sick people.

He gave as a specific example the DDI clinical trial disaster. Over a short 12-week study, DDI showed efficacy based on viral load. But after 12 weeks, patients on DDI experienced severe toxicity. Robert Yarchoan of the National Cancer Institute had discussed the severe toxicity of DDI just before Cameron's talk, which only emphasized the point.

Cameron also showed that the placebo arm of a surrogate marker clinical trial can also show a pronounced clinical benefit, indistinguishable from drug therapy, if only the studies were allowed to go longer. The end result is that there would be no difference between drug and placebo as long as the drug was not toxic.

It should be pointed out that to date all protease inhibitor clinical trials were terminated prematurely before it could be determined that people taking the drugs actually lived longer and better lives than those not taking the drugs.

Cameron suggested that any therapeutic benefits due to the HIV protease inhibitors may result from their anti-microbial activities since many pathogens have essential aspartyl proteases. (HIV protease inhibitors inhibit other aspartyl proteases.) However, he told me later that the people he'd seen on HAART looked like hell. They were wasting away to nothing among other problems. He was clearly not impressed with the drugs.

I was sitting at the back of the room during Cameron's talk. I had a good view of how he was being received. A number of people were noticeably uncomfortable, for example Martin Markowitz of David Ho's Aaron DiamondAIDS Research Center. About halfway through Cameron's talk, Markowitz grabbed a newspaper, turned toward the wall and pretended to read it. Cameron's lecture received only short, polite applause. It was the only time I applauded the whole week.

On to other topics. By and large the week was pretty boring. Nevertheless, there were a few scraps of information that some may find useful.

On Sunday, Angela McLean of the UK defined what is meant by acute HIV infection or acute illness. A person is acutely ill with HIV if he or she has a detectable viral load, i.e. the presence of HIV RNA, and does not have antibodies to HIV as determined by the ELISA antibody test.

This definition, of course, does not take into consideration those people who are false positive for the viral load and antibody tests or people who go back and forth.

McLean said that at the peak of acute illness with HIV that 6 new cells are infected with HIV by each previous HIV infected cell. (Peter Duesberg told me that in the laboratory one retroviral-infected cell will produce enough virions to infect 100 new cells.) She said that cytotoxic lymphocytes (CTL) kill wild-type HIV-infected cells in about 2 days. She went on to speculate that CTLs do not kill mutant HIV-infected cells, implying that this was the reason for the drug failures. McLean admitted during questioning that no other

'CASTRO AND MARKET. The bars have closed and I see a fare, a young man about 30. He has some trouble walking and uses a cane. "Franklin and Fell,""he says, getting in. I ask him how it's going. "I don't know, really," he says. "I just had a heart attack and I'm trying to recover." I look at him in the rearview mirror and tell him he doesn't seem to be in the right age group for that. "I have AIDS and I'm taking protease inhibitors," he says. "One of the side effects that no one talks about is heart attacks. The pills make your heart weaker." Wow, I tell him, as if you don't already have enough to deal with. At his stop he says, "I'm getting better, but I don't know for how long." He gives me $8 in paratransits and exits.'

The Night Cabbie appears every other Monday in *The Examiner*. You can write him c/o *The Examiner*, P.O. Box 7260, San Francisco 94120. Or send e-mail to cabbie@examiner.com

infectious agent had been put through her analysis. That means there is no way to judge the physiological significance of McLean's studies.

McLean made the curious statement that the better the anti-HIV drugs work, the more likely they will fail. Figure that one out. After a week of this stuff I think I know what she was getting at. Shortly after a person begins taking anti-HIV drugs his viral load drops. The greater the drop, the greater the supposed therapeutic effect. However, virtually everyone on the cocktails eventually shows a rise in viral load. This rise in viral load was interpreted by most at the meeting to reflect drug failure. However, there were a number of attendees who pointed out that a rise in viral load did not mean those patients were experiencing a increase in clinical symptoms.

Brendan Larder of Virco UK Limited began Monday's session on anti-HIV drug resistance. There are now 5 HIV protease inhibitors available. The ubiquitous viral load is the work horse of anti-HIV research and therapy. A rise in viral load in people taking the anti-HIV drugs is interpreted as drug failure due the appearance of drug resistant mutants. However, responding to a questioner, Larder stated that the presence or absence of mutations have nothing to do with "viral load resistance" seen in people. This was echoed Tuesday by Philip Furman of Triangle Pharmaceuticals in Durham, NC. Furman said that even a person with multiple inhibitor resistant mutant HIVs responds to the protease inhibitor combos as determined by a reduction in viral load in the first week. Furman did not explain this curious observation.

Later that morning, Jaap Goudsmit of Holland continued the drug resistance story. He began by contradicting the media reports that drug resistant mutant strains of HIV represent a growing threat. Goudsmit said that inhibitor resistant mutants are not transmitted from person to person. This was due to the very poor fitness of the mutant virions. In Holland, the appearance of mutant HIV resistant to reverse transcriptase inhibitors peaked in 1995, he said.

Goudsmit made the obvious point that with antibiotics, the appearance of drug resistant strains of bacteria, for example, increase with drug use. It puzzled him that with increased drug use the appearance of drug resistant mutants of HIV actually declined in Holland.

On Tuesday I had an interesting conversation with Che-Chung Tsai, a pathologist at the University of Washington, Seattle. I learned that T-cells pass through the entire lymph system, including all tissues, in 2 hours. At least 85% of T-cells reside in the gut. Because of this, he asks: why doesn't AIDS start in the gut?

Dr. Tsai works with monkeys in his AIDS research. He said that HIV grows 2-3 times as fast in monkey lymphocytes but monkeys don't get AIDS and do not incorporate HIV pro-viral DNA.

At the evening session on Tuesday the speakers tried to blame the metabolic abnormalities seen in people taking the protease inhibitor combos on HIV. I asked Kathleen Mulligan of UCSF why not treat a bunch of animals with HAART (PI combos) and see what happens? The moderator interrupted saying that my suggestion was irrelevant since the animals don't have HIV. That, of course, was precisely the point: to separate the effects of the drugs from HIV. Later a fellow in the audience told me that he was disappointed that my question was not answered. He clearly saw the simple logic behind the proposed experiment.

On Saint Patrick's Day our old friend Martin Markowitz of the Aaron Diamond reported on their on-going study of 27 people still on HAART. As in 1997, Markowitz didn't say a word about how those 27 people had been doing over the past 2 years on the drugs. Two years ago I asked Markowitz if his patients on HAART were doing better, the same, or worse while on the drugs. He didn't answer after asking the question three times. He knew I was in the audience, but this time I decided not to ask. If his patients had been doing well I'm sure he would have let us all know, especially me.

Wednesday included a discussion of long-term non-progressors: those folks who in spite of having either antibodies to HIV or HIV-RNA do not get sick after 20 years and longer. Eric Rosenberg of Massachusetts General Hospital said that viral load goes up and down in people whether they take the anti-HIV drugs or not. In people taking the drugs, the therapy is given credit for the reduction in viral load. In long-term non-progressors, the immune system is given the credit for low viral loads or reductions in viral load. Again, Rosenberg admitted without knowing it that the secret to long-term non-progression is not taking the anti-HIV drugs.

Thursday, Anthony Japour of Abbott Laboratories cited the 1998 paper by Palella *et al.* [Palella FJ, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *The New England Journal of Medicine* (1998) 338(13): 853-860] as the best evidence that HAART was responsible for the decline in AIDS deaths. After his talk I pointed out that the paper by Palella was not a report of a clinical trial but was a retrospective survey. He acknowledged that fact. Then I asked him didn't he think it unusual that he used a survey and not a clinical trial as the best evidence that HAART was extending people's lives or at least improving their quality of life? To his credit, after the coffee break he acknowledged to the audience that his earlier reference had been to a survey and not to clinical trial data.

Japour made it clear that clinical endpoints are no longer used in clinical trials of anti-HIV drugs. The viral load surrogate is the sole basis for determining clinical efficacy. Drug toxicity is apparently the only clinical outcome that is noted. Current Phase III clinical trials are not even blinded; they are open labeled. Both the physician and the patient know whether they are on the drugs.

Robert Yarchoan of the NCI admitted that HAART has made the process of clinical trial drug evaluations very difficult. He recommends that we go back to extensive clinical trials of mono-therapy in drug naive people. The current process is so complicated that it is virtually impossible to

The AIDS Treatment Technical Assistance Council

NEW YORK, May 17
PRNewswire

'At the 12th World AIDS Conference in Geneva this past year the clinical necessity for immune reconstitution for patients living with HIV became a priority as the implications of viral resistance produced **projections of almost universal failure of the present classes of antiretrovirals in the next few months for thousands** of patients whose clinical options have been exhausted...'

6/30/99 **ABC (USA) '20/20' TV program**

Features LaGena Lookabill, a young model, poised for stardom, who is diagnosed with AIDS after a brief affair with star race car driver Tim Richmond who later died of AIDS. Excerpts from the program's transcript concerning an interaction between Dr. Joseph Jemsek, an AIDS specialist, and ABC's Sylivia Chase :

SYLVIA CHASE
(VO) And another problem - protease inhibitors seem to stop working after a couple of years. And in addition, the drugs themselves could kill her by damaging her heart, liver, her pancreas.
DR JOSEPH JEMSEK
The drugs aren't perfect. They cause side effects, which are cumulative and inexorable. Now I'm starting to see people die again.
SYLVIA CHASE
(on camera) So people are actually dying of the side effects of these ...
DR JOSEPH JEMSEK
Yes, you,re ...
SYLVIA CHASE ... antiviral drugs?
DR JOSEPH JEMSEK
You're starting to see that.

Transcript freely available at ABC's website: http://www.abcnews.go.com/onair/2020/2020Index.html

Dangers of increased lipids in individuals using 'HIV' protease inhibitors.

Carr* *et al.* (1999) state: "Hyperlipidaemia at degrees associated with cardiovascular morbidity occurred in 74% of protease-inhibitor recipients. Our cut-offs may be conservative because cholesterol concentrations above 5.0 mmol/L and triglyceride concentrations above 1.6 mmol/L have been identified as clinically significant."

Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. *Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study.* ***Lancet*** 1999 June 19;353(9170):2093-9.

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AIDS virus may last 60 years in body

UPI Science News
WASHINGTON, April 26
Monday, BC cycle

'AIDS patients would have to take powerful drug cocktails for at least six decades ... suggests a disturbing new study. In another related report, scientists also found that these AIDS drugs, known as highly active antiretroviral therapy (HAART), may weaken the body's own ability to fight the AIDS virus. HAART consists of drugs like AZT, combined with newer drugs known as protease inhibitors or non-nucleoside reverse transcriptase inhibitors.... Both studies are published in the May issue of the journal *Nature Medicine*.... This finding suggests that long-term strategies to fight AIDS will have to include programs in which patients periodically stop taking drugs, a sort of vacations from the therapies..."

conduct a clinical trial and interpret the results. In other words, we don't know what the clinical trials are telling us. The FDA representative in the audience said that the FDA supports mono-therapy on a case by case basis.

In addition to relating the fiasco of the DDI clinical trials discussed above, Yarchoan went into some detail about another tragedy: FIAU. FIAU was supposed to treat hepatitis B and was approved after a short clinical trial. However, after people were taking FIAU for periods just a little longer than the clinical trials, they began dying at alarming rates before the FDA finally pulled the drug off the market.

Yarchoan admits that the NCI is currently testing AIDS drugs that are "likely to have severe toxicity," e.g. F-ddA.

Jeffrey Murray of the FDA gave a talk on the design of Phase III clinical trials. By way of background, normal phase III clinical trials run from 1-4 years and cost $30-50 million.

However, as of 1997, the FDA changed the rules for anti-HIV drug clinical trials. Murray said this change was based on a new knowledge of HIV pathogenesis. Maybe he was referring to David Ho's viral dynamics stuff.

Ho said that "long-term non-progressors have something important to tell us."

Accelerated Approval Protocol is as follows: 24 week double-blind study; all patient should receive standard of care (he immediately then said this changes by the minute); report viral load proportion below assay limit; show that CD4 cell changes are consistent with viral load; report viral load vs proportion below 400. He said that relying on mean changes in viral load is too limiting.

Pediatric clinical trial: 48 weeks based on last patient entered; all should receive standard of care (i.e. AZT); report time to virologic failure (i.e. rise in viral load); report proportion below assay limit; show consistency between CD4 and clinical event.

Murray acknowledged that the FDA has not formally validated the HIV viral load assay. Nevertheless, he said that, "the time to loss of virologic response (i.e. how long it takes before a rise in viral load) is in a sense a clinical endpoint." He even said that "the FDA believes in viral load."

That statement gave me the shivers. The FDA should be in the business of evaluating evidence - not beliefs.

Murray said that failure is defined as viral load rebound. He also said that "active drugs do not arrest symptom progression and certainly does not return the patient to normal." This is probably why Martin Markowitz never talks about how well his 27 patients are doing after 2 years on HAART.

Regarding safety, Murray said that toxicity studies in humans should last 48 weeks with 300-600 people evaluated over 6 months and a smaller number over 1 year.

The FDA now asks for metabolism data for all trials. Jules Levin of NATAP (a gay activist group in New York) told Murray that the "Community" will be watching for the FDA to require metabolic abnormality measurements in clinical trials.

During the question period a guy in the audience proposed that the rise in viral load may not represent drug failure but actually immunological success. He based this twist of viral load interpretation on the rise in CD4 cells is the same patients.

Following Murrary's talk, William Cameron tore to pieces the viral load mania as I described at the beginning.

David Ho's talk was Thursday evening, following the banquet. It was much ado about very little. He reported on 8 selected patients who had been on HAART for some time and had no detectable viral load. They took biopsies from a variety of tissues and examined 175 different tissue sections for the presence of replicating HIV. They found 13 sections containing at grand total of 19 cells replicating HIV. I repeat: 19 cells in 8 people. Even if this were true and not an artifact, this number of cells is physiologically irrelevant. A guy in the audience asked Ho how significant were those 19 cells? Ho answered that when HAART was stopped that the viral load rebounded, implying that those few cells were responsible for the rebound. Concluding, Ho said that "long-term non-progressors have something important to tell us." They certainly do but not what he wants to hear. Finally, I presented a poster on Tuesday by Peter Duesberg and me on the Drugs-AIDS Hypothesis. Surprisingly, it went quite well. The 18 copies of the AIDS Dilemma paper by Duesberg and me were all taken during the poster session. I only took 18 because I thought hardly anyone there would want to be seen reading it. The 20 copies of my HIV kinetics paper were all gone in 30 min. That paper was certainly less threatening and could actually be of use to some of those folks. Some people even came up and asked questions. What amazed me the most was that instead of avoiding me at meal times (we all eat together at Gordon conferences) my table was almost always full even though I made a point of being the first to sit down. It just goes to show that things are hard to predict.

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REAPPRAISAL GROUP Newsletter:
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Babies at risk

Michael Day

New Scientist, June 26, 1999

'EVIDENCE IS EMERGING that AIDS drugs can cause serious birth defects in a minority of babies born to HIV-positive mothers. Most specialists... say that larger studies are now needed to quantify the risks associated with taking AIDS drugs during pregnancy.
The concerns stem from a study led by Stéphane Blanche of the Necker Hospital in Paris. He has examined the cases of around a thousand pregnant women with HIV and found that eight gave birth to babies who, though HIV-negative, suffered from a neurodegenerative condition that kills its victims in infancy. The condition...is thought to be caused by abnormalities in mitochondria, the energy "factories" within our cells. The babies' mothers had all taken a combination of the drugs AZT and 3TC from week 32 of their pregnancy....
Concerns are being fuelled by a second study from a team led by Ofelina Olivero of the National Cancer Institute near Washington DC. In the journal AIDS (vol 13, p 919), the researchers report that AZT is incorporated into the DNA of white blood cells in people treated with the drug -including pregnant women and their babies...Olivero and her colleagues warn that the changes may increase the chance of developing cancer.
Experts say that neither study changes their advice to pregnant women who are HIV-positive...'