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Report From the 4th Retrovirus and Opportunistic Infections Conference - Friday January 24, after first 2 days
from Jules Levin

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The following are brief highlights from the first 2 days of the conference. My usual procedure is to follow-up with more comprehensive reports upon return from the conference. As well, NATAP will begin distributing a written newsletter. In order to subscribe to our printed newsletter and other important printed treatment information (we have 3 important books on Protease Inhibitor compliance, data, viral load and when to begin therapy), you can e-mail us at JuLev@aol.com

Opening Session

The session was titled-- Can HIV Be Eradicated? He prefaced his presentation by saying that we have not eradicated HIV from anyone and that his studies are experiments to see what occurs from treating drug-naive or sero-converters with potent multiple drug protease inhibitor therapy. Obviously, he is responding to the media attention whereby the potential for eradication is being exaggerated.

David Ho, MD, discussed the early results of looking for:

1. virus inside the cellular compartments (inside cells) in the semen;
2. virus inside the lymph tissue of the gut: rectum, sigmoid, and descending colon.

The subjects examined in this study were receiving treatment with nelfinavir + AZT/3TC (length of treatment time ranged from 7 to 16 months) in his study of treatment naive chronically HIV-infected individuals. These individual's plasma viral load was undetectable-- at least below 100 copies and they were able to identify some as being below 25 copies.

He said there was an absence of RNA expression in the cells in the seminal fluid. This means he could not find virus inside the cells. However, HIV DNA (proviral DNA) was found in all 5 patient samples. He believes that this pro viral DNA may not be infectious. Others disagree with him and believe that it may be infectious. Nonetheless, residual pro viral DNA appears to persist; the implication of the finding of pro viral DNA is not understood and like all of these findings Ho described will need further exploration and study.

By no means do the results of these studies mean that potent antiretrovirus therapy reduces the potential for sexual transmission of HIV. Safe sex is required.

Ho also analyzed biopsies of 5 patients taken from gut associated lymph tissue. The

samples were biopsied from the rectum, sigmoid, and descending colon. Ho reported that no evidence of RNA signal was found (both with or without PCR amplification) by in situ hybridization or from HIV culture. However, he did find spliced mRNA in some samples which may represent residual virus on the FDC in the lymph tissue. He did find pro viral DNA persists but again he believes it may be defective.

Ho also reported CTL and antibody responses decreased for these individuals, which may mean the immune system is not being presented with virus replication.

In summary, for these individuals he found:

1. no detectable virus in blood,
2. no culturable HIV in PBMC,
3. no evidence of active HIV replication in cells, in semen or in gut-associated lymph tissue.

In the same opening session Peter Piot, MD, who directs AIDS efforts at the United Nations and is recognized as a leader and expert on international issues related to AIDS, spoke of the unrelenting epidemic in developing and undeveloped countries around the globe. He said, although some of us are able to realize the benefits of new advances in HIV therapy from the availability of new drugs--protease inhibitors, NNRTIs, etc., the incidence of disease continues to worsen. He presented a series of sobering statistics to make his point. There is little hope of access to these new drugs in many of the countries where a basic medical infrastructure is sorely lacking. Adequate treatment is unavailable for TB and other diseases, before even beginning to discuss AIDS treatment and care.

There are -- 8,500 new infections per day; 90% are in developing countries; greater than 40% are women; last year 3.1 million people became infected; there are 5.2 million infected in south and southeast Asia; 14 million are infected in Sub-Saharan Africa; In East Asia and the Pacific, only 100,000 are infected but the incidence is rising particularly quickly there. Infection is also spreading quickly in Eastern Europe as countries there start to open up economically to the outside world. India has the largest number of infected in the world. AIDS has become the leading cause of death for women 20-34 in Sao Paulo, Brazil. Last year over 1.5 million died from AIDS. The impact of AIDS is accelerating and the epidemic is far from taking a turn for the better in these aforementioned countries.

TREATMENT HIGHLIGHTS

ABT-378, new protease inhibitor.

Abbott Labs, for the first time, revealed initial information and data for their new protease inhibitor called ABT-378. The information and data presented at this conference is from pre-clinical research. The standard study of single-doses in humans are ongoing. It is expected that if all proceeds well, early phase II studies in HIV infected individuals should begin within months.

The data presented here characterizes ABT-378 as being much more potent than

ritonavir; a small dose of ritonavir greatly increases blood levels of 378 in pre-clinical experiments. The blood levels are able to remain sustained at high levels for at least 8-12 hours. They suggested the potential for once-a-day dosing of the combination of 378 and ritonavir, and of course they will look at twice a day dosing. 378 will be used in combination with ritonavir in planned Abbott studies. Abbott is planning studies examining a variety of doses of ritonavir (ranging from 50 to 200 mg per dose) with 378. These dosing levels are vastly less than the currently used dosing regimens for ritonavir and would much reduce the incidence of side effects and drug interactions that now can result from using ritonavir.

In vitro, ritonavir resistant virus was able to be suppressed by the combination of 378 with ritonavir. 378 displays potent activity against virus with multiple mutations including mutations at the 82 position, which is important to resistance to indinavir and ritonavir. There is hope that this combination could suppress virus resistant to other protease inhibitors. Much of this potential for suppressing resistant virus will depend on the amount of ritonavir they will be able to dose up to with 378. These upcoming dose ranging studies will be telling of this. As a person with AIDS, this is a promising development to be watched closely.

Nelfinavir Phase III data.

As you all should know, nelfinavir (Viracept) is completing phase III and the FDA is reviewing the data for consideration of marketing approval. It is expected that FDA approval will be forthcoming within 4 to 6 weeks, and that the drug will be available in pharmacies shortly after that. Agouron Pharmaceuticals unveiled some their important data submitted to the FDA from phase III at this conference.

After 24 weeks, treatment-naive individuals achieved and sustained a 2.3 to 2.5 log reduction in viral load (n=74) from taking nelfinavir with AZT/3TC. The mean baseline viral load and CD4 were 153,000 and 283 CD4, respectively. The viral load results were highly statistically significant. The mean change in CD4 from baseline was an increase of about 155 CD4 at 24 weeks. 80% of those taking 750 mg of nelfinavir three times per day with AZT/3TC were below the level of detection of the viral load test (500 copies). Agouron said most of these individuals were also below 100 copies. The Chiron bDNA viral load tests were used for the under 500 and under 100. 70% of those individuals taking 500 mg nelfinavir 3 times per day were below 500 copies of viral load. For those individuals whose baseline viral load was above 100,000, 50% taking the 500 mg dose were undetectable, and 80% of those taking 750 mg dosing were undetectable. For those with under 100,000 viral load at baseline the proportion of undetectable was the same whether taking 500 mg or 750 mg dosing regimen.

Nelfinavir is to be taken 3 times per day, although ideally every 8 hours. They say it is not necessary to strictly adhere to an every 8 hr regimen. I will explore this further and report back to you. This dosing regimen was used in their phase III studies and produced the results described.

In the 3 phase III studies analyzed, the incidence of diarrhea ranged from 13 to 26%. This may be misleading. In the study of nelfinavir + D4T/ddI, the study investigator described the experience of diarrhea as consisting of 3 loose stools per day, and characterized it as

grade I.

The discontinuation rate in the 3 studies was characterized as low by Agouron officials at 11% with 4% due to adverse events and only 1.6% due to diarrhea.

There were "scattered" LFT elevations (rises in liver enzymes function tests--ALT) which were often associated with hepatitis in the individual. In other words, the incidence of LFT elevations were low and if it occurred it appeared to be associated with the person having Hepatitis.

Amy Patick, of Agouron, again described their findings that nelfinavir has unique resistance profile. They report that a mutation at D30N is the primary cause for resistance; that individuals taking nelfinavir as a first protease therapy and then developing resistance are still sensitive to other protease inhibitors. They also reported some individuals who were resistant to other protease inhibitors displayed sensitivity to nelfinavir. I will further discuss this in follow-up reports. This information, as is the cross-resistance information from the other protease inhibitor manufacturers, is still preliminary and needs more study for confirmation.

Indinavir/nevirapine/3TC.

A research group from Canada reported 20 weeks of data for this combination in a small number of individuals from an open-label study.. At 20 weeks for 12 individuals the median RNA decline was 3.0 log as measured by an ultra-sensitive viral load test measuring down to 20 copies. 55% were below 500 copies, 20% were below 20 copies. They experienced a rise from baseline of 100 CD4.

I must go to today's meetings. To be continued.

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