

# HIV/HCV Coinfection: Clinical and Research Challenges

Baltimore, Maryland Oct 11<sup>th</sup> – 12<sup>th</sup>, 2001

## PART FOUR

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### Session Twelve: Management of Treatment for HIV/HCV Coinfection – A Panel of Experts

**Moderator: Douglas Dietrich, M.D.**

**Members: Jules Levin, NATAP**

**Michael Marco, Treatment Action Group (TAG)**

**Teresa Wright, M.D. UCSF and VAMC San Francisco**

**Margaret Ragni, M.D. Hemophilia Center of Western Pennsylvania**

This session was a series of questions and answers on the management and treatment of the HIV/HCV coinfecting patient. The general consensus among the panel was that any HIV/HCV patient who wants to be treated should be able to get treatment if they know the natural history of HCV disease, the risk and potential toxicities and they have realistic ideas of the perceived benefits – what is the estimated chance of success to therapy.

The first scenario that was posed by Dr. Dietrich was an HIV/HCV coinfecting patient that from liver biopsy has Grade O fibrosis. He then asked the panel members individually to give their viewpoint on treating the HIV/HCV coinfecting patient and whether in their opinion this patient based upon the profile given should be treated for HCV.

Mr. Marcos brought up a lot of key issues. Firstly, if the patient wants to be treated, is the patient truly informed of their risks and benefits? Does the patient know what their likelihood of a sustained virologic response (SVR) is based upon their genotype and viral load? In his opinion, unless the patient really wanted to be treated for HCV he felt that the HIV should be treated first since this patient does not have advanced fibrosis or cirrhosis. He also discussed the fact that over 50% of patients have poor prognostic factors including being genotype 1 high viral load. Mr. Marcos state that even though HIV/HCV coinfecting patients respond just as well to therapy as patients with only HCV, the new therapy Peg Intron + ribavirin in the genotype 1 high viral load population has no better an SVR than Rebetron.

Dr. Wright stated that even though she tends to lean towards therapy in the coinfecting patient in the case of this patient having no fibrosis she would have to weigh the fact that depression is higher in the HIV/HCV coinfecting population than the HIV only population and that Peg Intron + ribavirin therapy has no benefit over Rebetron with a much higher side effect profile. Dr. Wright felt that in HIV/HCV coinfecting patients it is very important to liver biopsy and try and identify when infection occurred as well as address transmission issues. Dr. Wright emphasized the need for drug development to develop non-interferon based therapies that will be important for this population.

Dr. Ragni based upon the hemophiliac population that she sees felt that this patient should not be treated. She stated that this patient in her hemophiliac population is also likely to be infected with HBV, have a low CD4 count, be genotype 1 plus it is probable that their mitochondria is 'shot' and the HCV medications could ultimately make them sicker. She also pointed out that there is a high likelihood that this patient has

been infected with HCV for 20+ years and if they have no fibrosis then they definitely should not be exposed to treatment.

Jules Levin commented that there are studies that show that HAART is detrimental and that the jury is still not out on HAART and HCV. He feels that it is a mistake to hide behind the feeling that HIV/HCV coinfecting patients do not want to be treated. He also asked that there not be a generalization that African Americans do not want to be treated because the results are lower – how is treatment being presented to this subset of patients? Mr. Levin feels that treatment should definitely happen before fibrosis 2/3 as fibrosis becomes more rapid at this point. He also feels that drug therapy should not be denied to the injection drug user, the cirrhotic or the depressed. Mr. Levin also stated that the right support systems need to be put in place to make treatment of these groups possible and this should be done as a collaborative effort between the government and pharmaceutical companies. Regarding the patient in question he felt that he would probably only encourage therapy if the patient was genotype 2 or 3 as early treatment might give this patient the highest chance of clearing the virus. Mr. Levin concluded by saying that the HIV/HCV coinfecting patients are confused. They are overwhelmed enough with knowing that they have HIV and no cure and then HCV is thrown in there too and most likely they are going to a physician that really doesn't understand how to handle the combination.

As the level of fibrosis increased in the profile of the patient the panel became much more inclined to treat. Even though there was some concern about treating a HIV/HCV coinfecting patient with advanced fibrosis with a CD4 count <50. One panel member commented that with a CD4 count of <50, a patient on HIV treatment has a 70% five year survival so it would probably be in the patient's interest to treat the HCV. It was also pointed out that if the patient had had a high CD4 count before the decline that patient will probably do well as it is likely that they will get a restoration of CD4 with response to HCV therapy.

Dr. Dietrich then asked the panel what they would do if this HIV/HCV coinfecting patient had compensated cirrhosis. The general consensus was that transplantation in this patient is unlikely so treatment should be initiated. If the patient did not clear virus then maintenance therapy would be initiated which would be a reduced dose of pegylated interferon. What was interesting is that Dr. Wright recommended that in this patient the ribavirin should be continued too if the patient was tolerating it.

A few other cases were briefly touched upon that brought up some interesting points. For example, a patient that had attempted antiretroviral therapy three times but had elevated ALT's to 500. The panel agreed that they would definitely treat the HCV for 3-4 months just to get the ALT levels down and then initiate the HIV therapy again. This is an example of utilizing HCV therapy to facilitate HIV therapy. It was also the consensus of the panel that any identified acute cases whether in HCV or HIV/HCV coinfection should be treated based upon the recent data published in the NEJM.

This session ended with some closing comments on the need for cross training grants for Infectious Disease/Hepatology and Mental Health so that HIV/HCV coinfection can be much better addressed. It was also agreed that more education for providers and patients is needed on treatment and management of HIV/HCV coinfection.

## **Session Thirteen: Antiretroviral-Associated Hepatotoxicity: The Role of Chronic Viral Hepatitis**

***Dr. Mark Sulkowski, Johns Hopkins University***

Dr. Sulkowski opened his session discussing hepatotoxicity associated with NRTI's. There have been cases of lactic acidosis and severe hepatomegaly with steatosis including fatal cases. NRTI related mitochondrial toxicity and hepatotoxicity is a classic syndrome that occurs in <1% of patients. It presents as hepatomegaly, nausea, ascites, edema, dyspnea, increased ALT/AST, increase lactate and micro/macro vesicular steatosis.

He next discussed hepatotoxicity associated with NNRTI's. Most of the data to date has focused on Nevirapine (Viramune). He quoted a study of the hepatotoxicity of Nevirapine which showed a 2.5 increase in

liver toxicity for HIV/HCV coinfecting individuals. Dr. Sulkowski stated that of the four clinical trials that looked at Nevirapine hepatotoxicity the incidence was 3.4% versus 2.2% in placebo. He went on to say that in his practice, he will keep people on therapy as long as ALT's do not rise above 5 times the upper limit for patients that had normal ALT's or 3.5 times above the upper limit for patients that had pre-existing elevated levels. Dr. Sulkowski stated that even with elevated ALT's, 63% of patients were able to continue treatment. It was also stated that HIV/HCV coinfecting patients were two to five times more likely to have liver injury from protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Dr. Sulkowski also commented that due to immune reconstitution, cases have been noted of hepatitis B (HBV) seroconversion in previously resolved HBV.

Dr. Sulkowski then went on to discuss the impact that HCV can have on impaired drug metabolism of HIV medications. For a patient on Ritonavir that has either HCV or HBV and mild liver disease the AUC (area under the curve - combines information on concentrations achieved and the length of time the drug stays around.) increased by 40% and Cmax (maximum concentration) increased by 27%. There is also a 2.8 fold increase in indinavir nephrolithiasis (kidney stones). With Nevirapine in moderate liver dysfunction there is a 40% increase in the AUC and for patients on Efavirenz there is no difference in the AUC but the half-life is increased. Despite these well-documented effects of liver disease on HIV medications there is only one antiretroviral agent that has an HCV recommendation. That recommendation is a dosage reduction of Crixivan to 600mg q 8 hours in patients with mild to moderate hepatic insufficiency due to cirrhosis. According to Dr. Sulkowski this recommendation is not happening in clinical practice.

Dr. Sulkowski commented that there was not enough data on HIV/HCV coinfection and more research is needed especially in the area of intrahepatic immune response. He concluded by asking a question. Does HCV blunt immune recovery following effective antiretroviral therapy, as the CD4 recovery is not as vigorous in the HCV coinfecting patients?

## Session Fourteen: Liver Transplantation in the HIV Positive Candidate

***Dr. John Fung, University of Pittsburgh***

Dr. Fung opened up his session talking about the pre-HAART era and poor survival rate for HIV patients. Even though there are still only few transplants in HIV patients performed, the survival rate is relatively good. Now that HIV is considered a chronic treatable illness, more and more people with HIV are in need of organ transplants. Dr. Fung noted that issues that need to be addressed for transplantation in this population include drug interactions, funding issues and donor availability. Additionally there is concern over the public perception of offering transplantation to HIV positive individuals, but Dr. Fung believes that physician's willingness to operate could have a positive impact on the public's perception. Transplantations are now being performed at various centers around the country including Pittsburgh, Miami and San Francisco. More information on transplantations for HIV individuals will be discussed in an upcoming article from the HCV Advocate.

## Session Fifteen: Management and Treatment of HBV/HIV Coinfection in 2001

***Dr. Marion Peters, University of California at San Francisco***

Dr. Peters opened her session discussing the natural history of hepatitis B (HBV). Dr. Peters commented on the prevention of HBV through vaccination and about a large vaccination campaign in Taiwan that resulted in a huge decrease of hepatocellular carcinoma in only 15 years. The majority of people that contract HBV clear the virus on their own. Dr. Peters noted that the diagnosis of HBV is complex with different markers for different stages such as acute and chronic disease. Only approximately 5% of people that contract HBV develop chronic infection and there is a high survival rate in this population. HBV disease state is complicated by HIV disease. In the HBV population, approximately 12-20% develops cirrhosis. 20-23% develops decompensated cirrhosis from the population that develops cirrhosis and finally 6-15% develops

hepatocellular carcinoma (HCC) after developing decompensated cirrhosis. This as with HCV is accelerated in the HBV/HIV coinfecting patient.

Lamivudine (Epivir, 3TC) and interferon alpha are FDA approved to treat HBV. Lamivudine treatment consists of 100 mg daily for 12 months and interferon is given at doses of 5 million units daily for four months or 10 million units three times a week for 4 months. The response to therapy is measured with the loss of HBV DNA. Both medications have limitations especially for the HBV/HCV population. Side effects from interferon require dose reductions in approximately 20% of those treated. Lamivudine is more easily tolerated but drug resistance is common from prolonged therapy. This is complicated in the individual with HIV because Lamivudine is also used in HIV therapies.

Dr. Peters noted that the goal of therapy is viral suppression and improved liver histology. HBV can not be eradicated so there is potential for viral rebound especially in the HBV/HIV coinfecting patient.

Experimental therapies for HBV include Adefovir, an adenosine nucleotide analog. Adefovir was originally developed as a therapy for HIV but was discontinued because of the severe toxic side effects in doses of 120 mg. However, at the lower dose of 10 mg a day for HBV it may be an effective therapy for HBV including the wild mutant form which is difficult to treat. In clinical trials it has been noted that there is a transient flare in ALT's but that the levels slowly come down.

Another drug under consideration is Tenofovir (TNV), a nucleoside reverse transcriptase inhibitor that is currently available for HIV therapy. Tenofovir has been shown to be an effective treatment for HIV in individuals with lamivudine resistance. Clinical trials are needed to evaluate the treatment for HBV.

Combinations of various medications are also under consideration.

Dr. Peters noted that it might be difficult to diagnosis HBV due to occult HBV infections especially in the HIV positive individuals.

Recommendations for HBV/HIV coinfection include:

- ◆ Avoid corticosteroids
- ◆ Closely monitor patients for HBV DNA
- ◆ Monitor for Alfa-fetoprotein (AFP) for liver cancer
- ◆ Imaging tests for changes in the liver

This concludes the first day of the conference. The second day of the conference was titled "HIV/HCV Coinfection: Development of a Research Agenda." The invited attendees were divided into working groups to come up with recommendations for 11 areas of future research including clinical trial design, drug interaction/hepatotoxicity, issues pertinent to IDUs, quality of life, recommendations for cohorts, triple-infected patients – HBV/HCV/HIV, special populations, future therapies and their role in research, transplantation, cost and access to care and Steatosis. This is the most important part of this conference that will help direct future research. A conference of this kind is long overdue and the Forum for Collaborative HIV Research is to be commended for organizing and sponsoring the first conference that focused on HIV/HCV coinfection.

The Forum for Collaborative HIV Research will publish their official report and recommendations for future research at the end of November, 2001 on their web site: [www.hivforum.org/](http://www.hivforum.org/). In the meantime, please check out their excellent website.