

HIV / HCV / HGV Plenary Session

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LIVER MORTALITY IN PATIENTS WITH HIV INFECTION – Abstract 255

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The course of Hepatitis C is accelerated in patients with HIV infection and therefore liver mortality is expected to be high in this group. Less is known of liver outcomes in patients with HBV coinfection or in those without any viral hepatitis. HAART including PI's are associated with decrease in liver fibrosis progression.

The aim of this study is to assess liver mortality in patients with HIV infection with or without viral hepatitis coinfection. (HBV or HCV).

474 patients with HIV infection were prospectively followed for a total of 8,300 patient-months at the USC HIV Clinic (5P21). Laboratory data were collected using a computerized database. Mortality data were obtained via the Los Angeles County HIV Epidemiology Unit. Kaplan-Meier survival curves were constructed with Stata software. The main risk factors for HIV and HCV were homosexuality, IDU, intranasal cocaine use or transfusion. Mortality was attributed to liver disease if primary diagnosis or contributing cause of death.

233 patients were HCV-RNA positive, 73 were HBsAg positive, 154 had HIV alone (HBsAg and HCV RNA negative), and 14 pts had multiple hepatitis viruses. Raw mortality data are shown in the table. Patients with HIV infection and no viral hepatitis had higher all-cause mortality rates, compared to HIV/HCV or HIV/HBV coinfecting patients ($p=0.06$) by Kaplan-Meier survival curves. However, when these data were adjusted for CD4 counts, this difference was no longer seen. Similarly, controlling for CD4 counts, liver mortality was not statistically different in those coinfecting with either HBV or HCV vs. HIV alone ($p=0.14$). Furthermore, both all-cause and liver mortality curves for HIV/HCV and HIV/HBV groups were superimposable ($p=0.8$). In the group of 320 patients with hepatitis B or C, an initial CD4 count <200 and an average lifetime alcohol use >50 g/d was associated with significantly higher liver mortality ($p=0.001$, $p=0.03$, respectively) vs. those with CD4 >200 and alcohol use <50 g/d. The HIV group was the most immunocompromised and the HIV/HCV group had the highest alcohol consumption. Liver mortality was also significantly higher in the subgroup of patients first evaluated in clinic prior to HAART (1996) vs. those seen in 1996 and beyond ($p=0.002$). The presence of all 3 factors (CD4 <200 , alcohol >50 g/d, evaluation prior to 1996) was associated with a 12-fold higher mortality risk compared to those with none of these factors. Age, gender, ethnicity or risk factors for HIV were not associated with liver mortality.

In summary:

- ◆ Pts with HIV/HCV coinfection had survival similar to patients infected with HIV alone
- ◆ HIV patients without viral hepatitis have significant liver mortality
- ◆ Patients with HIV/HBV coinfection have the same liver mortality as patients with HIV/HCV coinfection
- ◆ Independent risk factors for liver mortality were: CD4 <200 , alcohol use >50 g/d ($p=0.02$), and evaluation

before 1993-1996 versus 1997-2001($p=0.0004$). The advent of HAART is the most likely decrease in liver mortality in the HIV/HCV coinfecting population.

Mortality in the HIV cohort

Diagnosis	N=	All deaths	Percentage	Liver deaths	Percentage of deaths
HIV	154	52	34%	10	19%
HIV/HCV	233	56	24%	31	55%
HIV/HBV	73	20	27%	10	50%

PREVENTING LACTIC ACIDOSIS IN HIV HCV COINFECTED PATIENTS DURING INTERFERON AND RIBAVIRIN TREATMENT. DEVELOPMENT OF A REAL TIME PCR FOR MITOCHONDRIAL DNA COPY NUMBER IN PBMCs – Abstract 256

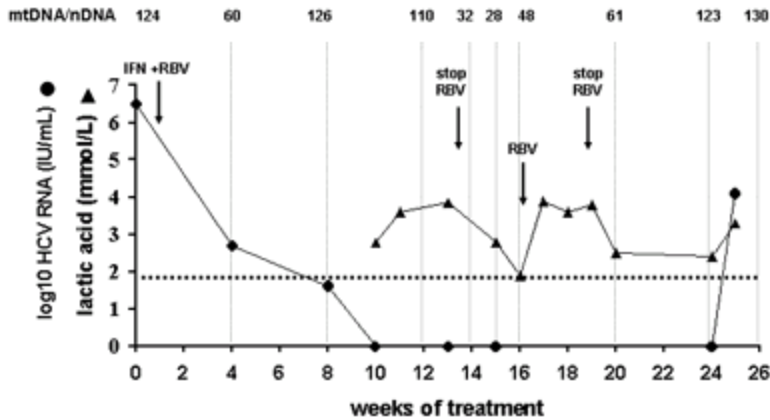
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HIV/HCV coinfecting patients on HAART require anti-HCV treatment because of the risk of liver-related complications. However, severe lactic acidosis during IFN and RBV treatment has been reported in such patients. This complication is due to mitochondrial DNA (mtDNA) depletion which is exacerbated by ribavirin.

The aim of this study is to develop a high throughput real time PCR for mtDNA quantitation in PBMCs and investigate its potential utility to monitor coinfecting patients during combination therapy. Patients and methods: We developed a single tube real time PCR assay with 2 TaqMan probes: one (FAM-labeled) targeting 12SRNA mtDNA gene and one (VIC-labeled) complementary to single-copy nuclear RNase P gene (ABIPrism 7700 sequence detector). Standard curves from 10-fold PBMC serial dilutions from healthy subjects showed a dynamic range of 20 -20000 cells/reaction, parallel slopes for mtDNA and nuclear DNA, and inter-assay CV<7%. Results were expressed as mtDNA copies per nuclear DNA copy. Cryopreserved PBMCs obtained before, during and after IFN+RBV treatment from 33 coinfecting patients (20 haemophiliacs, 13 IVDUs; 90% male; 35+/-7 years; cirrhosis 38%) was tested. Controls were 17 healthy subjects and 4 IFN+RBV treated HAART-naive coinfecting patients.

Results: At baseline mtDNA copy number was significantly lower in HAART-treated patients than in healthy controls and HAART-naive patients (100+/-59 vs. 136+/-28 and 129+/-29, respectively; $p=0.001$). Baseline mtDNA did not correlate with type of NRTI (stavudine-containing: 93+/-56, vs. other NRTI 116+/-80; NS), presence/absence of cirrhosis (86+/-34 vs. 105+/-66; NS) or treatment outcome (sustained responders [$n=17$]:117+/-72 vs. non responders [$n=16$]:82+/-37; NS). During treatment mtDNA copy number remained stable in 27 (82%) of the patients, none of whom had side effects. In contrast, mtDNA decreased significantly during treatment in 6 patients (95+/-35 at baseline vs. 66+/-36 at 6 months; $p=0.028$) all of whom developed side effects requiring discontinuation of RBV or complete treatment withdrawal (asymptomatic hyperlactatemia: 3; full-blown lactic acidosis: 2; liver failure: 1). Two patients died despite interruption of IFN/RBV and HAART (lactic acidosis and liver failure). In the remaining 4 patients interruption of RBV led to rapid return of mtDNA to baseline values (figure).

In summary, coinfecting patients on HAART have significant mtDNA depletion compared to controls or HAART-naive patients. Combination therapy with IFN/RBV does not further decrease mtDNA in the majority of patients. A significant decrease occurs in 18% of patients and is associated with hyperlactatemia, full-blown lactic acidosis and liver failure. The test should be useful for monitoring coinfecting patients during anti-HCV treatment and prevent life-threatening complications of mtDNA depletion.



DOWN REGULATION OF CC-CHEMOKINE RECEPTOR 5 IN HEPATITIS G VIRUS-INFECTION – Abstract 257

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Epidemiological data demonstrate that hepatitis G virus (HGV, or GB virus C) co-infection of human immunodeficiency virus (HIV) positive individuals is associated with delayed progression of HIV disease and a significantly improved survival (Xiang et al., 2001; Tillmann et al., 2001). However, the mechanism by which HGV alters the course of HIV-infection remains unclear. Here, we studied whether natural HGV-infection affects expression of the HIV-receptor CD4 or its co-receptor CC-chemokine receptor 5 (CCR5).

METHODS: Peripheral blood mononuclear cells (PBMC) of 11 HGV-positive (5 mono-infected, 6 HIV co-infected) and of 12 HGV-negative persons (including 6 HIV-infected patients) were prepared by Ficoll density gradient separation. Expression of the cell surface receptors was determined by flow cytometry. All subjects were tested homozygous for the CCR5 wild-type gene.

We found that expression of CCR5 was about 40% lower on CD4+ cells from HGV mono-infected individuals as compared to those from HGV-negative subjects, whereas CD4 expression was not altered. CCR5 expression on CD8+ cells showed a 38% reduction. Down regulation of CCR5 by HGV-infection was also confirmed in HIV co-infected individuals. Furthermore, exposure of PBMC to immobilized serum proteins obtained from a HGV-positive person reduced expression of CCR5 on the cell surface, whereas co-incubation of cells with serum proteins of a HGV-negative donor did not affect chemokine receptor expression.

Our results demonstrate that replicative HGV-infection is associated with decreased surface expression of CCR5, which might be due to interaction of viral proteins with cellular receptors. Down regulation of CCR5 expression might contribute to the delayed progression of HIV-infection in HGV-positive patients.

TREATMENT OF CHRONIC HEPATITIS C WITH PEGYLATED INTERFERON AND

RIBAVIRIN IN HIV CO-INFECTED PATIENTS – Abstract 258

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Morbidity and mortality related to HIV infection continues to decrease with the introduction of highly active antiretroviral therapy (HAART). However, morbidity associated with hepatitis C (HCV) is increasingly affecting the HIV/HCV co-infected cohort. With response rates to pegylated interferon and ribavirin in the HCV mono-infected cohort approaching 50%, it is essential that clinical studies are performed to identify the safety, tolerability and efficacy of interferon and ribavirin in the co-infected cohort.

Safety, tolerability and efficacy of Pegylated interferon 1.5mcg/kg/weekly (Schering- Plough) and Ribavirin 1000-1200mg/d for 6-12 months was assessed in a prospective open labeled study in chronic HCV/HIV co-infected patients. All patients had a CD4 count $> 200 \times 10^6/\text{ml}$. Patients on HAART were also recruited to a pharmacokinetic sub-study assessing clinical interactions with HAART, HIV infection and intracellular levels of nucleoside reverse transcriptase inhibitors pre and post the commencement of ribavirin. Recruitment of patients is ongoing with 40 patients enrolled to date. Intention to treat analysis (where discontinuation = failure) was used to assess efficacy and statistical analysis was performed using SPSS 10.0.

Infection was predominantly acquired through intravenous drug users (76%). Other risk groups were haemophiliacs (10%), heterosexual (10%) and homosexuals (4%). The majority were virologically stable on HAART (58%); the remainder did not require HAART as per current international guidelines. 34% patients were infected with genotype 1/4 and 66% with genotype 2/3. 85% were male and mean age was 37 years (Range 24-49yrs). Median liver biopsy score was 3 (Range 2-6). To date 19 patients have completed therapy (genotype 1, n=6 and genotype non-1, n=13). Overall SVR is 47% with an SVR of 0% in the genotype 1 and an SVR of 69% in the genotype non-1. All SVR's had responded at week 12 with a minimum of a 3 log drop. All responders had also responded by week 4 but this did not reach statistical significance. The only predictor of response was genotype. Non-predictors of response included gender, age, baseline HCV viral load, CD4 count, HAART, normalization of liver function tests or grade of fibrosis/cirrhosis. Severe adverse events were seen in 28% resulting in premature discontinuations in 20% of total cohort. These were predominantly hematological (managed with erythropoietin, G-CSF and blood products) and psychiatric. Two patients died while on study medication (hepatocellular carcinoma and chronic obstructive pulmonary disease). One patient self discontinued and did not return for follow up.

Conclusion: Early response rates in genotype non-1 populations appear to be similar to the HCV mono-infected cohorts. However, rates of treatment discontinuation and severe adverse events were higher in this HCV/HIV co-infected cohort. This study provides early evidence for successful treatment of co-infected patients in specialized centers.

Additional Points:

- ◆ What was interesting regarding early predictability is that in the HIV/HCV cohort about 50% of genotype 1 showed a 2 log drop of HCV RNA at both 12 weeks and 24 weeks but NONE of these patients went onto be viral responders. It appears that the 12 week NPV used in the mono-infected patients does not hold true in this patient population.
- ◆ In addition a change in CD4 counts while on therapy appears to be a more myelosuppressive (bone marrow suppression) effect of interferon rather than immunosuppressive.

LIVER TRANSPLANTATION FOR HCV CIRRHOSIS IN HIV-HCV COINFECTED PATIENTS. EVALUATION OF ANTIRETROVIRAL TOXICITY AND OF HCV RECURRENCE – Abstract 259

Didier Samuel, Daniel Vittecoq, Jean-Charles Duclos-Vallee, Cyrille Feray, Elena Teicher, Daniel Azoulay, Faouzi Saliba, Anne Marie Roque Afonso, Philippe Ichai, Denis Castaing, Rene Adam, Catherine Guettier, Elisabeth Dussaix, Henri Bismuth, Hopital Paul Brousse, Villejuif, France

HIV infection was considered until recently as a contraindication for liver transplantation (LT). The prognosis of HIV infection has dramatically improved with antiretroviral treatment. Many HIV patients have severe life-threatening HCV liver disease.

The aim of this study is to evaluate the feasibility of LT in HIV HCV coinfecting patients, and the impact of antiretroviral therapy (HAART) and of HCV recurrence.

Seven patients (6 M, 1 F) mean age 40 (30-49 years) years underwent LT from December 1999 to March 2002. All patients have Child C cirrhosis, controlled HIV replication, mean CD4 275 /mm³ (100-500). 6 of the 7 patients were genotype 1 and 1 patient was genotype 4. HIV and HCV serum viral load were performed before and after LT, liver biopsy was performed at 6, 12 and 24 months post-LT. Immunosuppression was a combination of Tacrolimus and steroids.

3 patients received a domino graft (from a donor transplanted for familial amyloidotic polyneuropathy); 2 a living related donor graft and 2 a cadaver graft. All but one patient are alive, mean follow-up 12.8 months (3-30). Protease inhibitors and tacrolimus interaction was responsible for acute rejection by low tacrolimus level in 1 and for toxic levels of tacrolimus in 1. After LT, HIV RNA was undetectable in 5 patients, transiently positive in one and high in one after discontinuation of HAART, one patient developed an esophageal candidosis. HCV recurrence was detected in all patients with a 1-2 log₁₀ increase of HCV RNA within the 3 first post-LT months (Range 6-8 log₁₀ copies/ml). HCV acute hepatitis was diagnosed in all 7 patients. One patient developed a severe chronic hepatitis C requiring combination therapy of interferon plus ribavirin, which induced a complete antiviral response, 4 developed mixed lesions of microvesicular steatosis, and of hepatitis C. One patient died of multiple organ failure due to HAART toxicity and of hepatitis C at 4 months. A significant improvement of quality of life and gain of weight was observed in 5/7 patients.

In summary, HAART liver toxicity and HCV recurrence are the 2 main complications in this preliminary experience. Liver transplantation in HIV HCV coinfecting patients is feasible but requires a cautious monitoring of HCV reinfection, of drug interactions and of antiretroviral toxicity.

Additional Points:

- ◆ There were no opportunistic infections
- ◆ HIV RNA was adequately controlled.
- ◆ The HAART liver toxicity was as follows: (microvesicular steatosis in 3 patients DNA mitochondrial toxicity in 2 patients (lactic acidosis and pancreatitis).

PREDICTORS OF HAART INDUCED HEPATOTOXICITY IN PATIENTS WITH HIV AND HEPATITIS C – Abstract 260

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The use of the HAART on HIV/HCV co-infected patients has been associated with variable outcomes. Transaminases increase early but return to baseline without stopping HAART. Reconstitution of the immune system with HAART may allow T-lymphocytes to attack infected hepatocytes worsening hepatocellular injury. Increased risk for hepatotoxicity has been reported in some studies with the use of ritonavir, stavudine, and nevirapine. However, ritonavir has also been associated with improved outcomes.

Our objective was to study the incidence of acute hepatotoxicity after the introduction of HAART in HCV co-

infected patients, establish predictor factors for toxicity, and evaluate clinical outcomes.

We **retrospectively** reviewed the medical records at the Miami VAMC. We included patients with diagnosis of HIV and hepatitis C who began HAART after Jan 1996 till March 2002, and who had been followed up for at least one year. Hepatotoxicity was diagnosed if any of the following criteria was present: 1) Two fold increase in the baseline of AST or ALT; 2) Total bilirubin >2.0 mg/dl; 3) Decrease in the albumin from normal to <3.0g/dl; or 4) Increase in the PT >4 seconds above control. Clinical hepatotoxicity was defined as ascites, variceal bleeding, encephalopathy, HCC or hepatorenal syndrome.

Five hundred and ninety-one patients were HIV positive. One hundred and eighty-eight of them were co-infected with hepatitis C (31.8%). Eighty-eight patients began HAART and were followed for at least one year. Eighty six (97.7%) were men with a mean age of 47 ± 7.44 years (mean \pm SE), and 1031 ± 541 days of follow up. Before HAART, CD4 count was 254 ± 199 and HIV viral load was $101 \pm 267 \times 10^3$ copies. Forty-eight (54.5%) met criteria for hepatotoxicity: 77.1% by ALT; 68.5% by AST; 16.7% by total bilirubin; and 14.6% by albumin. Patients with hepatotoxicity were all men; 21.7% white (10/46), 60.9% black (28/46) and 17.4% Hispanic (8/46). There was no difference between age, race, transmission route, alcohol use, prior hepatitis B infection, or type of HAART medication used when compared to the patients without hepatotoxicity. CD4 counts were lower at baseline in the group with hepatotoxicity ($p=0.036$). CD4 counts increased significantly from 221 to 385 ($p=0.000002$) and from 298 to 464 ($p=0.000001$) in the group with and without hepatotoxicity respectively. Using logistic regression analysis a CD4 count less or equal to 250 ($p=0.0268$, O.R: 2.69) and a lower baseline ALT ($p=0.0022$) predicted hepatotoxicity. Hepatotoxicity never led to discontinuation of HAART. Mortality was similar in both groups (18.75% vs. 15.79%). There was no correlation between toxicity and alcohol use, HBV, CD4 changes from baseline, opportunistic infections or mortality.

Baseline values in non-toxicity group versus toxicity group that met statistical significance

Mean CD4 $p=0.0361$

Mean ALT $p=0.0103$

Mean AST $p=0.0241$

In summary, asymptomatic hepatotoxicity occurred in 56% of patients treated on HAART. HAART induced hepatotoxicity is very common in patients coinfected with HCV. CD4 values below 250 and lower ALT at baseline are associated with hepatotoxicity. Hepatotoxicity was not associated with increased morbidity or mortality, and did not lead to interruption of therapy.

Additional Points:

What can you expect of HIV/HCV coinfectd on HAART?

- ◆ >2 X baseline of aminotransferases
- ◆ Low ALT is an independent predictor of hepatotoxicity