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Final Results of Daily vs 3-times Weekly Interferon alpha-2b plus Ribavirin for the Treatment of Hepatitis C Infection in HIV-infected Persons: A Multi-center, Randomized Open-label Study

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Background

Hepatitis C (HCV) is an opportunistic infection that causes substantial morbidity and mortality in HIV-infected patients (pts). Few studies have evaluated the safety and efficacy of Interferon (IFN)/Ribavirin (RBV) in co-infected patients. We present the final results of a randomized, controlled trial of IFN/RBV use in co-infection.

Objective

To assess the efficacy and safety of RBV with Daily (QD) or 3 Times Weekly (TIW) IFN for chronic HCV in HIV-infected pts.

Methods

Randomized, controlled, open-label, multicenter (68 sites) trial comparing IFN 3 mIU QD vs TIW + RBV (800 g/d) for 48 wks in 180 IFN/RBV-naïve, HIV-infected pts with compensated liver disease on stable antiretroviral therapy (ART). Those with active OIs, active substance abuse, severe psychiatric disease, or CD4 < 100/mm³ were excluded. Efficacy (HCV RNA) was assessed at treatment (Tx) wks 12, 24, and post-Tx wk 24. Safety assessments included incidence of AEs, rate of dose modification/discontinuation. CD4 count and HIV RNA levels were monitored. The Chi-squared test was used to test differences in proportions.

Results

Patient characteristics (QD/TIW): mean age, 44/44 yrs; male, 78/74%; Caucasian, 58/44%; genotype 1, 78/80%; ART, 89/82%, mean CD4, 551/533/mm³, mean HIV RNA, 1,531/3,698 c/mL. A total 162 (79 QD/83 TIW) were eligible for the intent-to-treat (ITT) analysis. Discontinuation for AEs was similar in both groups (p = 0.24); however, more pts taking QD IFN completed of 48 wks of Tx (30.0% QD vs 12.0% TIW, p = 0.0003) since 43.4% of pts taking TIW IFN stopped due to virologic failure compared to only 20.2% of those taking QD IFN (p = 0.0003). HCV RNA response (undetectable < 600 IU/mL) was assessed at week 12 (EVR) and wk 24 post-Tx (SVR). On-treatment results: EVR QD 44.3%/TIW 17.1% (p = 0.004); SVR: QD 42.9%/TIW 28.% (p = 0.03). Intention to treat results: EVR: QD 32.9% /TIW 13.3%; SVR: QD 9.3%/TIW 4.3% (note:

missing data = failure). No significant effect was seen on HIV RNA levels; absolute CD4 fell in both groups (QD > TIW), but no decrease in CD4% was observed. EVR was a strong predictor of SVR (90.9% sensitivity, NPV 93.9%).

Conclusions

Both EVR and SVR were significantly greater in HIV-infected pts taking QD IFN/RBV than in those taking TIW IFN/RBV. The adverse event rate was similar in both groups; however, more pts taking QD IFN completed Tx. However, the attrition rate for both Tx arms was substantial, and the intention-to-treat SVR rates observed were low.

Predictive Value of Early Virological Response (12 Weeks) to Pegylated Interferon plus Ribavirin in HIV-HCV Co-infected Patients

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Background

HCV-related liver disease is a growing cause of morbidity/mortality among HIV co-infected patients (pts). Treatment of chronic hepatitis C offers now cure to 60% of HIV pts. Response rates seem to be lower in HIV⁺ pts, but side effects may be more frequent, as result of the interaction between RBV and nucleoside analogs. Therefore, the recognition of early predictors of lack of treatment response may allow discontinuing anti-HCV therapy when no benefit is expected to be obtained. Recent guidelines have pointed out that reductions in HCV-RNA > 2 logs at 12 wks of anti-HCV therapy have a negative predictive value (NPV) of 97%. No data are available on the validity of this rule in HIV co-infected pts. Moreover, preliminary reports have claimed that HCV-RNA clearance under treatment may be slower in HIV⁺s.

Methods

We analyzed 89 HIV-HCV co-infected pts who completed a course of anti-HCV combination therapy. Pegylated interferon (IFN) was administered to 63 and regular IFN to the remaining 26 pts, always using standard doses. All received a fixed dose of RBV (400 mg bid). HCV genotypes were distributed as follows: 1-4 (62%) and 2-3 (38%). Treatment was provided for 6 months (mos) in genotypes 2-3 and for 12 mos in genotypes 1-4. Overall, sustained virological response (SVR) occurred in 29 pts. End-of-treatment response with further relapse was seen in 15. The remaining 45 were non-responders.

Results

A drop in HCV-RNA > 2 logs was seen in 38 (43%) and 52 (58%) of pts at 4 and 12 wks, respectively. Of those subjects, only 18 (48%) and 29 (56%), respectively, reached SVR. In contrast, SVR occurred in 11 (38%) and 0 pts who did not show a > 2 log drop in HCV-RNA at wks 4 and 12, respectively. Thus, the NPV was 100% at wk 12. There were no significant differences between HCV genotypes, baseline HCV-RNA, and use of either pegylated or regular IFN. In pts with HCV 2-3, a high rate of relapse in early

responders was noticed, suggesting that extending treatment beyond 6 mos might have provided a higher SVR rate in them.

Conclusions

The use of an early time-decision point at 12 wks to identify which subjects will not benefit from continuing anti-HCV treatment is valid for HIV⁺ pts. However, a delayed clearance of HCV-RNA in early responders with HIV might account for a higher relapse rate when treatment is stopped prematurely (e.g., 6 mos in genotypes 2-3).

Cost Impact of Adjunctive G-CSF and/or Darbopoetin Therapy in Maintenance of Pegylated-interferon Alpha and Ribavirin Doses in HIV/HCV Co-infected Patients

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Background

Pegylated interferon alpha (P-IFN) + ribavirin (RBV) combination (P-R) is effective in eradicating HCV in some HIV+ patients (pts). However, P-R use is complicated by serious dose-limiting neutropenia and hemolytic anemia. Dose reduction and/or interruption of therapy are major obstacles to treating HIV/HCV co-infected pts. This study evaluated the cost of adjunctive growth factor (GF) therapy to maintain P-IFN and RBV doses in an attempt to enhance the response rate.

Methods

Pts with HIV/HCV co-infection and CD4+ T-cell ≥ 100 cells/mm³ were treated in an open-label prospective trial of P-IFN α -2b sc 1.5 μ g/kg/wk + RBV 600 mg po bid for 48 wks. G-CSF was initiated for ANC < 750 cells/mm³ and darbopoetin (DARB) for Hct < 30%. The costs of HCV, HAART, and GF were extrapolated to 48 wks based on 2002 Average Wholesale Prices (AWP).

Results

Nineteen (19) subjects (mean age 46 yrs; mean CD4+ T-cell 628; median HIV-RNA < 50 copies/mL; 16 genotype 1 or 4) received P-R for a median of 22 wks (1–46 wks), 16/19 (84.2%) pts were on HAART. 8/19 (42%) pts required initiation of G-CSF (median dose = 300 mcg/wk) at a median of 5 days (3–28 days) and 7/19 (36.8%) pts required DARB (median dose 40 mcg/wk) at a median of 4 wk (1.4–25 wks). Twelve (12; 63.2%) pts required either G-CSF or DARB, 3 required both. With adjunctive G-CSF, no pt required P-IFN dose reduction for neutropenia; with addition of DARB, 1 pt dose-reduced and 1 pt discontinued RBV due to refractory anemia. One-third (33.3%) pts without ARV needed GF vs 11/16 (68.8%) HAART-treated pts. The AWP price for a 48-wk course of P-R is US\$38,649. Total mean cost for P-R, HAART, and GF extrapolated to 48 wks is \$54,473/pt for the entire cohort. The mean drug costs for pts who did and did not require

GF are \$58,559 (\$46,629–\$77,508) and \$47,740 (\$35,051–\$59,330), respectively. For pts who completed >12 wks of P-R, 12/17 (70%) had a ≥ 2 -log decline in HCV viral load within the first 12 wks.

Conclusions

GF are useful adjuncts to support the bone marrow suppressive effects of P-R. GF therapy resulted in an added cost of over US\$10,000/pt for the 63% of pts who required this treatment. Maintaining therapeutic doses of P-R may increase the chance of HCV eradication. Considering the poor response to anti-HCV therapy in HIV co-infected pts, cost of GF therapy is justifiable, provided the early virologic response is sustainable.

Serious Ophthalmologic Pathology with Visual Compromise in HIV/HCV Co-infected Patients Treated with Pegylated Interferon Alpha-2b and Ribavirin

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Background

Ophthalmologic disorders are recognized side effects of interferon-alpha (IFN). While retinal vascular occlusions, retinal hemorrhages, and cotton wool spots (CWS) have been reported in patients (pts) treated with IFN, optic neuropathy is uncommon but sight threatening.

Methods

An open-label prospective trial treated HIV/HCV co-infected pts (CD4⁺ T-cell counts = 100 cells/mm³) with Peg-IFN alpha-2b 1.5 mug/kg sc qwk and RBV 600 mg po bid for 48 wks. Ophthalmologic evaluations including visual acuity, threshold visual field testing, color vision exam, and indirect ophthalmoscopy were performed at baseline and at least every 3 months.

Results

Nineteen (19) pts enrolled on study for a median of 26 wks (range, 1-46) with 16 followed for at least 12 wks. Subjects had a baseline median CD4⁺ T-cell count of 704 cells/mm³ (range, 108-1,273), median baseline HIV log VL of 1.69 copies/mL (range, 1.69-4.52) and median baseline HCV log VL of 6.61 copies/mL (range 5.80-7.35). Seven (7) of the 16 pts (44%) developed ophthalmologic pathology. Six (6) had CWS on 12 wk follow-up funduscopic examination. These lesions waxed and waned while therapy was continued. One (1) of these pts was found to have bilateral cataracts at 12 wks while another developed a unilateral cataract. One (1) pt exhibited a 50% decrease in color vision requiring cessation of interferon therapy. Color vision has improved over the 4 wks since peg-IFN was discontinued, but has not returned to normal.

Conclusions

The incidence of serious ocular pathology associated with treatment with anti-HCV therapy may be very high and is likely associated with peg-IFN. While HIV, hypertension, and diabetes mellitus are associated with these ocular lesions, incident cases of CWS and cataracts occurred in pts with high CD4⁺ T-cell counts and developed soon after beginning peg-IFN therapy. As with pts treated with ethambutol, medications toxic to retinal ganglion cells can cause lesions such as optic neuropathy and result in color blindness or loss of vision. Our findings suggest a need for increased vigilance in monitoring pts treated with peg-IFN for visual changes. Color vision testing should be a routine component of the standard examination, as loss of color vision may be a harbinger of serious optic neuropathy.

A Genetic Screen to Monitor the Activity of the Hepatitis C Virus NS3 Serine Protease

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Background

Post-translational proteolysis is an essential step in the life cycle of viruses. For that reason, site-specific proteolysis has been an attractive target for antiviral agent development. The emergence of hepatitis C virus (HCV) as a major human pathogen has promoted the study of the virally encoded NS3 serine protease as a potential antiviral target. The development of antivirals for this virus has been hampered by the lack of cell culture or small animal model systems.

Methods

Previously, a genetic screen assay was developed for the characterization of the human immunodeficiency virus type 1 (HIV-1) protease. This genetic screen system is based on the bacteriophage lambda regulatory circuit where the viral repressor cI is specifically cleaved to initiate lysogenic to lytic switch. We have adapted this simple lambda-based genetic assay for the analysis of the activity of HCV NS3 serine protease. An HCV protease-specific target, NS5A-5B, was inserted into the lambda phage cI repressor.

Results

This repressor efficiently repressed the infecting phage. The target specificity of the HCV NS5A-5B repressor was evaluated by co-expression of this repressor with a beta-galactosidase (betagal)-HCV NS3/4 protease construct. The betagal-HCV NS3/4 protease construct contained the NS4 residues 21-34 fused in frame to the amino terminus of the NS3 protease domain (residues 2-181). *E. coli* cells were then co-transformed with plasmids encoding the cI.HCV5AB-cro and the betagal-HCV NS3/4 protease constructs. Upon infection of this strain, lambda phage replicated up to 8,000-fold more efficiently than in cells that did not express the HCV NS3/4 protease. Moreover, the specificity of this trans-cleavage reaction was further demonstrated by the lack of phage replication in cells expressing mutated forms of the HCV NS3/4 protease that included the substitutions H57A, D81A, or S139A. Likewise, a control mutant cI.HCV5ABmt-cro target site also

prevented phage replication.

Conclusions

In summary, we present here a simple and rapid genetic screening system for the characterization of the activity of the HCV NS3 serine protease as well as to search for new protease inhibitors

Survival in HIV-infected Liver Transplant Recipients

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Background

HIV infection has been considered an absolute contraindication to solid organ transplantation because of the poor survival associated with immunosuppression. However, the improvement in viral suppression and survival made possible through highly-active antiretroviral therapy (HAART) led us to hypothesize that transplantation (OLT_X) would be safe and effective in HIV+ recipients receiving postoperative HAART.

Methods

Twenty-three (23) HIV+ subjects with end-stage liver disease undergoing OLT_X after the availability of HAART were prospectively followed for CD4 number, HIV RNA, and post-transplant survival.

Results

Cumulative survival among HIV+ recipients was similar to age- and race-comparable HIV- UNOS recipients, $p = 0.643$. At 12, 24, and 36 months after OLT_X, survival was 90.9%, 75.9%, and 75.9% vs 86.6%, 82.3%, and 79.2%, respectively. Survival was poorer in subjects with post-OLT_X antiretroviral intolerance, $p = 0.007$, post-OLT_X CD4 < 200/ml, $p = 0.005$, and post-OLT_X HIV viral load > 400 copies/ml, $p = 0.016$. One-year survival in these groups was 71.4% vs 100.0%; 25.0% vs 88.9%; and 0% vs 85.7%, respectively. Neither the type of antiretroviral therapy, $p = 0.091$, type of anti-rejection therapy, $p = 0.401$, pre-OLT_X CD4 < 200/ml, $p = 0.984$, nor pre-OLT_X HIV RNA > 400 copies/ml, $p = 0.989$, affected survival. HCV was associated with poorer survival, $p = 0.037$, but there was no difference between HCV+/HIV+ and HCV+/HIV-, $p = 0.145$. One-year survival in these groups was 85.7% vs 100.0%, and 85.7% vs 85.6%, respectively.

Conclusions

Survival in HIV+ subjects undergoing OLT_X is comparable to that in HIV- OLT_X UNOS recipients. These findings suggest HIV infection should no longer be a contraindication to OLT_X and warrant further prospective studies.

GBV-C Infection Inhibits CCR5 and CXCR4 HIV Strains and Alters Chemokine and Cytokine Gene Expression in PBMC Culture

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Background

GB Virus type C (GBV-C) HIV co-infection is associated with prolonged survival or clinical benefit in 8 clinical studies, and GBV-C HIV (R5 strain) co-infection of PBMC cultures resulted in decreased HIV replication. The mechanism by which GBV-C may slow HIV disease progression is not known. In this study we characterized the effects of GBV-C infection on HIV replication and on cellular gene expression in a PBMC co-infection model.

Methods

Clinical isolates of GBV-C or mock-control preparations were used to infect PBMCs and CD4-enriched T-cell cultures. Both CCR5 and CXCR4 co-receptor usage HIV strains were used. Cell viability was determined by trypan-blue exclusion and protein synthesis determined by ³⁵S-methionine uptake. HIV replication was determined by measuring p24 antigen in culture supernatants. GBV-C replication was determined by real-time PCR. Mock- or GBV-C infected cellular RNA was prepared, ³²P labeled, and hybridized to membranes containing cytokine or chemokine probes and relative quantitation determined by phosphor-imager.

Results

Virus derived from an infectious clone and clinical isolates of GBV-C inhibited both XR4 and R5 strains of HIV. HIV inhibition required GBV-C replication. Infection of cells with GBV-C for 6–24 hrs prior to HIV resulted in increased inhibition compared to simultaneous infection, and inhibition increased further if GBV-C infection proceeded 48 hrs prior to HIV. GBV-C infection resulted in improved cell viability and increased protein synthesis when compared to mock-infected cells. Preliminary experiments found increased IL-2, IL-8, and decreased IL-13 expression in PBMCs, and increased expression of Rantes, MIP-1a, MIP-1b, and SDF-1 by GBV-C infected cells compared with mock-infected controls. Furthermore, the inhibition of an R5 HIV strain was decreased when cells were incubated in neutralizing anti-RANTES, MIP-1a, MIP-1b anti-sera.

Conclusions

GBV-C inhibits R5 and XR4 strains of HIV in vitro, with maximal inhibition occurring 48 hrs post-infection. GBV-C infection of PBMCs appears to increase expression of the CCR5 chemokines RANTES, MIP-1a, MIP-1b, and SDF-1. Survival benefits associated with GBV-C co-infection may reflect a direct inhibitory effect of GBV-C on HIV replication. Additional factors may be involved, including effects on cytokine expression and decreased lymphocyte death.

Morphine Enhances Hepatitis C Virus Replicon Expression

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Background

Although injection drug users (IDUs) are the single largest risk factor for Hepatitis C Virus (HCV) transmission, there is little information available regarding whether substance abuse enhances HCV replication and promotes HCV disease progression. Therefore, we investigated whether morphine alters HCV mRNA expression in a HCV replicon-containing cell clone (Huh.8) that derived from human hepatoma cells (Huh7).

Methods

RT-PCR and Western blotting were used to determine the expression of mu-opioid receptor at mRNA and protein levels, respectively. HCV RNA copy numbers in the Huh.8 cells were quantified by real-time RT-PCR. pNF-kappaB-Luc, a plasmid containing NF-kappaB promoter linked with a luciferase gene, was transfected into Huh7 cells to study the effect of morphine on the NF-kappaB activity. CD8⁺ T lymphocytes were purified from PBMC isolated from whole blood of HCV-infected adult subjects using MACS CD8 Microbeads.

Results

Both Huh.8 and Huh7 cells express mu-opioid receptor. The addition of morphine to the Huh.8 cell cultures resulted in significant increase of HCV mRNA expression. Morphine diminished the anti-HCV effect of IFN-alpha in Huh.8 cells. This stimulatory effect of morphine on HCV mRNA expression was abolished by naltrexone (an opioid receptor antagonist) or beta-funaltrexamine (a specific mu-opioid receptor antagonist). Investigation of the mechanisms responsible for morphine action revealed that morphine activated NF-kappaB promoter and caffeic acid phenethyl ester (CAPE), a potent and specific inhibitor of activation of NF-kappaB, abolished morphine-activated HCV RNA expression in Huh.8 cells. In addition, culture supernatants from the activated CD8⁺ T-lymphocytes isolated from HCV-infected adult subjects, when added to Huh.8 cell cultures, significantly inhibited HCV RNA expression. This CD8⁺ T-cell-mediated anti-HCV effect was partially reversed by the addition of morphine to Huh.8 cell cultures.

Conclusions

Our data indicate that morphine may play an important role as a positive regulator of HCV replication in human liver cells *in vivo*. This enhancing effect of morphine on HCV RNA expression may compromise IFN-alpha therapy as well as CD8⁺ T-cell-mediated immunity against HCV infection.

Persistent GBV-C virus Type C (GBV-C) Infection is Associated with Decreased Risk of Death in HIV-seroconvertors in the Multicenter AIDS Cohort Study (MACS)

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Background

GBV-C is not known to cause disease, replicates in lymphocytes, inhibits HIV replication *in vitro*, and has been associated with a decreased risk of death among HIV positive persons in some, but not all, studies. Previous studies based on convenience samples could not rule out bias due to unknown durations of HIV and GBV-C infection.

Methods

Stored plasma obtained from MACS participants with incident HIV infection 1 - 1 1/2 years (early visit; N=271) and 5-6 years (late visit; N=138) after HIV seroconversion were tested for GBV-C infection. Viremia was measured by GBV-C RNA RT-PCR (RNA), and prior GBV-C infection by anti-GBV-C E2 antibodies (Ab).

Results

At the early visit, 39% were GBV-C RNA pos, an additional 46% were GBV-C RNA neg but E2 Ab pos, 1% were positive for RNA and Ab, and 14% were neg for both RNA and Ab. Acquisition of GBV-C between visits was rare (N=1); however, 12 (8.7%) of the 138 men tested at both visits cleared GBV-C viremia between visits. GBV-C RNA status at the early visit was not associated with a difference in survival. In contrast, GBV-C RNA at the late visit was strongly associated with survival: compared to men who were RNA pos at both visits, men who were GBV-C RNA negative at both visits were 2.43 times more likely to die (95% CI 1.2 - 5.2; P<0.01) and those who cleared GBV-C infection between visits were 5.87 times more likely to die (95% CI 2.2 - 15.4; P<0.01). The mean rates of CD4 cell loss per year in those persistently positive, persistently negative, and who cleared GBV-C RNA were 26, 37, and 107 cells per year, respectively. The median duration of follow-up, date of seroconversion, use of HIV therapy, median log₁₀ HIV-RNA values and prevalence of CCR5 32 polymorphisms did not vary by GBV-C status.

Conclusions

GBV-C viremia assessed 5-6 years after HIV seroconversion was a strong predictor of survival, and loss of GBV-C predicted a higher risk of death. Mis-classification of those who cleared GBV-C as "positive", based on the early visit, proved important as there was an increased risk of death with the clearance of GBV-C. GBV-C infection has a high attributable benefit in HIV infection, since both the prevalence of GBV-C and size of its protective effect were high. Understanding the mechanisms for the interaction between GBV-C and HIV may provide insights into ways to control HIV disease progression.

GB Virus C Viremia During the Natural Course of HIV-1 Infection: Viremia at Diagnosis Does Not Predict Mortality

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Background

GB virus C (GBV-C) viremia has recently been proposed to be associated with improved survival in HIV-infected subjects. We have assessed whether GBV-C status at diagnosis of HIV-1 infection can be used to predict the disease course in patients not receiving combination antiretroviral therapy, and whether longitudinal changes in GBV-C status occur during the course of HIV-1 infection.

Methods

We followed 230 HIV-1 infected patients (pts) until either death or initiation of combination therapy (median follow-up: 4.33 yrs). Markers for GBV-C infection (viremia:GBV-C RNA; resolved infection: anti-E2 antibodies [anti-E2]) were assessed in serum samples obtained within two years of HIV-1 diagnosis. From 163/230 patients, an additional sample obtained before the study endpoint was available for GBV-C testing. Kaplan-Meier survival curves were used for survival analysis.

Results

At baseline, GBV-C viremia was found in 62 pts (27%), and anti-E2 in 69 (30%). GBV-C viremia was less prevalent in pts presenting with AIDS (2/31) than in patients with asymptomatic infection (54/175; $p = 0.008$). No differences in mortality or AIDS incidence were observed with respect to baseline GBV-C status ($p = 0.12$ and 0.97 , respectively). Similar results were obtained in 63 subjects with documented duration of HIV infection. During follow-up, 11/44 pts with GBV-C viremia at baseline lost GBV-C RNA without showing anti-E2 seroconversion. These pts were characterized by increased mortality (8/11 vs 16/89; $p = 0.007$), AIDS incidence (10/11 vs 19/70; $p < 0.001$), and a faster CD4+ cell decline (145 cells/mm³/year vs 56 cells/mm³/year; $p = 0.006$).

Conclusions

GBV-C status at diagnosis of HIV-1 infection does not predict the natural course of disease. The decreased prevalence of GBV-C viremia in patients with AIDS, and the observed loss of GBV-C viremia without anti-E2 seroconversion in patients with progressive disease support an interaction between these two viruses. However, the GBV-C status in HIV-1 infection is probably a secondary phenomenon during disease progression rather than an independent prognostic factor.

Recent Trends in HIV-related Hospitalizations by Selected Diagnoses: A 12-state Study

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Background

Reports of HIV-related inpatient hospital admissions have typically been based on local, cross-sectional data. Using comprehensive hospital discharge data from 12 states (including CA, FL, NJ, and NY), we evaluated trends in HIV-related inpatient admission rates and lengths of stay in 1996, 1998, and 2000 as a function of selected discharge diagnoses.

Methods

Using ICD-9 diagnoses from discharge abstracts in the Health Care Utilization Project-State Inpatient Database (SID), we identified HIV-related admissions and classified them as involving opportunistic illness (OI), complications of injection drug use (IDU), and liver related complications (LRC). IDU complications were defined as abscess, cellulitis, osteomyelitis, bacteremia, endocarditis, and poisoning by analgesics. LRC were identified as acute and subacute necrosis of the liver, chronic liver disease and cirrhosis, liver abscess, hepatic coma, portal hypertension, hepatorenal syndrome, hepatocellular carcinoma, gastrointestinal bleed, Mallory-Weiss Tear, and viral hepatitis.

Results

We evaluated 327,306 HIV hospitalizations in the 12 states under study. Between 1996–2000, HIV hospitalizations for OIs decreased significantly from 41%–29% of all HIV hospitalizations ($p < 0.001$); hospitalizations for complications of IDU remained relatively constant between 5.9%–6.9%; and hospitalizations for LRC increased significantly from 13%–18% of all HIV hospitalizations ($p < 0.001$). Mean length-of-stay was significantly longer for LRCs than non-LRCs (10.4 vs 8.9 days, $p < 0.0001$). The proportion of all HIV admissions covered by Medicare increased from 17%–23%. By contrast, the proportion of LRC Medicare admissions rose from 17%–25% ($p < 0.0001$).

Conclusions

Our results show, in multiple states, declines in OI-related hospital admission rates, but an increase in hospitalization rates for LRC as well as longer LOS for LRC admissions between 1996–2000. If this trend continues, LRC may become one of the principal comorbidities in HIV infected patients. This could have a dramatic impact on the burden of disease, the costs of care, and publicly funded insurance.

Impact of Hepatitis C, HIV, or Both on Survival in Veterans in Care Before and After the Introduction of HAART (1996)

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Objectives

To determine 1) whether a survival difference exists between patients (pts) diagnosed with hepatitis C, HIV, or both, compared to controls, and 2) whether these differences were affected by the introduction of highly active antiretroviral therapy (HAART) in 1996.

Methods

Male HIV+ pts and age-, race-, and site-matched controls were identified from VA administrative databases. Demographic characteristics and dates of death were extracted. Kaplan-Meier survival curves and Cox proportional hazards regression analysis were performed to determine the impact on survival of infection with HIV, hepatitis C, or both, controlling for age and race.

Results

We identified 35,290 HIV+ pts and 34,626 controls with 10,888 and 3,053 deaths, respectively. In the pre-1996 time period, survival differences occurred across all four groups. In a Cox proportional hazards model, HIV diagnosis (Hazard ratio [HR] 6.5) had a larger impact on survival than hepatitis C diagnosis (HR 1.8), while co-diagnosis had an even greater impact (HR 7.9). Post-1996, HIV and hepatitis C diagnoses had equal hazard ratios (HR 2.5 and 2.2, respectively, $p = 0.2$ for comparison), while co-diagnosis had a larger detrimental effect on survival (HR 5.0). Both models controlled for age and race. All predictors were significant at the $p < 0.0005$ level. In both controls and HIV+ subjects, the relative mortality hazard of hepatitis C co-diagnosis increased in the post-1996 time period. There was a trend towards a larger increase in the effect for HIV+ pts ($p = 0.06$).

Conclusions

Significant differences in the relative hazard of mortality existed in pts diagnosed with hepatitis C, HIV or both, prior to the introduction of HAART in 1996. While the hazard of mortality with HIV infection declined after this time period, the relative hazard of mortality due to hepatitis C has increased in both mono- and co-diagnosed patients, and trended towards a larger effect in co-diagnosed patients. The growing impact of hepatitis C on mortality is of note and may reflect an aging cohort effect. The larger increase in mortality among co-diagnosed pts should spur further research into the interaction between HIV and hepatitis C infections and increased clinical focus on management of co-infection.

The Association of Hepatitis C Virus Prevalence, Activity, and Genotype with HIV Infection in a Cohort of New York City Drug Users

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Background

We assessed in drug users the factors associated with prevalence, activity, and genotype of Hepatitis C Virus (HCV) infection, which is an increasing cause of co-morbidity and mortality in persons with HIV infection.

Methods

Standardized interview of current and former drug users and assay of HCV serum antibody, RNA level, and genotype, HIV antibody and viral load, CD4⁺ lymphocyte counts, and hepatitis B markers.

Results

We enrolled 557 drug users; 318 (57%) were men, 82 (14.7%) white, 105 (18.9%) black, and 366 (65.7%) Hispanic; median age was 44 years (range 25–72); 328 (58.9%) were HIV⁺, median HIV load was 1,247 copies/ml (range < 50 – 5 x 10⁵). One hundred fifty-seven (157; 28.2%) reported never having injected drugs. Four hundred eighteen (418; 75%) were anti-HCV⁺, of whom 313 (75%) had detectable HCV RNA (median 5.04 x 10⁵ IU/mL, range 1,020 to 15.7 x 10⁶). On multivariate analysis HCV seropositivity was independently associated with history of drug injection (OR_{adj} = 22.6, 95% CI, 13.1–39.0), HIV seropositivity (OR_{adj} = 5.3, 95% CI, 2.8–10.2), and increased age (OR_{adj} = 1.1 per year, 95% CI, 1.04–1.1), and inversely with drug snorting (OR_{adj} = 0.02, 95% CI, 0–0.7). Among anti-HCV positive persons, detectable HCV RNA (≥ 600 IU/ml) was independently associated with HIV seropositivity (OR_{adj} = 2.3, 95%CI 1.5-3.7), male gender (OR_{adj} = 2.2, 95% CI, 1.4–3.5), and history of injection (OR_{adj} = 1.5, 95% CI, 1.02–2.3), and inversely associated with HBsAg (OR_{adj} = 0.14, 95% CI, .03–0.6). Among persons with detectable HCV RNA, higher levels were independently associated with higher HIV viral load (p = 0.048), increased age (p = 0.04), and genotypes 2a and 2b (p = 0.003).

Conclusions

Among drug users, drug snorting was inversely associated with risk of HCV infection. Detectable HCV RNA was associated with HIV infection, male gender, and history of injection, and inversely associated with HBsAg. HCV RNA level was associated with HIV viral load, independent of the level of immunosuppression, increased age, and genotypes 2a and 2b. However, a substantial degree of the person-to-person variability in the prevalence and level of detectable HCV RNA remains unexplained.

Histological Damage in Liver Biopsy Specimens from 492 HIV-HCV Co-infected Patients: A European Collaborative Study

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Background

HCV-related liver damage progresses faster in HIV co-infected patients (pts) than in HIV-negative individuals. In HCV mono-infected patients with elevated ALT levels 51% and 24% have no (F0) or just portal fibrosis (F1), respectively; whereas portal fibrosis with septa (F2), many septa (F3), or cirrhosis (F4) is recognized in 9.9%, 9.7% and 5.3%, respectively, but this information is not well known for HIV-positives.

Methods

All participants were invited to fill a case report form in which the main demographics, clinical, laboratory, and histological findings from HIV-HCV co-infected patients with elevated ALT levels were recorded. The liver biopsy had been performed in all instances to assess the indication for anti-HCV treatment.

Results

We analyzed 492 pts: 78.5% were male; 86% had been IDUs; and 25% admitted high alcohol intake (> 80 g/d). Median age was 35 yrs (IQ 31-39). Median estimated duration of HCV infection was 14 yrs (IQ 10-18). Median CD4 count was 463 cells/ul (IQ 300-630). Median ALT elevation was 2-fold (IQ 1-4 fold). Antiretroviral therapy: HAART in 32%, mono or dual tx 22.5%, and no drugs 57%. HCV genotype was 1 (57%), 2 (1%), 3 (36%), and 4 (6.3%). Up to 69% of pts harbored > 800,000 IU/ml. Liver fibrosis stage was F0 (13.2%), F1 (35%), F2 (18.7%), F3 (21.5%), and F4 (12%). In the multivariate logistic regression analysis, 3 factors were the best predictors of severe liver fibrosis (F3-F4): duration of HCV infection > 15 yrs (OR 3.6; CI 95%, 1.5-4.4); age > 20 yrs at the time of HCV infection (OR 3.3; CI 95%, 1.9-5.6); and history of high alcohol intake (OR 2.5; CI 95%, 1.5-4.4). Pts estimated to be infected for more than 15 yrs had severe liver fibrosis in 46% of cases. Severe liver fibrosis was not associated with the CD4 count, HCV genotype, HCV viremia, gender, or use of HAART.

Conclusions

More advanced stages of liver fibrosis are seen in HIV-HCV co-infected pts than in HCV-mono-infected pts. Overall, up to 1/3 of those with elevated ALT levels show severe liver fibrosis (F3-F4), but increases significantly with duration of HCV infection mounting up to 50% after 15 yrs of carrying HCV. Thus, treatment of HCV infection should be not delayed unnecessarily given that lower response rates are seen in cirrhotics.

Progression of Liver Histological Status in HIV Hepatitis C Virus Co-infected Patients Started on HAART: A Prospective Study

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Background

Liver deterioration has been reported in HIV-Hepatitis C Virus (HCV) co-infected patients starting HAART. We analysed the impact of HAART and immune restoration on liver histological status in HIV-HCV co-infected patients.

Methods

Eligible patients had a HCV RNA load above the limit of detection, no cirrhosis or liver failure, no HCV treatment within the 12 last months (mos). They were enrolled at initiation of HAART (mo 0), and followed at mo 1, 3, 6, 9, and 12, in a prospective multi-centre cohort (TRIVIR-ANRS HC EP1). A liver biopsy was performed at mo 0 and mo 12. Histological progression (HP) was defined as an increase of ≥ 2 units in the Knodell score and ≥ 1 unit in the Metavir score between mo 0 and mo 12. Potential factors associated with HP were studied: sex, age, body mass index, HIV and HCV transmission category, AIDS, CD4 cell count, HIV and HCV viral load, HCV genotype, alcohol use and type of antiretroviral treatment of HAART at baseline, immunologic response (IR; a double CD4 cell count or a $100/\text{mm}^3$ increase between M0 and M12), onset of transaminases elevation (TE; alanine aminotransferase level ≥ 5 -fold the upper limit of normal value).

Results

Among the 33 patients (pts) initially enrolled, 25 (21 men) had both liver biopsies: 5 (20%; 95% confidence interval: 4%–36%) had HP. Median age was 38.1 yrs. At baseline, median CD4 cell count was $278/\text{mm}^3$, median levels of HIV and HCV RNA were $4.4 \log_{10}$ copies/mL and 6.2 IU/mL, respectively. Four (4) pts (16%) were alcohol consumers. Nine (9) pts (36%) were started on protease inhibitor, 14 (56%) on non nucleoside reverse transcriptase inhibitor and 2 (8%) on Abacavir, in addition to 2 nucleoside reverse transcriptase inhibitors. During follow-up, 13 pts (52%) had IR, 19 pts (76%) had a HIV RNA load $< 1.70 \log_{10}$ copies/mL at M12, and there was no change in HCV RNA load. No relationship was found between IR and HP (23% of HP in pts with IR, 17% in pts without IR, $p = 1.00$) or other baseline characteristics and HP. However, TE occurred in 5 pts (20%) and 1 case was considered drug-related, 2 were alcohol-related and 2 were HCV-related. TE was significantly associated with HP (80% of HP in pts with TE, 5% in pts without TE, $p = 0.002$).

Conclusion

These data suggest that IR following the initiation of HAART is not associated with a progression of liver lesions. However, careful monitoring of liver enzymes and alcohol suppression are highly recommended in HIV-HCV co-infected pts.

High Frequency of CCR5-delta32 Homozygosity in HCV-infected, HIV-1 Uninfected Hemophiliacs Results from Resistance to HIV-1

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Background

A previous study suggests that the CCR5-Delta32 allele may be an adverse host factor in HCV infection. Because most subjects in that study had hemophilia, we examined this hypothesis in a large cohort of hemophiliacs.

Methods

The Multi-center Hemophilia Cohort Study is a prospective cohort study of U.S. and European patients (pts). CCR5-delta32 genotypes of 1,419 Caucasian subjects were determined by PCR and SSCP. HCV RNA levels were measured with a bDNA assay.

Results

Ninety-six percent (96%) of the subjects were infected with HCV and 72% were infected with HIV-1. Among the 1,362 pts who were infected with HCV, the genotypic distribution was very similar to that of all enrolled hemophiliacs and other Caucasian populations; 13 (1.0%) were CCR5-delta32 homozygotes and there was no deviation from Hardy-Weinberg equilibrium (HWE; $p > 0.05$). Per the previous report, we examined the genotypic distribution among the 358 pts who were infected with HCV, but not HIV-1. Of the HCV⁺ 3.4% were infected, HIV⁻ uninfected hemophiliacs were CCR5-delta32 homozygotes, which is 3-fold higher than expected under HWE ($p < 0.0001$). However, CCR5-Delta 32 homozygosity was increased among HCV-infected, HIV-uninfected hemophiliacs because only 1/13 (8%) CCR5-delta32 homozygotes were infected with HIV-1, compared to 75% of wild-type pts and 72% of CCR5-delta32 heterozygotes. Furthermore, median HCV RNA levels were similar among CCR5-delta32 homozygotes (2.0×10^6 equivalents/ml) and wild-type pts (3.1×10^6 equivalents/ml; $p > 0.05$).

Conclusion

The CCR5-delta32 allele is not an adverse host factor in HCV infection. The previously reported increased frequency of CCR5-delta32 homozygosity in HCV-infected, HIV-1-uninfected hemophiliacs is due to the protective role of this genotype against HIV-1 infection.

Hepatitis C Virus Load Measured Prior to HIV Seroconversion is not Associated with Subsequent HIV Disease Progression in Injection Drug Users

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Background

In some studies, the serum hepatitis C virus (HCV) RNA level determined after HIV seroconversion has been associated with progression to AIDS/death. However, the relationship of the HCV RNA level prior to HIV seroconversion (SC) and subsequent HIV disease progression is unknown.

Methods

HIV disease progression and survival were analyzed in a prospective, cohort of active/former injection drug users (IDUs) followed semi-annually in Baltimore, MD (the ALIVE cohort). HCV-antibody-positive, HIV antibody-negative persons who acquired HIV infection before 1/1997 were studied using longitudinal data, including blood tests, clinical outcomes (e.g., AIDS and death). Cox regression was used to assess time to AIDS-related death, progression to AIDS-defining illness (first OI), and to CD4 < 200/ μ L.

Results

We analyzed 225 HCV seropositive, HIV seroconverters: male, 76%; median age at HIV SC, 35.9 yrs (IQR 31.4-40.4); Black, 94%; median duration of IDU prior to HIV SC, 11.8 yrs (IQR 4.7-18.8); median initial CD4 cell count, 647/ μ L (IQR 449-894); median initial HIV RNA level, 31,339 c/mL (IQR 7,699-8,6484). HCV RNA levels were obtained a median of 9.3 months (IQR 6.9-12.3) prior to HIV SC. The median HCV RNA level was 40,100 eq/mL (IQR 1,550-257,000). The median duration of follow-up was 4.9 yrs (IQR 3.5-7.4), during which time only 11% received HAART. Progression to AIDS, AIDS-related death, and CD4 cell count < 200/ μ L was observed in 53 persons (24.6%), 31 persons (13.7%), and 104 persons (46.6%), respectively. HCV RNA level determined before HIV SC was *not* associated with progression to AIDS (HR 1.07, 95% CI, 0.84-1.34), AIDS-related death (HR 1.16, 95% CI, 0.85-1.58), or CD4 cell count < 200/ μ L (HR 1.11, 95% CI, 0.95-1.30).

Conclusions

In this cohort, the HCV RNA level measured prior to HIV seroconversion was not associated with subsequent progression to AIDS, AIDS-related death, or CD4 cell decline. Further research is needed to determine the relationship of hepatitis C infection and HIV disease progression.

A Model for Predicting Liver Fibrosis Using Non-invasive Biochemical Markers When Biopsy is Not Appropriate

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Background

Hepatitis C (HCV) is an opportunistic infection that causes substantial morbidity and mortality in HIV-infected patients (pts). The prominent feature of HCV progression is

fibrosis leading to cirrhosis and possibly liver failure and hepatocellular carcinoma. The gold standard for assessing the stage of fibrosis is liver biopsy, which may not be available. Nevertheless, the level of fibrosis or "stage" of the liver is important when deciding whether to initiate or modify treatment for HCV.

Objective

To determine whether a panel of non-invasive markers can adequately predict the level of fibrosis in HIV/HCV co-infected pts.

Methods

Data from 5 randomized clinical trials of HCV treatment were reviewed for all pts who had a biopsy prior to study entry. Baseline markers of liver function, as well as demographic and other clinical variables were incorporated in regression and classification models to maximize predictive value. Linear and logistic regression and feed forward neural network models were evaluated.

Results

Pt characteristics: 46 HIV⁺ and 114 HIV⁻ (control). Age 47.1 ± 7.6 (mean \pm SD). The sample was 60% Caucasian and 49.7% male. Pts were characterized as having no/mild fibrosis, fibrosis, or severe fibrosis/cirrhosis based on existing biopsy. ALT was significantly associated with fibrosis stage, with and without controlling for HIV status. The mean ALT for HIV⁺ pts with no or mild fibrosis was 96.8 ± 68.8 (mean \pm SD) and the mean ALT for pts with severe fibrosis or cirrhosis was 137.9 ± 163.7 . The final stepwise logistic regression model included platelet count, gender, HIV status, and ALT. The strengths and weaknesses of linear models versus nonlinear classification systems will be compared.

Conclusions

Linear and logistic regression models can be used to provide information about the possible stage of liver fibrosis when biopsy is not appropriate or possible. Nonlinear classification systems such as the feed-forward neural network will also have applications in this area. These pilot data demonstrate that significant predictive value can be extracted from non-invasive panels of biochemical and morphological values.

Hepatitis C Increases the Risk of DM in HIV-infected Veterans in Care

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Background

Human immunodeficiency virus (HIV) infection and the highly active antiretroviral therapy (HAART) used to treat HIV have been associated with various metabolic abnormalities including insulin resistance, glucose intolerance and diabetes mellitus (DM). Hepatitis C virus (HCV) infection has also been associated with a higher risk of developing DM. Hence it is plausible that patients (pts) co-infected with HCV and HIV,

especially those on HAART, would have a higher risk of DM than those with HCV alone. We undertook this study to find out if pts with HCV-HIV co-infection have a higher risk of being diagnosed with DM than those with HCV infection alone.

Methods

Pts with an ICD-9 diagnosis of HIV were identified from the VA administrative database from 1989 onwards. Data on age, gender, race, history of and first date of HIV, HCV and DM diagnoses, and history of alcohol use was extracted from the VA administrative database. The disease data was based on ICD-9 codes. The ICD-9 codes for HIV and HCV have been validated in the Veterans Aging Cohort Study (VACS)

Results

A total of 41,262 veterans in care with HIV infection were identified. Of these, 14.8% had a diagnosis of DM and 17.9% had a diagnosis of HCV. The prevalence of DM in HCV infected pts was 19.7% compared with 13.7% (chi square = 167; $p < 0.001$) in the HCV negative pts. In a logistic regression model, the unadjusted odds ratio of having a DM diagnosis in HCV infected pts was 1.3 (95% CI 1.23-1.37). After controlling for age, race, history of drug and alcohol use, the adjusted odds ratio was 1.69 (95% CI 1.57-1.81). Adjustment was not made for 2 important predictors of DM in general population, body mass index and family history, because of lack of data.

Conclusions

HCV infection increases the risk of DM in HIV-infected veterans in care, which persists after adjusting for age, race, alcohol and drug use. Pts with HCV-HIV co-infection should be regularly screened for DM.

Frequent Detection of ex vivo CD8⁺ Responses against Hepatitis C Virus in HIV Co-infected Individuals on HAART

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Background

Co-infection with HIV accelerates the course of HCV, now a leading cause of morbidity and mortality in this population. HCV-specific CD8⁺ lymphocytes may be involved in the pathogenesis of accelerated hepatic fibrosis as well as immune reconstitution syndromes following initiation of highly-active antiretroviral therapy (HAART). Prior studies have detected these responses only in HIV⁺ persons not on HAART. However, these studies may have been limited due to reliance on only previously described epitopes.

Methods

We have developed a peptide-based ELISpot that screens peripheral blood mononuclear cells (PBMC) ex vivo for interferon-gamma production (IFN-gamma) in response to the whole expressed HCV polyprotein. Fifteen (15) to 20-mer peptides overlapping by 10 amino acids were placed in a matrix of pools containing 20 peptides each. PBMC were

added and IFN-gamma secretion measured in SFC/million PBMC after an overnight incubation. Confirmation was performed via single-peptide ELISpot as well as generation of T-lymphocyte cell lines. Ex vivo intracellular cytokine staining (ICS) and tetramer staining was performed on expanded cell lines. This methodology was applied for cross-sectional study of 17 HIV⁺ HCV⁺ persons, each of whom had chronic HCV viremia. Thirteen (13) were taking HAART for a minimum of 1 year.

Results

Application of the above techniques in co-infected individuals detected immune responses against HCV in 7/17 (41.2%) of patients (pts) studied. Five (5) of 13 (38.4%) pts on HAART exhibited responses. We found as many as 7 ex vivo CD8⁺ responses within the same individual (range 0-7 responses). The magnitude of ex vivo responses varied between 40-750 SFC/million PBMC per response. Expansion of cells found additional responses beneath the level of detection of the ELISpot, revealing a hierarchy of responses. Multiple novel HCV-specific responses were detected and mapped.

Conclusions

HCV-specific CD8⁺ cells secreting IFN-gamma can be detected at high frequencies in HIV⁺ individuals using novel and comprehensive techniques. These responses are present in pts on long-term HAART and despite chronic HCV viremia. Direct comparison of breadth, magnitude, and phenotype of HCV- and HIV-specific immune responses is now possible and will shed insight into the reciprocal effects of these 2 viruses. These cross-sectional data provide the basis for longitudinal study to determine correlates of HCV-specific immune reconstitution while on HAART.

The Association of Hepatitis C Virus-specific Immune Responses with Liver Histology and Treatment Outcomes in Subjects with HIV/HCV Co-infection

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Background

The relationship of HCV-specific immune responses to liver injury and treatment outcome is poorly understood, but is important to understanding the pathogenesis of liver damage and improving treatment outcomes. We tested the hypotheses that 1) vigorous HCV-specific Th1-like immune responses are correlated with milder liver disease, and 2) HCV-specific Th1 responses are associated with a higher probability of HCV virological response during treatment. This is the largest cohort characterized to date with respect to HCV-specific immune responses and clinical outcomes.

Methods

A representative subset of the subjects enrolled in ACTG 5071 (n = 102/133 eligible) was studied. This trial compared 2 forms of interferon plus ribavirin for the treatment of HCV, with the primary endpoint being HCV clearance at 24 wks. Subjects had liver biopsies prior to entry. PBMCs were isolated at baseline and 24 wks. ELISpot assays were performed for IFN γ and IL-10 using HCV antigens (Ag) Core, NS3 and NS5, recall Ag candida (Can), and PHA. Data were analyzed using nonparametric methods, including Spearman rank correlation and recursive partitioning (CART).

Results

There were significant negative correlations between the inflammatory score (IS) and IFN γ production at baseline in response to the HCV proteins core (p = 0.02) and NS5 (p = 0.002). Fibrosis scores (FS) were negatively correlated with IFN γ production at baseline in response to NS5 (p = 0.03). There were also strong negative correlations between IFN γ production at baseline in response to Can and the IS (p = 0.001) and FS (p < 0.001). There was no correlation for IL-10 production in response to Ag or Can with either FS or IS at baseline. CART suggested important joint associations of IFN γ core and Can responses, and IL-10 Can and NS3 responses with IS. There was no association of HCV-specific response and CD4 count in this cohort (median CD4 count 486, range 177-1,001). In contrast, only IL-10 production in response to NS3 at baseline was associated with being a treatment responder at 24 wks (p = 0.02). There was no association between changes in Th1 HCV-specific responses from baseline to 24 wks and treatment outcome.

Conclusions

In this large cohort of subjects co-infected with HIV and HCV, HCV-specific Th1 responses in PBMC are correlated with milder inflammation and fibrosis but are not associated with treatment outcome.