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Abstract Book

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11 - 12 June 2015, London, United Kingdom

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Abstracts

Abstract: 1

Treatment issues --- HBV-HIV coinfection

The impact of HIV and hepatitis B virus on hepatic stellate cell activation using a novel in vitro system

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Introduction: HIV accelerates progression of HBV associated liver disease, however the mechanisms are notrib known. Hepatic stellate cells (HSC) are directly responsible for the production of collagen and liver fibrogenesis. We hypothesized that increased microbial translocation resulting from HIV-associated damage to the gastrointestinal tract, HIV and HBV alone or in combination would increase HSC activation, thereby accelerating fibrosis.

Materials and Methods: Primary HSC (pHSC) were isolated and expanded from healthy human liver margins obtained from resections for metastases, and cryopreserved. Thawed aliquots of pHSC were cultured and stimulated overnight *in vitro* with lipopolysaccharide (LPS)-EB, HIV gp120, purified HBV surface (HBsAg) and core (HBcAg) antigens, conditioned media from hepatocyte cell lines, and sera from HBV infected individuals on and off treatment and healthy controls. We used conditioned media from both the HBV replicating HepG2 2.215 and the parent HepG2 cell line, both with and without the addition of an enhanced TNF-related apoptosis-inducting ligand (TRAIL) 'superkiller TRAIL™', which was added to increase hepatocyte apoptosis. Flow cytometry was used to quantify markers of pHSC activation, including intercellular adhesion molecule 1 (ICAM1) and CC chemokine ligand 2 (CCL2), and hepatocyte apoptosis using expression of caspase3.

Results: statistically significant increase in pHSC ICAM1 and CCL2 was seen after stimulation with LPS-EB and HIV gp120 ($p<0.05$ for both), but not following incubation with HBsAg or HBcAg. There was no difference in pHSC activation following incubation with HBV-infected versus uninfected hepatocyte conditioned media. The addition of superkiller TRAIL™ to hepatocyte cell line cultures (both HBV infected and uninfected) resulted in an increase in caspase3+ hepatocytes. Stimulation with this media led to a statistically significant increase in pHSC ICAM1 and CCL2 ($p<0.05$). The expression of ICAM1 and CCL2 on pHSC correlated with the proportion of apoptotic hepatocytes used to generate the conditioned media (ICAM1 R squared=0.72, p=0.033, CCL2 R squared=0.76, p=0.023 respectively). Incubation with serum from untreated HBV-infected patients (n=5) led to a statistically significant increase in pHSC ICAM1 expression which was greater than that resulting from incubation with serum from HBV uninfected controls (n=6) or HBV infected patients on treatment (n=6) ($p<0.05$).

Conclusions: pHSC are activated in vitro by LPS-EB,HIV gp120 and hepatocyte apoptosis. Given all of these parameters are elevated in both treated and untreated HIV-HBV co-infection, they could each potentially contribute to the accelerated fibrogenesis seen in HIV-HBV coinfection.

No conflict of interest

Abstract: 2

Treatment issues --- HCV-HIV coinfection

European mitochondrial DNA haplogroups impact on liver fibrosis progression among HCV and HIV/HCV coinfected patients from Northwest Spain

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Introduction: Mitochondrial DNA haplogroups are associated with the clinical outcome of several chronic diseases (i.e. Alzheimer, Parkinson, osteoarthritis, multiple sclerosis). Moreover, mtDNA haplogroups might be also related with the outcome of liver disease among HCV-infected patients.

Material & Methods: This is a retrospective study in a large cohort of HCV and HIV/HCV co-infected patients in clinical follow-up at two hospitals in Northwest Spain. Epidemiological, clinical and virological data were recorded. The European mtDNA haplogroups were determined using PCR-RFLP and Single Base Extension (SBE) techniques.

Results: A total of 259 HCV and HIV/HCV co-infected patients were included. From these, we excluded 5 patients without Caucasian ethnicity. Overall, 34.4% were HCV monoinfected patients and 65.6% were HIV/HCV co-infected. Most were male (73.9%), median age was 49 years and 98.8% were Spanish citizenship. European mtDNA haplogroups were recognized in 97.6% of patients as follows: H (52.6%), U (10.1%), J (6.1%), K (6.1%), T (8.9%), V (3.2%), SHV (2.8%) and others (I, W, X, M) (10.2%).
For further analysis, individuals were separated into the most common European clusters (HV, KU, JT and others). Overall, we did not find differences between mtDNA haplogroups and median age, gender, IL28B polymorphism, HCV G1-subtypes or HCV-RNA viral load levels at the diagnosis time. A higher prevalence of cluster HV was observed among HCV genotype 4 infected patients (G4 75%; G3 64%; and G1 54.4%).
Interestingly, a relationship between mtDNA haplogroups and liver fibrosis was observed. Fibrosis was scored as low fibrosis (F0-F2) and high fibrosis (F3-F4). A higher prevalence of cluster HV was observed among patients with low fibrosis (F0-F2 61.6% vs. F3-F4 53.3%). Moreover, considering the median fibroscan values (Kpa), clusters HV and KU had lower values than clusters JT and others (8.8 and 8.5 vs. 10.15 and 12.49, respectively). Finally, a lower prevalence of cluster HV (26.5%) was observed among patients with cirrhosis (>12.5 Kpa), compared with clusters others, KU and JT (47.4%, 39.4%, 39.3%, respectively). The multivariate analysis showed a trend to higher level of fibrosis in clusters JT [OR= 1.8 (0.82-3.96)] and others [OR=2.36 (0.91-6.15)] compared with cluster HV. Indeed, multivariate analysis shows that cluster JT and others had higher prevalence of elevated fibroscan values in 2.64 and 3.15 fold, respectively, compared with cluster HV. Moreover, the cluster others was significantly associated with cirrhosis compared with cluster HV [p=0.04; OR=2.97]. Male gender and an advanced age were also identified as risk factors for the development of liver fibrosis. Multivariate analysis was adjusted by age, gender, the HCV-diagnosis time and HIV/HCV co-infection.

Conclusions: The mtDNA cluster HV was more prevalent among HCV genotype 4 infected patients. A higher prevalence of the cluster HV was observed among patients with lower fibrosis (61.2%). Moreover, clusters HV and KU had lower median fibroscan values than clusters JT and others. Finally, cluster HV was identified as a protective factor for cirrhosis. These results might be useful for priorization of treatment strategies among HCV-infected patients.

No conflict of interest

Abstract: 3

Treatment issues --- HCV-HIV coinfection

Hepatitis C virus co-infection independently increases the risk of cardiovascular disease in HIV-positive patients

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Background: Patients infected with HIV are at increased risk for cardiovascular disease (CVD) despite successful antiretroviral therapy. Likewise, chronic hepatitis C virus (HCV) infection is associated with extrahepatic complications, including CVD. The risk of CVD has scarcely been examined in HIV/HCV-coinfected patients.

Methods: A retrospective study was carried out to assess the influence of HCV coinfection on the risk of cardiovascular events in a large cohort of HIV-infected patients recruited since year 2004. As end-point, a composite event of CVD was used, including myocardial infarction, angina pectoris, stroke or death due to any of them.

Results: A total of 1,136 patients (567 HIV-monoinfected, 70 HCV-monoinfected and 499 HIV/HCV-coinfected) were analyzed. Mean age was 42.7 years, 79% were males, and 46% were former injection drug users. Over a mean follow-up of 79.4±21 months, 3 patients died due to CVD whereas 29 suffered a first episode of coronary ischemia or stroke. HIV/HCV-coinfected patients had a greater incidence of CVD events and/or death than HIV-monoinfected individuals (4% vs 1.2%, p=0.004) and HCV-monoinfected persons (4% vs 1.4%, p=0.5). After adjusting for demographics, virological parameters, and classical CVD risk factors (smoking, hypertension, diabetes, high LDL-cholesterol), both HIV/HCV coinfection (HR 2.91; CI 95%: 1.19-7.12; p=0.02) and hypertension (HR 3.65; CI 95%: 1.34-9.94; p=0.01) were independently associated with CVD events and/or death in HIV-infected patients.

Conclusions: Chronic hepatitis C and hypertension are independently associated with increased CVD risk in HIV-infected patients. Therefore, treatment of chronic hepatitis C should be prioritized in HIV/HCV-coinfected patients regardless any liver fibrosis staging.

No conflict of interest

Abstract: 4

New anti-HCV agents

NS3 resistance-associated mutations occurring as high-frequency and low-frequency variants among treatment-naïve patients infected with hepatitis C virus (HCV) genotype 1a

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Background. Mutations in HCV strains of treatment-naïve subjects can reduce *in vitro* and *in vivo* susceptibility to NS3 protease inhibitors. This study established the prevalence of NS3 resistance-associated

mutations among HCV-1a carriers attending for care in England, and quantified the frequency of the mutants within each patient's sample using deep sequencing.

Methods. The population comprised 238 patients infected with HCV-1a and naïve to all HCV therapy that in 2010-2014 attended for care in the North-West (NW) or the South-East (SE) of England. A total of 61/238 (25.6%) subjects, all from the SE, were co-infected with HIV. Stored plasma samples underwent Sanger and deep (Illumina) sequencing of the NS3 gene. Maximum-likelihood (ML) phylogenies were estimated using NS3 sequences from the UK, North America, and Europe.

Results. By Sanger sequencing, the most prevalent mutation was Q80K, which occurred in 43/238 subjects (18.1%, 95% CI 13.2%-23.0%), including 19/70 (27.1%) in the NW and 24/168 (14.3%) in the SE (p=0.026). Prevalence in the SE was 17/107 (15.9.%) among HCV mono-infected subjects vs. 7/61 (11.5%) among HCV/HIV co-infected subjects (p=0.498). HCV RNA load was median 6.3 $\log_{10}$ IU/ml overall (IQR 5.8-6.8), without difference between the NW and SE, and between samples with vs. samples without Q80K (6.4 vs. 6.3 $\log_{10}$ IU/ml; p=0.83). Overall 178 samples underwent deep sequencing, comprising 27 with and 151 without Q80K by Sanger sequencing. The 27 samples showing Q80K by Sanger sequencing also showed the mutation by deep sequencing, with mutant frequencies ≥98% in 25 samples, and of 41% and 46% respectively in 2 samples. None of the 151 samples lacking Q80K by Sanger sequencing showed the mutation by deep sequencing when applying an interpretative cut-off of 1%. A further 3% of samples showed Q80K at a frequency <1% and >0.5%. Relative to Sanger sequencing, deep sequencing detected 8 additional mutations occurring at NS3 codons 36, 54, 55, 80 (Q80L and Q80R), 168 and 170 with frequencies ranging between 1% and 10%. By phylogenetic analysis, HCV-1a strains separated into the two recognised lineages with and without Q80K. Sequences showing Q80K at frequency <1% did not cluster within the Q80K lineage. Overall 148/238 (62.2%) UK sequences occurred within regional or inter-regional clusters, but there was also a high degree of interspersing with strains circulating in continental Europe and North America.

Table 1

Mutation	Number with mutation		Mutant frequency (%) within Illumina reads
	Sanger (n=238)	Illumina (n=178)	
V36L	3	3	All >99
V36M	1	2	100, 3
T54S	6	6	All >99
V55A	6	6	All >96
Q80K	43	27	All >40
Q80L	1	4	88, 6, 5, 1
Q80R	0	3	2, 2, 1
D168E	1	1	100
V/I170A	1	1	36
V/I170T	0	1	2

Conclusions. Unlike other resistance mutations in NS3, Q80K occurred always as a dominant variant (>40%), allowing detection by Sanger sequencing. Detection of Q80K at frequency <1% was most likely a technical artefact. The findings indicate that Q80K mutants have a high replication capacity, allowing transmissibility and persistence at high frequency within the viral quasispecies without effects on HCV RNA levels. Although appearing to vary geographically as a result of regional transmission clusters, the prevalence of Q80K in the United Kingdom is among the highest in Europe.

No conflict of interest

Abstract: 5

New anti-HCV agents

Real-World Data on HIV positive patients with Hepatitis C on Simeprevir and/or Sofosbuvir

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Background and Aims: We are investigating the effectiveness of simeprevir (SMV) and sofosbuvir (SOF) in a real-world setting for patients with HIV/HCV co-infection.

Methods: Data of 78 HIV/HCV co-infected patients who initiated therapy between 12/2013 and 8/2014 were analyzed. Baseline and week-2 on-treatment data are reported. Week-4 and Week-12 post end-of-treatment responses were examined to determine the sustained virologic response (SVR) rates for patients who have completed therapy. Advanced fibrosis/cirrhosis was defined as a FIB-4 score ≥ 3.25. By 6/2015, SVR12 data will be available for nearly all 78 patients. By 6/2015, data will also be available for additional co-infected patients from a second Mount Sinai affiliated Medical Center (Brooklyn Hospital) and for a comparison cohort of patients with HCV mono-infection.

Results: Median age of the 78 HIV/HCV co-infected patients was 57 yr (range, 25-73 yr), 83% were male, 63% were white, 25% were black, and 37% were Hispanic. Nearly half (44%) were naïve to HCV treatment. Comorbidities were common: 50% had hypertension, 37% had depression, 17% had diabetes, 52% had advanced fibrosis/cirrhosis, and 6% had HCC. The baseline median HCV VL was 6.31 IU/mL (IQR: 5.9-6.7 IU/mL), platelet count was 135 $x10^3$/μL (IQR: 97-195 $x10^3$/μL), albumin was 3.9 g/dL (IQR: 3.6-4.2 g/dL), total bilirubin was 0.6 mg/dL (IQR: 0.5-1.0 mg/dL), and the CD4 count of 54 patients with data was 490 (IQR: 326-629); HIV VL was undetectable in 49/65 (75%). All but four patients were on HAART. Of 65 patients with genotype (gt) 1 patients: 31 (48%) on SOF/ribavirin (RBV), 15 (23%) were on SMV/SOF/RBV, and 19 (29%) were on SMV/SOF; 15 (23%) patients changed HAART to accommodate SMV. All 13 patients with gt 2 or 3 HCV were on SOF/RBV. SVR 12 data is available for 54 gt 1 patients. 26/29 (90%) of the patients on a SMV-containing regimen achieved SVR 12, while 13/25 (52%) of patients on SOF/RBV achieved SVR 12. For gt 2, 3/5 (60%) of patients achieved SVR 12 on 12-24 weeks of SOF/RBV. For gt 3, 2/5 (40%) of patients achieved SVR 12 on 24 weeks of SOF/RBV.

Conclusions: SMV in combination with SOF is an important and highly effective DAA regimen for HIV/HCV co-infected patients, a group that was notoriously difficult to treat with interferon (DA031095, DK090317).

No conflict of interest

Abstract: 6

Liver toxicity

Effect of nevirapine on the activity of liver enzymes among HIV infected mothers in rural South India

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Introduction: Nevirapine may cause severe or life-threatening liver toxicity, usually in the first six weeks of treatment. The objective of the study was to evaluate the abnormalities in liver function enzymes after taking single dose nevirapine in HIV infected mothers.

Material & Methods: HIV infected mothers who received a single dose nevirapine at the onset of labour were recruited from PMTCT center in Namakkal, Tamilnadu, India. After obtaining written informed consent, the demographic characteristics such as age, occupation, literacy and breast feeding practices were recorded. The blood samples were collected to determine total bilirubin, total protein and albumin by enzymatic-linked colorimetric method and the activities of the liver marker enzymes (AST, AST, ALP and GGT) were estimated by kinetic method. The results were compared with HIV negative mothers (controls) who were from similar socio-economic backgrounds. Statistical analysis was done using SPSS, Mean and SD was estimated, *p*-value of less than 0.05 was considered to be statistically significant.

Results: A total of 125 HIV infected mothers and 50 HIV seronegative mothers were enrolled into the study. The age ranged between 19 and 34 years (25.2±3.6) in HIV infected mothers and 19 - 30 years (24.8 ± 2.9) in controls. There was no significant difference in the occupation and literacy between HIV infected mothers and controls ($p > 0.05$). There was no significant difference in total bilirubin and albumin ($p > 0.05$). Total protein was found to be significantly lower in HIV infected mothers ($p < 0.05$) than controls. The elevation of AST activities was observed in 4 % of HIV infected mothers, (mean= 57.4 IU/L, $p < 0.001$) which was more than 1.25 times the upper limit normal (ULN). Increased ALT activities were found in 10.4 % of HIV infected mothers (mean 61.38 IU/L, $p < 0.001$) which was 1.5 times higher than ULN. Elevations of both AST and ALT activities were detected in 13.6 % of HIV infected mothers, the mean levels were 66.23 and 78.05 IU/L respectively (1.5 and 1.7 times higher than ULN). The elevated enzymes of both AST and ALT levels were observed between 23 and 45 days after initiation of nevirapine drug, except for one mother who had elevations at 8 months after the exposure of nevirapine. The activities of ALP and GGT were found to be higher in one HIV infected mother after 5 months of nevirapine intake. To estimate severity, increased activities of AST and ALT were graded based on toxicity grading scale, the elevations were in the mild category -grade 1 level and no hepatotoxicity was observed.

Conclusions: The study has demonstrated that the levels of ALT alone were increased in 10.4 % of HIV infected mothers and both AST and ALT levels were increased in 13.6 % of HIV infected mothers. Our study suggests that the activities of liver enzymes should be monitored periodically before the initiation of ART.

No conflict of interest

Abstract: 7

New anti-HCV agents

Antiviral activity of novel glycosyl sulfoxides mimicking tunicamycin structure against hepatitis C virus

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Introduction: Hepatitis C virus (HCV) of the *Flaviviridae* family is a serious global health problem with an estimated 3% of the world's population infected. HCV is a major cause of acute and chronic hepatitis which can eventually lead to permanent liver damage and hepatocellular carcinoma. To this date there is no vaccine against HCV and the available therapeutic approach has a variable success rate, causes severe side effects and is high in cost. Thus, new, improved and more effective therapeutics against HCV are required. Viral structural proteins, such as E1 and E2 envelope glycoproteins that facilitate the infection process, constitute a promising target for antiviral research. Fitness of those proteins depends on proper N-glycosylation, a process which is effectively blocked by tunicamycin. However, due to its high toxicity, tunicamycin is unsuitable for clinical use. In this research, compounds mimicking tunicamycin function were designed and synthesized. The aim of the present study was to evaluate the antiviral activity of three glycosyl sulfoxides belonging to tunicamycin mimetics: Gp1, Gp6 and Gp7 against hepatitis C virus.

Material & Methods: The antiviral activity of Gp1, Gp6 and Gp7 was assessed using four different *in vitro* systems. Mammalian T7 cell line containing a bicistronic replicon that carries nonstructural viral protein sequences as well as luciferase reporter gene was used to determine the effect of synthesized compounds on the replication process. Second approach, using a baculovirus expression system, was utilized to examine the influence of tested compounds on the first stages of protein glycosylation in insect Sf9 cells. The effect of proposed glycosylation inhibitors on HCV particle assembly, release and infectivity was studied using the retroviral-based system producing HCV pseudoparticles (HCVpp) in transfected HEK293T cells. Finally, the cell-culture adapted HCV (HCVcc) was used for examination of the influence of tested compounds on HCV propagation in cell culture.

Results: As expected, neither of the tested compounds affected the replication process. The baculovirus expression system confirmed no variation in viral protein synthesis and accumulation within insect cells after the treatment of proposed glycosylation inhibitors, suggesting that synthesized compounds do not act as tunicamycin at early steps of the glycosylation process. Acquired results in combination with preliminary experiments using the retroviral-based HCVpp system allowed the selection of one hit compound, Gp7, as possible glycosylation inhibitor with potential anti-HCV activity. Experiments performed in Huh7-J20 cells having SEAP reporter system proved that Gp7 inhibits the HCVcc replication in the JFH1 infectious model in a dose-dependent manner without any cytotoxicity.

Conclusions: Selected Gp7 compound did not affect cell replication nor protein glycosylation in insect cells, suggesting Gp7 is not the inhibitor of the first stages of N-glycosylation process. Gp7 proved to sufficiently limit HCV propagation in *in vitro* cell culture system, which indicated its potential use in antiviral approach against hepatitis C virus, however future studies are obviously needed.

No conflict of interest

Abstract: 8

Non invasive assessment of liver fibrosis

Severe fibrosis and cirrhosis in HIV/HCV co-infected patients: a retrospective study

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Background: The course of chronic HCV is accelerated in HIV/HCV co-infected patients, with more rapid progression of liver fibrosis. Consequently, HCV related liver complications, particularly hepatic decompensation have emerged as important causes of morbidity in co-infected patients.

Materials & Methods: The authors collected information of HIV/HCV co-infected patients with severe fibrosis and cirrhosis for staging the hepatic disease. Liver fibrosis was assessed by Fibroscan®. We considered as advanced fibrosis, values of liver stiffness ≥ 9.5 kPa.

Results: From 143 HIV/HCV co-infected individuals with liver fibrosis assessed by Fibroscan® in the last 5 years, we studied 56 with severe fibrosis (Metavir stage F3) or cirrhosis (Metavir stage F4). The majority of them were Caucasian (96.4%) male (85.7%) with median age of 47 years [32-75]. The most prevalent route of transmission was intravenous drug use (87.5%), followed by the sexual route in 7.1% individuals. The median time of exposure to HCV infection was 17 years [2-41] (with mean follow-up of 14 years [2-30]), 71.4% patients had a high HCV viral load (> 600 000 UI/ml) and the medium ALT was 104 UI/L [34-928]. The distribution of HCV genotypes was 66.1% for genotype 1 (75.7% 1a; 24.3% 1b), 19.6% for genotype 3, 10.7% for genotype 4 and 1.8% for genotype 2. There were 44.6% patients with detectable HIV viral load, with mean value of 19280 c/mL [22-176271]. The median T CD_4^+ cell count was 470 cells/mm^3 [62-1032]. The mean liver stiffness was 22.4 KPa (19.7% between 9.5 to 12.5 kPa and 80.3% ≥ 12.5 kPa). The median platelet count was 160 x10^9/L [10-391] (<100000 x10^9/L in 25% patients) and albumin levels were 4.2 g/dL [2.7-5.2] (<3.5 g/dL in 12.5% patients). Hepatomegaly was present in 23.2% patients, splenomegaly in 14.3% and 5.4% had evidence of esophageal varices. Only 37.5% patients have been treated: 3 patients had sustained virologic response (one was genotype 4 and the other were 3), 15 did not respond and 1 relapsed. Two patients have been diagnosed with hepatocellular carcinoma, both with Metavir stage F4, and both died 8 months after Fibroscan® was performed. Another two patients died due to hepatic decompensation one month and 3 years after staging fibrosis.

Conclusions: The authors conclude that HIV/HCV co-infected patients with advanced liver fibrosis or cirrhosis have clinical and laboratory evidence of hepatic insufficiency which can culminate in hepatic decompensation. Due to faster progression of the disease, these patients need to be treated urgently with the new therapies.

No conflict of interest

Abstract: 9

Resistance --- Hepatitis B

Adverse treatment response of lamivudine continuation/ tenofovir add-on among lamivudine non-responder HIV-HBV co-infected patients from eastern India

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Introduction: Presently, tenofovir disoproxil fumurate (TDF) is the most effective anti-viral agent for the treatment of hepatitis B virus (HBV) in individuals co-infected with HIV and HBV as TDF has activity to suppress both wild type and lamivudine (3TC)-resistant HBV. However suboptimal response to TDF was reported in HIV-HBV co-infected individuals with prior 3TC therapy from different countries recently. Incidence of 3TC-resistant HBV strains is quite high in HIV-HBV co-infected patients experiencing long-term anti-retroviral therapy (ART) in eastern India. In spite of this risk, most of the patients with long-term 3TC treatment are continued with the same anti-viral agent in this country. Only few have received TDF in addition to 3TC in the ART regimen since TDF has been available in India for the treatment of HIV infected patients in 2012. In this preliminary study we investigated the virologic and biochemical parameters among HIV-HBV co-infected patients who are non-responder to 3TC treatment during continuation of 3TC or TDF add-on to 3TC in their ART regimen.

Materials and Methods: Fifteen HIV-HBV co-infected patients who experienced long-term 3TC (mean duration months 36.87 ± 24.08 months) were identified with high HBV viremia (>20,000 IU/ml) or harbouring 3TC-resistant HBV. These patients receiving ART from Calcutta School of Tropical Medicine, the main ART centre in eastern India were followed-up semi-annually for next three visits. Different virologic parameters including quantification of plasma HBV load by real-time PCR, detection of hepatitis B e antigen (HBeAg) by commercial ELISA and anti-viral resistant mutations by sequencing were studied.

Results: During three follow-up among study subjects, 86%, 47% and 43% had 3TC-mono-therapy (mean treatment-duration 41.54±18.84, 49.67±11.67, 54.17±12.37 months respectively) whereas 14%, 53% and 57% experienced TDF in addition to 3TC (mean treatment-duration 4.5±2.12, 16.56±11.06 and 23±4.07 months respectively). Mean CD4 cell count in patients receiving 3TC was tended to be lower during third follow-up as compared to the first and the second [520.67±380.30(1st), 454.8±196.90(2nd) and 397.5±189.24(3rd) cells/mm^3) and similar trend was seen in patients experiencing TDF in addition to 3TC [334.5±330.218(1st), 476.5±194.25(2nd) and 461.17±269.89(3rd) cells/mm^3]. Serum HBV load was increased during successive follow-up of patients with 3TC-mono-therapy. Initiation of TDF lowered serum HBV-load among 3TC-non-responders at the time of second visit (<2,000 IU/ml), interestingly during third follow-up, mean HBV viraemia increased >1 log IU/ml (mean 3.56±2.84 log IU/ml). Persistence of 3TC-resistant double and triple mutations was also observed in both the treatment regimens. Mean serum alanine aminotransferase remained elevated in these patients during this follow-up study.

Conclusions: Persistence of high HBV viraemia and 3TC-resistant mutation in HBV during continuation of 3TC might lead to major public health threat in India. Inclusion of TDF in the ART regimen of 3TC non-responder HIV-HBV co-infected patients showed adverse treatment response in terms of virologic and biochemical parameters. Therefore, serious attention is necessary for proper management of long-term 3TC experienced HIV-HBV co-infected patients with high HBV viraemia or 3TC-resistant HBV mutants in India.

No conflict of interest

Abstract: 10

Treatment issues --- HBV-HIV coinfection

Human Immunodeficiency Virus Type 1 and Hepatitis B Virus Coinfections among Injecting Drug Users in Malindi, Kenya

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There is currently no published data addressing the burden of Human Immunodeficiency Virus (HIV) and Hepatitis B Virus (HBV) co-infection among injecting drug users (IDUs) in Kenya. These two viruses share similar routes of transmission, with illicit drug use by injection being one of the major routes of infection. Injecting drug use has been identified as one of the growing problems in coastal towns of Kenya, just as is sex tourism.

In this study, we aimed to determine the prevalence of HBV in HIV positive IDUs within the coastal town of Malindi and correlate the findings with socio-demographic factors of the study population.

A cross-sectional study was carried out, where structured questionnaires were administered and laboratory testing of blood from the participants was done. For laboratory investigations, 5 ml of venous blood was drawn from each participant and used to test for HBV surface antigen (HBsAg) and HIV-1 antibodies using rapid test algorithms and finally using Hepanostika and Vironostika test kits, for HIV and HBV, respectively. The CD4+ T-cell count was determined by flow cytometry.

The prevalence of HBV infection was 14.3% (13/91). The mean age of detection was 33.2 (SD ± 8.1) years. The mean CD4+ cell count in the HIV/HBV co-infected individuals was significantly lower (p=0.001) compared to those with only HIV infection. Needle sharing and duration of active injection of drugs were significantly associated with infections of HBV mono and HIV/HBV co-infections (p=0.000).
In conclusion, this study reveals a high prevalence of HBV infection in HIV positive injecting drug users in Malindi.

This preliminary finding warrants an expanded serological survey of HIV/HBV co-infection in IDUs in the coastal area of Kenya so as to determine the true prevalence of this co-infection. These findings will aid in developing major intervention strategies for this high risk group in order to prevent the flow of viral infections from the IDUs into the general population.

No conflict of interest

Abstract: 11

Treatment issues --- HCV-HIV coinfection

HCV infection cascade: exemple of a portuguese center

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Background: Globally, hepatitis C chronic infection represents an important public health concern, with an estimated prevalence of 2-3% affecting about 170 million individuals. Seroprevalence data on particular patient populations, namely blood donors and intravenous illicit drug users (IVDU), published by Marinho et al estimates a HCV infection prevalence of 1,5% in Portugal, corresponding to about 150.000 patients. Of these patients, only a third are aware of diagnosis. In Portugal, HCV infection is considered a disease of mandatory notification but underreporting is a recognized situation. Facing the recent innovation in HCV treatment with the emergence of several direct antiviral agents, we have witness a change in treatment paradigm. A detailed knowledge of national and local epidemiology is needed in order to outline strategies and rationalized costs, aimed to achieve equity in care of HCV infected patients. Our main objective was to elaborate HCV infection cascade, concerning HCV monoinfected and HCV/HIV co-infected patients registered in West Lisbon Hospital Centre (CHLO) Infectious Diseases (ID) specialty. Determine the total number of individuals registered in CHLO ID, the retention in care rate, HCV treatment initiation and sustained virologic response (SVR) obtained.

Materials & Methods: Last Portuguese census (2011) reported 10.562.178 inhabitants. Assuming a HCV infection prevalence of 1,5% in Portugal, we estimate a total of 158.432 HCV infected patients. West Lisbon Hospital Centre (CHLO) is a university hospital that provides differentiated health care services to a resident population of 950.000 inhabitants. Considering the same HCV prevalence, we assumed that 14.250 HCV infected patients were currently living at the influence area of CHLO. Hospital records identified 669 patients registered in the Infectious Diseases specialty with a diagnosis of HCV infection that constituted our study group.

Results: 669 patients with HCV infection diagnosis were registered in CHLO ID specialty, corresponding to 0,41% of the total HCV Portuguese population and 4,8% of the infected population living in the hospital area. The majority presented concomitant HIV infection (66%). Regular medical follow up and retention in care was confirmed in 60% (n=399: 305 HIV/HCV and 94 HCV). Chronic HCV infection was documented in 53% (n=357: 285 HIV/HCV and 72 HCV). Spontaneous HCV clearance was found in 7% of total study population. HCV treatment was started in 38% of individuals (n=254: 137 HIV/HCV and 117 HCV) and sustained virologic response was obtained in 25% (n=169: 53 HIV/HCV and 46 HCV).

Conclusions: According with the last Portuguese Census (2011), the approximate estimation of HCV infected population living in the West Lisbon region was based on total population number and estimated HCV prevalence reported, which represents a limitation of this analysis. The progressive number of patient reduction found, in each phase, reinforces the need of early diagnosis and health care referral strategies implementation. Is fundamental to ensure individualized treatment options, to optimize SVR and retention in care rates.

No conflict of interest

Abstract: 12

Treatment issues --- HCV-HIV coinfection

Molecular epidemiology of HCV transmission among HIV intravenous drug users in Romania

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Introduction: In recent years Romania has faced an HIV outbreak among intravenous drug users (IDUs). While the local HIV infection is mainly driven by F1 subtype strains; in IDUs there is evidence for the co-circulation of F1 subtype and CRF14_BG strains. The majority of these patients are HCV co-infected. Genotype 1b is almost exclusively present in mono-infected HCV patients. HCV was acquired earlier than HIV in IDUs. Our aim was to analyse through molecular and phylogenetic approaches the HCV infection in this risk population.

Methods: Blood samples were obtained from 117 IDUs newly diagnosed with HIV and co-infected with HCV. We have also included for comparison 33 non-IDUs, HCV mono-infected patients. The NS3 and NS5b regions were amplified and sequenced using the 3500 Genetic Analyzer (Life technologies). The NS5b sequences were used for genotyping with the Oxford HCV Subtyping Tool. HIV-1 subtyping was done using the REGA HIV-1&2 automated subtyping tool version 2.0. Phylogenetic analysis of both NS5b and NS3 sequences was performed using maximum likelihood as implemented in PAUP, with the GTR (general time reversible) as nucleotide substitution model and gamma (Γ) distribution of rate variability among sites.

Results: HCV genotyping showed that non-IDUs were exclusively infected with genotype 1b (33 patients, 100%). In the IDUs group, HCV genotype distribution was more diverse: genotype 1a is the most frequent (48 patients), followed by 1b (40), 3a (14), 4d (8) and 4a (7).Several clusters of HCV transmission among IDUs were identified by phylogenetic analysis. HCV genotype 1b sequences isolated from IDUs and non-IDUs formed separate clusters. HIV-1 subtype analysis showed that 68% of IDUs were infected with subtype F1 viruses and 26% with CRF14_BG and recombinants of CRF_14 and subtype F1. The IDUs infected with recombinant forms had lower CD4 counts and more advanced HIV disease than IDUs infected with the F1 subtype. The two infections were most probably acquired together in only 17 IDUs.

Conclusions: IDUs from Romania have a different epidemiological and genotypic profile of HCV and HIV than the mono-infected population. According to phylogenetic analysis, HIV and HCV transmission occurred independently in Romanian IDUs. The association of HCV and HIV infections, especially in CRF14_BG infected patients, might have a negative impact on clinical evolution and treatment strategies.

No conflict of interest

Abstract: 13

Treatment issues --- HCV-HIV coinfection

Correlates of successful HCV treatment in HIV co-infected vulnerable populations

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Introduction: Vulnerable populations (including people who inject drugs, PWID) are over-represented among HIV-infected adults co-infected with HCV. Although clinical trial results suggest that all-oral treatment regimens for HCV infection are equally effective in the setting of HIV co-infection, this has not been clearly established in populations consisting of mainly of PWID and related vulnerable inner city groups.

Methods: We have established a multi-disciplinary outreach program designed to recruit and retain HCV-infected PWID in care. The program includes facilitated access to specialty medical care, access to extended social support services complimentary over-the-counter medications and vitamins, daily snacks and beverages, and weekly meals and HCV support groups. HCV treatment is offered to all who qualify for it on medical grounds and for whom funding can be identified. We have conducted a retrospective analysis of all HIV co-infected patients treated for HCV infection within our program and for whom a definite treatment outcome was ascertained. This analysis correlates the likelihood of achieving SVR with a range of baseline demographic and clinical variables, including housing and active drug use.

Results: The cohort of HIV-infected individuals in care numbered 512, with 248 (48.4%) co-infected with HCV. Among the latter, 172 (69.3%) were active (current/recent) PWID. In total, 47/248 (19.0%) have completed HCV treatment to date (5 on all-oral regimens), including 41 (87.2%) active PWID, and 31 (66.0%) with genotype 1 infection. The mean age was 52, 44 (93.6%) were male, 19 (40.4%) were on opiate substitution, 45 (96.0%) were on HIV treatment (43/45 with full virologic suppression), 13 (27.7%) were homeless, and 29 (61.7%) attended weekly HCV support groups. The SVR rate was 55.3% (26/47), 80% (4/5) on al-oral regimens, 43.8% with genotype 1 infection. Success rates were no higher in subjects on methadone 6 (31.6%), and no lower in those who were homeless 4 (30.8%) or active PWID 23 (56.1%).

Conclusions: Active PWID with HIV co-infection can be successfully treated for HCV infection within multi-disciplinary programs such as ours, which appears to serve as a tool of engagement to mitigate the effects of traditional negative predictors of treatment failure. Our program will serve as an important tool to address the HCV and HIV epidemics in vulnerable populations often considered as 'core transmitters' of HCV and HIV infections.

No conflict of interest

Abstract: 14

Treatment issues --- HCV-HIV coinfection

Cascade of Care of HIV/HCV Co-infected Patients on the Downtown East Side of Vancouver

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Background: The prevalence of Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) infections is very high in high risk vulnerable population of Downtown East Side (DTES) of Vancouver. There is little information regarding the cascade of care of people who are co-infected with HIV and HCV and what is preventing them from engaging in HIV and HCV care. The aim of this study was to elucidate the current cascade of care and survey this population using a targeted questionnaire to identify barriers to HIV and HCV care.

Methods: Participants were recruited at Community Pop-Up Clinics (CPCs) held at different community-based centers in the DTES. During these CPCs, participants were offered OraQuick HIV and HCV Rapid Antibody point of care testing for HIV and HCV, evaluation of their known HIV or HCV infection status, and a plan of short-term linkage to care and social services at our multi-disciplinary centre in Downtown Vancouver. The questionnaire was completed while participants awaited test results or other evaluations.

Results: From 03/13-03/15, 1257 individuals were tested for HIV and HCV. In total, 405 (32.2%) were infected with HCV and 25 (2%) were HIV/HCV co-infected. Of these 25, 13 (52%) were successfully linked to care, with 9 initiating long-term antiretroviral therapy, and one even being successfully treated for HCV infection. Starting 01/14, 764 completed a questionnaire, including 16 co-infected individuals. In this population, 56.3% were Aboriginal, 93.6% were active drug users, 31.4% shared needles and other injection equipment, and 87.5% stated they would consider antiviral treatment if made available to them. Despite the fact that 56.3% were previously aware of their HIV/HCV co- infection status, they were not productively engaged in medical care.

Conclusions: Despite extensive testing for HIV on the DTES through comprehensive government programs as part of a 'treatment as prevention' initiative, our community-based strategy was able to identify an additional 25 individuals who were unaware or unengaged in HIV and HCV care, many of whom remained at high risk of transmitting infection to others. Approaches such as ours are an important complement to addressing the HIV epidemic in a largely vulnerable, underserved and co-infected population that contributes significantly to disease incidence, prevalence and transmission.

No conflict of interest

Abstract: 15

Treatment issues --- HCV-HIV coinfection

Pegylated interferon and Ribavirin in the treatment of co-infected HCV/HIV patients

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Background: The treatment of hepatitis C virus (HCV), in the last few years, has been a priority. This infection became one of the most frequent causes of morbidity and mortality in the human immunodeficiency virus (HIV) population. With the emergence of new direct acting antiviral (DAA) therapies for hepatitis C, it is necessary to know what will be the place of pegylated interferon (Peg IFN) and ribavirin (RBV) in the treatment of HCV.

Aim and Methods: To evaluate the association between liver stiffness (LS) prior to the initiation of dual therapy (Peg IFN and RBV) and viral response in co-infected HIV/HCV patients.

Results: Between 2001 and 2012 we treated 258 co-infected patients with HIV and hepatitis C, 79,5% were male with a mean age of 39 years old. The great majority (89,5%) were intravenous drug users, 7% had heterosexual sex as risk factor and 3,5% had other risk factors; 84% of the patients was under antiretroviral therapy and all of them had undetectable HIV viral load. Fibrosis was evaluated in 133 patients by biopsy, and in 127 by biopsy and transient elastrography.

A sustained virological response (SVR) was achieved in 38,4%, null response in 28,3%, partial response in 14,3%, 13,2% relapsed and in 3,1% the treatment was stopped (secondary effects or abandon). The SVR rate was similar in both sex (males 38% vs females 38,5%; *p*=0,956), and we found no difference in age < 40 vs (37,8% in the group with < 40 years; 39% in those with ≥ 40 years; *p*=0,837) and CD4 cell counts in the beginning of treatment (28,9% in patients with < 350 cells/mm3; 40,1% in ≥ 350 cells/mm3; *p*=0,165). We obtained a SVR rate higher in patients with HCV RNA level <600000 UI/mL (48,4% vs 31,4 %; *p*=< 0,05) and in CC IL28B genotype (52,4% vs 31,9%; p < 0,05). We analyzed the SVR according to genotype and liver fibrosis. In patients with LS < 9 KPa the SVR rate was 30%, in genotype 1, and 77,3%, in genotype 3. Those with severe fibrosis (LS > 9 KPa) achieved a SVR of 17,4%, in genotype 1, and 78,6%, in genotype 3. Cirrhotic patients (LS > 12,5 KPa) obtained a similar result (genotype 1 vs genotype 3: 14,7% vs 75%).

Conclusions: We concluded that in patients with genotype 3 and LS < 12,5 KPa, the use of Peg IFN and RBV was a reasonable option for the treatment of HCV infection. The use of this regimen in combination with new DAAs can be a good choice in some cases. In genotype 1 this option should not be considered because of the lower SVR obtained with this treatment.

No conflict of interest

Abstract: 16

Treatment issues --- HCV-HIV coinfection

Hepatitis C treatment with first generation protease inhibitors - safety profile

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Background: Triple therapy (TT) with boceprevir (BOC) or telaprevir (TVR) in combination with pegylated interferon (pegIFN) and ribavirin (RBV) increases the efficacy of treatment of chronic hepatitis C, genotype 1, when compared to the double therapy (DT) with pegIFN and RBV alone. In this study we intended to analyse and compare the efficacy and safety of TT *versus* DT, in a 'real life' scenario.

Methods: In this observational, cross-sectional, analytical and retrospective study we analyzed 76 patients with chronic hepatitis C genotype 1 who were treated with both DT and TT. Co-infection with HIV was not an exclusion criteria and co-infected (HCV/HIV) patients were included. Two groups of 38 patients each were formed according with the type of treatment – the DT group and the TT group. We then evaluated the response to treatment at week 4, 12 and 24, side effects and discontinuation of treatment during the first 24 weeks.

Results: A significant percentage of patients in the TT group achieved rapid virological response (RVR) when compared to the DT group (84.2% vs. 31.8% (1) = 19.5, p < 0.001) as well as early virological response (EVR) (84.2% vs . 50% (1) = 8.58, p = 0.003). The proportion of patients with virologic response on week 24 post-therapy (SVR 24 – intention to treat) was also higher in the TT group (67.6% vs. 42% in the DT group). Infections were significantly more common in the TT group (42.1% vs. 15.8% in the TD group, (1) = 5.18 p = 0.023). Anemia was the most common hematologic adverse effect in both groups but about 20% higher in the TT group. Discontinuations of treatment due to adverse effects were only registered in the TT group (four patients). No serious adverse events were observed.

Conclusion: TT was associated with greater effectiveness in the treatment of patients with genotype 1 treatment. However, it is also associated with an increased incidence of adverse events and withdrawal of treatment for this reason.

No conflict of interest

Abstract: 17

Treatment issues --- HCV-HIV coinfection

Causes of mortality in HIV/HCV patients according to value of CD4 cell counts

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Background: The introduction of HAART reduced and changed the mortality causes in HIV patients. With the increase in life expectancy, co-infected patients are more prone to develop complications of liver disease.

Purpose: To evaluate the changes in the causes of death in HIV/HCV co-infected patients according to the value of CD4 cell counts, which was stratified in <200 cells/mm3 and >200 cells/mm3. The analyses were performed during two different periods.

Methods: Retrospective study of clinical and epidemiologic features of co-infected HIV/HCV patients who died in the Infectious Diseases Department - Centro Hospitalar do Porto - between January 2000 and December 2013, separated into two periods (2000-2006; 2007-2013).

Results: Globally we registered 373 deaths. We analyzed 280 who had CD4+ cell counts at the time of death. The great majority (90%) was of male sex and more than 90% had a history of intravenous drug use. Considering the median age at time of death, it was 38 years old in 2000-2006 and 42 years old in 2007-2013. The mean nadir of the CD4 cell counts was similar in two periods: 87 vs 102 cells/mm3. Only 10% of the patients were suppressed at the time of death in the 2000-2006 period; this percentage rose to 31% in 2007-2013.

In patients with CD4 cell counts below 200 cells/mm3, the causes of death between the periods were AIDS defining illness in 43,4% vs 40,4%; non opportunistic infections in 33% vs 26,6%; tumors 0,9% vs 3,3% and chronic liver disease in 14,2% vs 22,3%.

In patients with CD4 cell counts above 200 cells/mm3, the causes of death were AIDS defining illness in 41,3% vs 23,7%, non opportunistic infections in 24,1% vs 15,8%, tumors in 3% vs 13,2% and chronic liver disease in 20,6% vs 39,5% .

Conclusions:

The first cause of death, during the time in analysis, was opportunistic infections in the group of patients with less than 200 CD4 cell count.

In contrast, in patients with a CD4 cell counts above 200, we observed a reduction in the mortality caused by opportunistic infections and an increase in mortality related with neoplasms non related with HIV infection. In this group, since 2007, the first cause of death was chronic liver disease.

No conflict of interest

Abstract: 18

Treatment issues --- HCV-HIV coinfection

Changes to antiretroviral therapy while on HCV treatment in HIV/HCV co-infected patients

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Introduction: More attention needs to be paid to HIV regimens in HIV/HCV co-infected patients undergoing HCV treatment as management of both HIV and HCV treatments may be more complicated particularly in marginalized patients precariously engaged in care.

Methods: We have conducted a retrospective analysis of all HIV/HCV co-infected patients treated within our program and for whom definite HIV and HCV treatment outcomes were ascertained. We collected baseline demographic and clinical information including current or recent illicit drug use. The main focus of the study was to evaluate change of antiretroviral regimens while on HCV treatment, including reasons of change in case it was necessary. In addition, virologic and immunologic responses, side effects of HIV therapy and sustained virologic response (SVR) in patients undergoing HCV treatment were also evaluated.

Results: In this study, 47 co-infected patients were treated for both HIV and HCV. The average age was 52, 44 (93.6%) were male and 19 (40.4%) were on methadone. Regarding HCV treatment, 5 (10.6%) treatments were based on all-oral regimens, while the rest 42 (56.2%) were interferon based. Among the 47 co-infected patients, 32 (68.0%) carried on with the same HIV regimens that they had before the commencement of HCV treatment. Of these, 18 (56.3%) achieved SVR while 28 (87.5%) attained an undetectable HIV viral load by the end of their HCV treatment. Of the 15 (31.9%) patients who had to change their HIV regimen before the commencement of ARVs, 11 (73.3%) achieved SVR while 14 (93.3%) attained an undetectable HIV viral load by the end of their HCV treatment. There were no major toxicities associated with the switches in the HIV treatment regimens.

Conclusions: Treatment of HCV in HIV co-infected patients can be achieved successfully even in case changes to antiretroviral therapy is required without having negative consequences on HIV or HCV treatment outcomes.

No conflict of interest

Abstract: 19

Treatment issues --- HCV-HIV coinfection

A Case Of Successful HCV Clearance And Clinical Stabilization Of Cryoglobunemia In a HIV/HCV Coinfected Patient Treated With Sofosbuvir/Simeprevir

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Background: Hepatitis C chronic infection is associated with Hepatic Complications including liver cirrhosis, liver failure and Hepatocellular Cancer, but notably it is also associated with a spectrum of extra hepatic complications, with varying strengths of association. Type 11 mixed Cryoglobunemia is a small vessel vasculitis that has a strong association with Chronic Hepatitis C infection. In the era of curable Hepatitis C therapy we report a case of successful eradication of Hepatitis C infection and early clinical evidence of successful remission of active Cryoglobunemia in a patient with HIV/HCV coinfection.

Case: We report on a 49 year male with Haemophilia A and a diagnosis of HIV/HCV coinfection secondary to receiving infected pooled blood products in the 1980's. He is 3 class ARV(antiretroviral) experienced, currently on a regimen of Kivexa one tablet daily, with Rilpivrine 25mg once daily and Isentress 400mg twice daily with a CD4 count 180 and an undetectable viral load. He has Genotype 1a disease with 5.36x 10(6) IU/Ml, and a fibroscan has confirmed Child Pugh A liver Cirrhosis secondary to Hepatitis C infection. He was offered pegylated interferon alpha 2b and ribavirin in 2004 but stopped therapy in the first 2 weeks due to an acute drop in his Hemoglobin. His case has been complicated by Cryoglobunemia related vasculitis presenting with glomerulonephritis, rash in lower extremities that is managed with Prednisone and IVIG with partial response. Based on the COSMOS-2 data a decision was made to treat with Sofosbuvir 400mg daily with Simeprevir 150mg daily in combination for 12 weeks. He achieved undetectability at week 4 and on his SVR visit. Baseline on quantitative immunoglobulins he had low IgG levels that were supported by IVIG therapy with 2+ protein on his urinalysis. His week 12 measurements showed a normal IgG level despite reducing his IVIG dose by half and negative urinalysis. Further his clinical symptoms stabilized whilst lowering his prednisone dose something not achievable prior to Hepatitis C eradication.

Conclusions: The association of Cryoglobunemia and Chronic Hepatitis C is well established, review of the literature shows a variable response to stabilization of Cryoglobunemia with Hepatitis C therapy in the Interferon era. We report a case report and review the literature on clearance of Hepatitis C and stabilization of Cryoglobunemia in a coinfected HIV patient in the era of Interferon sparing regimens with higher SVR rates.

Conflict of interest: Advisory board for Janssen and Gilead