Mariantonietta Di Stefano[13], Leonardo Duca[3], Floriana Facchetti[14], Claudio Farina[15], Donatella Ferraro[16], Elisa Franchin[17], Daniela Francisci[18], Silvia Galli[19], AnnaRosa Garbuglia[20], William Gennari[21], Valeria Ghisetti[22], Pietro Lampertico[14,23], Nadia Marascio[24], Stefano Menzo[25], Valeria Micheli[26], Grazia Anna Niro[27], Antonella Olivero[2], Pierpaolo Paba[4], Concetta Ilenia Palermo[28], Orazio Palmieri[29], Stefania Paolucci[30], Mariantonietta Pisaturo[11], Teresa Pollicino[31], Giuseppina Raffa[31], Giulia Torre[1], Ombretta Turriziani[32], Sergio Uzzau[33], Maria Linda Vatteroni[34], Maurizio Zazzi[35], Antonio Craxi[36], Francesca Ceccherini Silberstein[3], Valentina Svicher[37]. [1]*University of Rome "Tor Vergata," Department of Biology, Rome, Italy;* [2]*University of Turin, Department of Medical Sciences, Turin, Italy;* [3]*University of Rome "Tor Vergata," Department of Experimental Medicine, Rome, Italy;* [4]*Tor Vergata Polyclinic Foundation, Unit of Virology, Rome, Italy;* [5]*University of Pisa, Dept of Clinical and Experimental Medicine, Pisa, Italy;* [6]*Pisa University Hospital, Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, Pisa, Italy;* [7]*University of Genoa, Genoa, Italy; Department of Health Sciences, Genoa, Italy;* [8]*ASST Bergamo Est, Medicina di Laboratorio, Bergamo, Italy;* [9]*Siena University Hospital, Microbiology and Virology Unit, Siena, Italy;* [10]*University Hospital of Pisa, Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, Pisa, Italy;* [11]*University of Campania Luigi Vanvitelli, Department of Mental Health and Public Medicine, Section of Infectious Diseases, Caserta, Italy;* [12]*Federico II University, Department of Neurosciences and Reproductive and Odontostomatological Sciences, Napoli, Italy;* [13]*University Hospital "Riuniti" of Foggia, Clinical and Surgical Sciences, Section of Infectious Diseases, Foggia, Italy;* [14]*Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy;* [15]*ASST "Papa Giovanni XXIII," Microbiology and Virology Unit, Bergamo, Italy;* [16]*University of Palermo, Section of Microbiology and Clinical Microbiology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, PROMISE, Palermo, Italy;* [17]*University of Padova, Department of Molecular Medicine, Padova, Italy;* [18]*Santa Maria della Misericordia Hospital, Infectious Diseases Laboratory, Perugia, Italy;* [19]*IRCCS S. Orsola-Malpighi University Hospital, Operative Unit of Clinical Microbiology, Bologna, Italy;* [20]*"Lazzaro Spallanzani" National Institute for Infectious Diseases, IRCCS, Laboratory of Virology, Rome, Italy;* [21]*Azienda Ospedaliero Universitaria di Modena, Department of Laboratory Medicine and Pathological Anatomy, Molecular Microbiology and Virology Unit, Modena, Italy;* [22]*Amedeo di Savoia Hospital, ASL Città di Torino, Laboratory of Microbiology and Virology, Turin, Italy;* [23]*University of Milan, CRC "A. M. and A. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, Milan, Italy;* [24]*"Magna Graecia" University, Department of Health Sciences, Unit of Microbiology, Catanzaro, Italy;* [25]*Università Politecnica Delle Marche, Department of Biomedical Sciences and Public Health, Ancona, Italy;* [26]*Ospedale Sacco, Laboratory of Clinical Microbiology, Virology and Bioemergencies, Milan, Italy;* [27]*Fondazione IRCCS "Casa Sollievo della Sofferenza," Division of Gastroenterology and Endoscopy, San Giovanni Rotondo, Italy;* [28]*Azienda Ospedaliero-Universitaria Policlinico "G. Rodolico-S.Marco," Catania, Italy;* [29]*Fondazione IRCCS "Casa Sollievo Sofferenza," Gastroenterology Unit, San Giovanni Rotondo, Italy;* [30]*Fondazione IRCCS Policlinico San Matteo, Microbiology and Virology Unit, Pavia, Italy;* [31]*University Hospital "G. Martino" Messina, Department of Clinical and Experimental Medicine, Messina, Italy;* [32]*Sapienza University of Rome, Department of Molecular Medicine, Rome, Italy;* [33]*University of Sassari, Department of Biomedical Sciences, Sassari, Italy;* [34]*Pisa University Hospital, Virology Unit, Pisa, Italy;* [35]*University of Siena, Department of Medical Biotechnology, Siena, Italy;* [36]*University of Palermo, Section of Gastroenterology and Hepatology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, PROMISE, Palermo, Italy;* [37]*University of Rome "Tor Vergata," Department of Biology, Rome, British Indian Ocean Territory*
Email: rsalpini@yahoo.it

Background and aims: A reliable quantification of serum hepatitis D virus (HDV) RNA is of paramount importance for a proper monitoring of patients under antiviral therapy. This quality control study aimed at comparing the diagnostic performances of different quantitative HDV RNA assays, used in clinical practice.

Method: Two HDV RNA sample panels were quantified at 29 Italian labs by 6 commercial assays defined as #1 (RoboGene 2.0, N = 9 labs), #2 (Eurobio on In/BeGenius ELITech platform, N = 7), #3 (Altona RealStar, N = 5), #4 (Anatolia Bosphore, N = 3), #5 (Dia.Pro.Dia., N = 2), #6 (Nuclear Laser Medicine, N = 1) and 2 in-house assays defined as #7 (N = 2). Panel A comprised 8 serial dilutions of WHO HDV genotype 1 standard from 5 to 0.5 logIU/ml, while Panel B included 20 clinical serum samples with HDV RNA from 6 to 0.5 logIU/ml. Participating labs quantified each dilution of Panel A and B 9 and 5 times, respectively (3 independent runs). Panel A was used to define assay sensitivity by estimating the 95%LOD (limit of detection). Panel B was used to evaluate assay precision by calculating the intra-run and inter-run coefficient of variation (CV). Lastly, the accuracy was assessed by calculating the differences between expected and observed values at each HDV RNA load for both Panels.

Results: By analysing Panel A, 95%LOD varied across the assays highlighting different sensitivities. In particular, #3 had the lowest median 95%LOD (10 [min-max: 3–316] IU/ml), followed by #1 (31 [3–316] IU/ml), #6 (31 IU/ml) and #2 (100 [100–316] IU/ml). The remaining 3 assays had a median 95%LOD ranging from 316 to 1000 IU/ml. Moreover, 5 assays showed a <0.5 logIU/ml difference between expected and observed HDV-RNA values for all dilutions, with #1 showing the best accuracy (Median [IQR]: 0.0 [−0.2–0.0] logIU/ml). Conversely, for #5 and #6 these differences exceeded 0.5 logIU/ml (median [IQR]: −0.7 [−0.7–0.6] and −1.3 [−1.6–1.1] logIU/ml), highlighting substantial HDV RNA underestimation. With Panel B, different reproducibility levels were observed across the assays. Indeed, #2 and #3 had a median intra-run CV <10% (median [IQR]: 8.0% [6.5%–11.2%] and 9.9% [6.8%–12.3%]) while assays #1, #4 and #7 showed a median intra-run CV from 10% to 15% and #5 and #6 of 18.9% and 26.2%. Inter-run CV depicted a similar scenario with the highest reproducibility for #2 and #3. For samples with HDV RNA <5.0 logIU/ml, five assays exhibited a <0.5 logIU/ml difference between expected and observed HDV RNA. Conversely, for HDV RNA >5.0 logIU/ml, an underestimation >1 logIU/ml was observed for most assays (N = 5).

Conclusion: This study underlines different levels of sensitivities, that could hamper the proper quantification of low level HDV RNA. There is a need to improve the accuracy in HDV RNA quantification at high viral load for most assays. These results should be carefully considered for the proper monitoring of virological response to anti-HDV drugs.

FRI-406

Real world outcomes of hepatitis delta patients with mild or moderate fibrosis

Sabela Lens[1], Habiba Kamal[2], Arno Furquim d'Almeida[3], Segolene Brichler[4], Margarita Papatheodoridi[5], Adriana Palom[6], Marta Casado-Martin[7], Stefan Bourgeois[8], Moises Diago[9], Karin Lindahl[2], Marta Hernández Conde[10], Manuel Rodríguez[11], Christophe Moreno[12], Alvaro Giráldez-Gallego[13], Francisco Javier Garcia-Samaniego[14], Thomas Sersté[15], Joaquin Cabezas[16], JeAn Delwaide[17], Maria Buti[18], George Papatheodoridis[5], Dominique Roulot[19], Thomas Vanwolleghem[20], Victor de Lédinghen[21], Soo Aleman[2], José Luis Calleja Panero[10]. [1]*Liver Unit, Hospital Clínic, FCRB/IDIBAPS, CIBERehd, University of Barcelona, Barcelona, Spain;* [2]*Dept of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden;* [3]*Viral Hepatitis Research Group, Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Antwerp, Belgium;* [4]*Departement of Microbiology, Assistance Publique-Hopitaux de Paris, Hopital Avicenne, Bobigny, Université Sorbonne Paris Nord, Bobigny, France;* [5]*Academic Department of Gastroenterology, Medical School of National and*

Kapodistrian University of Athens, General Hospital of Athens "Laiko," Athens, Greece; [6]Liver Unit, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [7]Liver Unit, Hospital Universitario Torrecárdenas, Almería, Spain; [8]Department of Gastroenterology, ZNA Antwerp, Antwerp, Belgium; [9]Liver Unit, Hospital General Universitario Valencia, Valencia, Spain; [10]Liver Unit, University Hospital Puerta del Hierro, Madrid. CIBERehd. University Autónoma de Madrid, Madrid, Spain; [11]Liver Unit, Hospital Universitario Central de Asturias, Oviedo, Spain; [12]Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, CUB Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium; [13]Digestive Diseases Unit, Virgen del Rocío University Hospital, Sevilla, Spain; [14]Liver Unit, University Hospital La Paz, IDIPAZ. CIBERehd, Madrid, Spain; [15]Department of Hepato-Gastroenterology, CHU Saint-Pierre, Brussels, Belgium, Brussels, Belgium; [16]Gastroenterology and Hepatology Department, Marqués de Valdecilla University Hospital, IDIVAL, Santander, Spain; [17]Department of Hepato-Gastroenterology, CHU Sart-Tilman, Université de Liège, Liège, Belgium; [18]Liver Unit, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, CIBERehd, Barcelona, Spain; [19]Departement of Hepatology, Assistance Publique-Hopitaux de Paris, Hopital Avicenne, Bobigny, Université Sorbonne Paris Nord, Bobigny, France; [20]Department of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium; [21]Department of Hepatology, University Hospitals of Bordeaux, Bordeaux, France
Email: joseluis.calleja@uam.es

Background and aims: Hepatitis Delta is considered the most severe form of viral hepatitis. New therapeutic options are now available and, in some countries, therapy prioritization is recommended. We aimed to evaluate the real world outcomes of HDV-infected patients with mild or moderate fibrosis in order to identify risk factors for fibrosis progression.

Method: Multicenter international retrospective study of adult patients with active HDV infection (HDV-RNA+) and absence of advanced fibrosis at diagnosis. Baseline demographical, clinical and virological variables were collected. Cirrhosis development and liver-related events (decompensation, HCC) were recorded. Patients were followed until last follow-up (FU) visit, liver transplantation (LT) or death.

Results: The cohort included 170 adult patients with mild/moderate fibrosis assessed histologically (45%) and/or non-invasively [median (IQR) age at first visit: 37 (31–45) years, males: 53%]. Most patients were Caucasians (55%) or Asians (21%), <5% were coinfected with HIV or HCV and <15% had comorbidities (obesity, diabetes, hypertension). At baseline, only 36% of patients had ALT >2xULN. In 102 cases with LSM within year-1, median (IQR) values were 7.6 (6–9) kPa. During the study period, 33% of patients received Interferon, 36% NA and only 8% bulevirtide therapy. After a median (IQR) follow-up of 62 (21–108) months, 31 (18%) patients developed cirrhosis; of them, 5 developed liver decompensation and 2 HCC. One patient underwent LT and one patient with HCC died. Median LSM (IQR) of patients at cirrhosis diagnosis was 16 (10–17) kPa. By multivariate analysis, higher LSM at baseline (model 1) and albumin and platelet levels (model 2 excluding LSM) were the only independent predictors for cirrhosis development. The best cut-off for LSM value at baseline for cirrhosis development was 7.6 kPa (Se 84%). Neither baseline qHDV-RNA levels nor ALT influenced on cirrhosis development. In addition, 17 (10%) patients achieved HDV-RNA clearance during FU (6 after IFN therapy and 11 spontaneously) with only 1/17 patients developing cirrhosis during FU.

Conclusion: Some patients with active HDV replication and mild-moderate fibrosis may have a benign course, but up to 18% of such patients progress to cirrhosis within 5 years having increased risk for liver-related complications. LSM seems to be a reliable non-invasive predictor, as patients with LSM <7.6 kPa have a low probability of progression to cirrhosis. Dissecting the factors associated with fibrosis progression may be useful to prioritize the need of new antiviral therapies.

FRI-407

Screening rates, prevalence, and natural history of hepatitis B/delta virus co-infection vs. hepatitis B mono-infection: data from a large US integrated healthcare system

Varun Saxena[1,2,3], Lue-Yen Tucker[2], Xiaoran Li[1], Krisna Chai[1], Suk Seo[1], Nizar Mukhtar[1], Grace M. Chee[4], Kyung Min Kwon[4], Sreepriya Balasubramanian[1], Brock Macdonald[1], Julie Schmittdiel[2].
[1]Kaiser Permanente Northern California, Oakland, United States; [2]Kaiser Permanente Northern California Division of Research, Oakland, United States; [3]University of California San Francisco, San Francisco, United States; [4]Gilead Sciences Inc., Foster City, United States
Email: varun.saxena@kp.org

Background and aims: Hepatitis delta virus (HDV) among patients with chronic hepatitis B virus (HBV) is the most severe form of viral hepatitis. Despite this, HBV/HDV co-infection prevalence in the United States (US) remains uncertain. In this study, we aim to demonstrate screening rates of HDV, estimates of HBV/HDV prevalence, and natural history data of HBV/HDV vs. HBV alone from a large US integrated healthcare system.

Method: In this retrospective cohort study from Kaiser Permanente Northern California, an integrated healthcare system with over 4.6 million patients, all adult HBV infected patients identified from January 2009 to December 2018 were included. Proportions of anti-HDV testing, positive anti-HDV, HDV RNA testing, and detectable HDV RNA were studied. Three groups were identified: HBV mono-infected (included those without anti-HDV testing), HBV with anti-HDV positive (included those without HDV RNA testing) and HBV/HDV co-infected (those with detectable HDV RNA). Groups were followed until outcome of interest, insurance loss or study termination at end of 2022. Outcomes of interest included fibrosis progression (at least 1 fibrosis stage increase between serial transient elastography measurements), cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplantation and all-cause mortality.

Results: We identified 17,794 HBV infected patients, of which 10,461 (59%) underwent anti-HDV testing. 83 of 10,461 patients (0.8%) were anti-HDV positive; 73 of 83 (88%) had HDV RNA tested and 11 of 73 (15%) were HDV RNA detectable. Among the HBV mono-infected (n = 17,700) vs. HBV with anti-HDV positive (n = 83) vs. HBV/HDV (n = 11) patients, baseline characteristics showed highest proportion of female in HBV mono-infected (47%), median age youngest in HBV/HDV (44 years) and highest BMI in HBV/HDV (27 kg/m^2) (all $p < 0.05$). For comorbidities, diabetes and hypertension were highest in HBV with anti-HDV positive (23% and 13% respectively) with active tobacco users highest in HBV/HDV (10%) (all $p < 0.05$). The HBV/HDV had the highest proportion of patients with baseline cirrhosis at 45% ($p < 0.05$). HBV/HDV (vs. HBV with anti-HDV positive vs. HBV mono-infected) showed the most fibrosis progression (100% vs. 15% vs. 11%), cirrhosis development (75% vs. 18% vs. 7%), decompensation development (30% vs. 7% vs. 0.6%), liver transplantation (18% vs. 6% vs. 0.4%), and mortality (18% vs. 11% vs. 6%) (all $p < 0.05$). HCC development was most common in HBV with anti-HDV positive at 11% vs. 9% in HBV/HDV vs. 2% in HBV mono-infected ($p < 0.01$).

Conclusion: From this large US HBV cohort, HDV screening rate was 59%, revealing<1% anti-HDV positive rate and 0.1% HBV/HDV prevalence. The findings support the aggressive nature of HDV infection and that of HDV exposure as well. Controlled cox-regression analysis will be presented to confirm HDV as the cause for the more severe natural history.