

# **4<sup>th</sup> Central and Eastern European Meeting on Viral Hepatitis and HIV**

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## **Abstracts**

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## Real-life effectiveness of ledipasvir/sofosbuvir regimen and factors associated with retention in care among HIV/HCV co-infected PWID in Ukraine

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**Background:** Ukraine's HCV distribution epidemic is seen to be fueled by people who injected drugs (PWID) with limited access to the integrated services, which contribute to poor retention in care. Data about efficacy and tolerability of new directly antiviral agents (DAAs) among PWID in Ukraine are limited. The aim of this study was to assess real-life effectiveness of Ledipasvir/sofosbuvir (LDV/SOF) based regimen and to analyze factors associated with retention in care during the treatment among HIV/HCV co-infected PWID in Ukraine.

**Materials & Methods:** An observational retrospective study included 75 HIV/HCV coinfecting patients with history of injection drug use, who started LDV/SOF based regimen between April 1, 2017 and November 30, 2017 and who were assessed for sustained virologic response (SVR). SVR was defined as undetectable HCV RNA at least 12 weeks after completing treatment. Liver fibrosis was evaluated by real time elastography or biochemical markers. Bivariate comparisons were tested using Pearson's chi-square or Fisher's exact tests. Potential risk factors associated with dropout during treatment have been identified by using multivariate logistic regression models. Patients who missed two or more HIV clinic appointments during the treatment were considered as unengaged in care. SPSS version 22.0 was used for statistical analysis.

**Results:** Among 75 persons the median age was 41 years, 51 (68.0%) were men and all were infected through injection drug use with HCV genotype 1. The average time since HCV diagnosis was 8.7 years. Stage F3 and F4 by METAVIR were present in 26.6% of the patients (20/75). Mean HCV RNA was 1 961 043 IU/L. HCV viral load more than >600,000 IU/L were detected in 40.0% of the patients (30/75). The majority of

patients were HCV treatment naïve (n=71, 94.6%). The average CD4 count before HCV treatment was 340 cells/uL and all patients had undetectable viral load (< 40 copies/ml). All patients were under antiretroviral therapy. 35 patients were receiving opioid substitution therapy (OST). Overall SVR rate was 96.0%. By bivariate analysis there was no significant difference between SVR rates among patients being on OST and never receiving OST services (94.3% and 97.5%, respectively, p=0.5).

Among patients receiving OST more frequent observed the LDV/SOF adverse effects, such as tiredness (20.0% vs. 5.0%, p=0.05), nausea (17.1 % vs 2.5%, p=0.02) and headache (14.2% vs. 5.0%).

Retention in care during HCV treatment was best predicted by attending clinic of integrated services with access to OST (OR=1.1, 95% CI 1.0- 1.1), social support (OR=1.4, 95%CI 1.0- 2.1) and evidence of previous TB treatment (OR=1.2, 95% CI 1.1- 2.8).

**Conclusions:** LDV/SOF-based regimen used in our real-life cohort, consisted of people with history of drug use, achieved high overall SVR rate. The study has shown that treatment outcome is similar among patients being on OST with other patients with history of drug use. Significant prevalence of LDV/SOF adverse effects has been revealed among patients receiving OST. Retention in care during HCV treatment of HIV-infected PWID in Ukraine has been associated with good access to OST, social support, and evidence of previous TB treatment.

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## Possible misclassification of HIV transmission between men: results of phylogenetic analysis

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**Background:** Similar to other Eastern European countries, HIV epidemic in Georgia for many years was driven by injection drug use (IDU). However, in recent years more people are infected through sexual exposure, including men who have sex with men (MSM). Sex between men is highly stigmatized behavior in Georgia and this may result in misclassification of transmission category.

**Materials and Methods:** We explored possibility of misclassification using phylogenetics. Partial pol sequences, containing protease and partial reverse transcriptase, were generated through population-based sequencing and were used for phylogenetic reconstruction. Branches consisting of  $\geq 2$  sequences showing bootstrap value of  $\geq 70\%$  and intra-cluster genetic distance  $\leq 0.015$  were considered reliable and defined as "cluster".

**Results:** A total of 246 pol sequences sampled from newly diagnosed persons with HIV were analyzed. Among them 84 (34.6%) sequences were isolated from IDUs, 26 (10.7%) – from MSM, 53 (21.8%) – from heterosexually infected men, 75 (30.9%) – from heterosexually infected women and 5 (2.3%) – from persons with undetermined mode of transmission. Viruses from MSM and IDUs did not cluster together. Overall 17% (9/53) of sequences from heterosexually infected men were potentially misclassified. These sequences clustered exclusively with sequences from MSM, forming a total of 8 clusters (2 clusters of 9 sequences and 6 pairs). Of 4346 persons with diagnosed HIV living in Georgia by the end of 2016, 485 (11.1%) men were classified as infected through sex between men and 935 (21.5%) men – through heterosexual contact. Accounting for 17% possible misclassification number of infection due to sex between men increased to 644 (14.5%).

**Conclusions:** Accurate ascertainment of risk factor information is important for monitoring dynamics of HIV transmission. MSM in Georgia may have larger epidemic than previously thought, requiring expansion of targeted interventions, including PrEP.

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## Epidemiology of HIV in the Baltic countries (Estonia, Latvia, Lithuania)

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**Background:** The HIV epidemic in the Baltic countries (Estonia-EE, Latvia-LV, Lithuania-LT) has many similarities but also differences.

**Methods:** Countries national HIV databases overview.

**Results:** The first case of HIV in countries was reported in 1987 and 1988. Until the end of 2017 9711 cases have been registered in EE, 7343 in LV, and 3012 in LT. Estimated N of PLWHIV in 2016 in EE was 7900, in LV – 6600 and 2900 in LT. In 2016 the highest HIV incidence (cases per 100000 pop.) in EU/EEA was observed in LV (18.5), followed by EE (17.4). In LT -7.5. The highest incidence in EE was in 2001 – 105 (95% CI 32.7 – 59.3), in LV in 2001 as well - 19.9 (95% CI 32.7 – 59.3), in LT in 2002 – 10.9 (95% CI 0.2 – 12.7). HIV incidence in 2017 in LV was 19 and exceeded incidence in EE (16.6) for the second year in a row. Although LT has the lowest incidence (9.3), it has been increasing for the third year in a row due to HIV transmission among PWID, especially in prisons. HIV epidemic in Baltic countries has started in the MSM community but afterwards has developed rapidly among PWID. The highest increase of HIV cases in PWID was reported in LV and EE in 2001 (173% and 390% respectively as compared to 2000), in LT – in 2002 (551% increase as compared to 2001/ because of outbreak in prison). In some regions of EE more than every second drug user is HIV+. The epidemiology of HIV has changed substantially during the past decade - the heterosexual transmission has been increasing, but is more prevalent in LV compared to LT, especially since 2001 when 8% of all HIV cases in LV were attributed to heterosexual transmission, and in 2005 even 31% ( $p<0,0001$ ), in LT respectively 10% and 17% ( $p<0,05$ ). In 2016 in EU/EEA countries AIDS diagnoses rate was 0.8 cases per 100 000 population, in LT-1,7, in EE-3.1 and in LV-5.8. Totally 46 MTCT HIV cases were reported in EE, 75 in LV and 7 in LT. Least

number of MTCT cases prove the recently started epidemic in LT.

**Conclusions:** The HIV epidemic in the Baltic countries started about the same time. However, the prevalence of HIV in the general population is different. In all countries, the second decade of HIV epidemic was driven by PWID. The spread of HIV through bridging groups to the general population in EE and LV started earlier than in LT. The example of the Baltic countries shows that if there is no adequate and timely response to the problem of drug addiction (especially in prison settings) the HIV situation can change very quickly. It is natural that after having reached its peak, HIV incidence starts declining. However, since far more people have sex (including MSM) than inject drugs, even if sexual transmission is less infectious, then if not properly managed, this may eventually lead to a high number of new infections.

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## Socio-demographic risk factors for high HEV seroprevalence among liver transplant recipients in Croatia

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**Background:** Hepatitis E virus (HEV) is an emerging disease in Europe, especially important among solid-organ transplant (SOT) recipients who are at greater risk of developing acute and chronic hepatitis with progression to cirrhosis. The foodborne transmission is considered the main route of HEV infection in developed countries. However, risk factors for the HEV acquisition among SOT recipients are still incompletely understood. The aim of this study was to determine the HEV exposure in LT cohort and to identify socio-demographic risk factors related to HEV seropositivity.

**Methods:** 242 Croatian liver transplant (LT) recipients completed a risk factor assessment questionnaire and were screened for anti-HEV IgG during post-transplant outpatient visits. Blood samples were tested for anti-HEV IgG using an enzyme immune assay (Mikrogen, Germany), confirmed by Western blot (Mikrogen, Germany).

**Results:** Anti-HEV IgG seroprevalence in LT recipients was 24.38%. The median time after LT was 5 years (range 19 years). The majority of the recipients were male (69.0%) and the major indication for LT was alcoholic liver disease (50.4%). The HEV seroprevalence in our transplant cohort was associated with older age (OR=1.05; 95%CI=1.02-1.09), female gender (OR=2.61; 95%CI=1.42-4.81), rural area of residence (AOR=2.17; 95%CI=1.10-4.27), and specific factors within a household, a farm (AOR=2.79; 95% CI=1.31-5.92), a water-well (AOR=3.09; 95%CI=1.11-8.57) and a sewage system connected to a septic tank (AOR=3.38; 95%CI=1.64-6.95). The highest level of education (AOR=0.05; 95%CI=0.01-0.43) and a recent travelling experience (AOR=0.39; 95%CI=0.17-0.88) were linked

to a lower HEV seroprevalence. Contrary to initial assumptions, production and/or consumption of cured meat and occupational exposure had no statistically significant strength of association with anti-HEV IgG seropositivity.

**Conclusion:** Our results show that anti-HEV IgG seroprevalence is high (24.38%) among LT recipients in South-eastern Europe (Croatia). The identified socio-demographic factors associated with the seropositivity set up a platform for further research directions to evaluate sources/routes of transmission and clinical impact of HEV infection after solid-organ transplantation.

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## Spontaneous HCV clearance in HCV/HIV coinfecting patients from AIDS Center Prague

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**Background:** Approximately 30 % of HIV infected persons have also HCV coinfection. Spontaneous HCV clearance (SHCVC) is generally observed in 15-45 % of HCV infected persons; it is less frequent in HCV/HIV coinfecting persons. Male sex, higher age, high HCV viral load (VL), asymptomatic course of acute VHC, low ALT levels or HIV coinfection are negative predictors for SHCVC. Due to of expense limits for new anti-HCV drugs, which are still present in many regions, recognition of SHCVC may be helpful in assessing local anti-HCV treatment strategies. Approximately 59 % of all HIV-infected persons in the Czech Republic are monitored by AIDS Center Prague (ACP). The aim of the study was to assess the proportion of SHCVC in HIV/HCV coinfecting patients from ACP and to establish which elected factors contribute to SHCVC.

**Material & Methods:** Data were collected retrospectively from medical records. Out of all 1,639 persons monitored by ACP 171 (10.4 %) were anti-HCV positive. 147 (86 %) of those were men and 24 (14 %) women. The mean age was 37,4 y. (median=36.5). Factors as sex, age, ALT, bilirubin levels, CD4+ count, HCV VL and antiretroviral therapy (ART), which could possibly contribute to SHCVC were collected only in relation to patients with known time of acute HCV infection (data relating to 68 - 75 persons in different categories were validated). T-test, Fisher and Mann-Whitney tests were used for statistical analysis.

**Results:** In 43 (25.1 %) out of all 171 HCV/HIV coinfecting patients SHCVC was observed. The median of HCV VL (537) were lower in 21 patients with SHCVC compared to the median of HCV VL (84,100) in 47 patients without SHCVC ( $p < 0.001$ ). In 22 (41.4 %) out of 53 on ART patients SHCVC was observed compared in 4 (16.7 %) out of 24 patients without ART ( $p = 0.039$ ). Sex ( $p = 0.319$ ), age ( $p = 0.200$ ), ALT levels ( $p = 0.312$ ), bilirubin

levels ( $p = 0.324$ ) and CD4+ count ( $p = 0.896$ ) were not found as cofactors influencing SHCVC.

**Conclusions:** Spontaneous elimination of HCV infection was confirmed in every 4th HCV/HIV coinfecting person monitored by AIDS-Center Prague. Low HCV VL and ART as statistically significant independent factors contributing to spontaneous HCV clearance were observed.

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## Mortality and causes of death among HIV/HCV co-infected persons in the Eastern European country of Georgia

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**Background:** Georgia has high prevalence of hepatitis C virus (HCV) infection, disproportionately affecting persons with HIV. Antiretroviral treatment (ART) is widely available in Georgia since 2004 and from 2011 all HIV/HCV co-infected persons have unlimited access to anti-HCV treatment.

**Methods:** Study included adult (age  $\geq 18$  years) persons with HIV diagnosed in Georgia from 2004 through 2016, who were followed until December 31, 2017. Data were extracted from the national AIDS health information system. Mortality rates per 100 person-years of follow-up were calculated. Predictors of mortality were assessed in Cox proportional hazards regression model. Causes of death were classified according to Coding of Death in HIV protocol.

**Results:** A total of 4560 persons contributed 22322 person-years (PY) of follow-up. Among them 2058 (45.1%, 10676 PY) were co-infected with HCV. Among HCV positive persons 235 (11.4%) were women and 1823 (88.6%) were men. HIV/HCV co-infected persons were more likely to be drug users (76.5% vs. 11.6%,  $p < 0.0001$ ) and late presenters (61.3% vs. 48.8%,  $p < 0.0001$ ). Similar proportion of both populations started ART (86.1% and 86.2%,  $p = 0.48$ ). After the median 4.1 years of follow-up 954 persons died, including 615 HIV/HCV co-infected persons. Persons with HCV had higher overall mortality compared to HIV mono-infection (5.76/100 PY vs. 2.91/100 PY,  $p < 0.0001$ ). Mortality declined over time in both populations with almost 8-fold decrease among HIV/HCV co-infected persons. In multivariate analysis co-infection with HCV was significantly associated with mortality (hazard ratio: 1.33, 95% CI: 1.13-1.57) after adjusting for age, gender, mode of transmission, baseline CD4 cell count, HBV co-infection and ART use. AIDS was the leading cause of death among HIV/HCV

co-infected persons accounting for 43.1% of deaths, followed by end-stage liver disease (ESLD, 20.8%). Mortality rate due to ESLD before availability of anti HCV therapy (2004-2011) was 2.11 cases per 100 PY and this decreased to 0.56 cases per 100 PY after 2011 ( $p < 0.0001$ ). AIDS remained leading cause of death prior and after 2011.

**Conclusions:** Wide availability of ART and anti-HCV therapy translated into significant decline in mortality including due to liver related causes. Improving earlier diagnosis will decrease excess AIDS-related mortality among HIV/HCV co-infected persons.

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## HCV resistance-associated variants among HCV treatment naïve HIV-coinfected patients in Ukraine. A pilot study

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**Background:** Baseline HCV resistance-associated variants (RAVs) can impact the efficacy of some hepatitis C directly acting antiviral (DAA) regimens in some HCV genotypes. There is a lack of data of the prevalence of HCV RAMs in untreated subjects in Ukraine. Sofosbuvir/ledipasvir is the only DAA treatment available in Ukraine.

**Methods:** We evaluated the presence of HCV RAVs in the NS3 and NS5A regions by population sequencing in 22 [16 (72.7%) cases of genotype 1B (G1B) and 6 (27.3%) cases of genotype 3A (G3A)] consecutive untreated hepatitis C/HIV co-infected subjects from Lviv (Ukraine). For G1b both NS3 and NS5A were sequenced, while for G3A only NS5A region was analysed (NS3 inhibitors not used in this genotype). oth Sequencing was performed in the laboratory of the the Pomeranian Medical University in Poland, sequences assembled using Recall tool with the resistance interpretation performed following the Geno2Pheno HCV Web-based Interpretation System.

**Results:** Study group included 22 subjects (15 males 7 females), mean age of 41 years 6 individuals were cirrhotic at the time point of genotyping.

Median HCV viral load was 2 500 000 u/L. NS3 region sequencing was successful in 12 G1B infected cases, while NS5A sequences were obtained for 14 G1B and 6 G3A samples. We identified NS3 RAVs in 5/12 (41.66%) for G1B cases, all being 56F substitution associated with reduced grazoprevir susceptibility. NS5A RAVs were observed in one (7.14%) G1B case, with presence of three mutations (28M,31I,93H) notably affecting susceptibility to all NS5A inhibitors except for pibrentasvir. In two (20%) G3A infected cases 30K

variant, associated with reduced susceptibility/resistance to all NS5A registered drugs, was noted.

In total RAVs associated with resistance to the ledipasvir were identified in 3/20 (15%) of cases.

**Conclusion:** In this pilot study sequence data indicate that the HCV primary resistance associated variants may negatively affect treatment results even in DAA unexposed populations. In the path to the total HCV elimination in Ukraine use of the expanded therapeutic options with higher barrier to resistance may be necessary.

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## Early results of pre-exposure prophylaxis program in Georgia

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**Background:** For many years the HIV epidemic in Georgia was driven by injection drug use, but recent trends show increase in the sexually acquired infections. The epidemic is rapidly emerging among men who have sex with men (MSM), with HIV prevalence exceeding 20% in this population. We report early results of Georgian pre-exposure prophylaxis (PrEP) program.

**Materials and methods:** In September 2017 pilot PrEP program was launched for high-risk MSM and transgender women in the capital city of Tbilisi through the support of the Global Fund to Fight AIDS, Tuberculosis and Malaria. Enrollment started in October 2017 based on pre-defined eligibility criteria, which included high risk for HIV infection, negative for anti-HIV on 4th generation antibody test; negative for HBsAg and creatinine clearance of  $\geq 60$  ml/min. Persons were also screened for HCV and syphilis. Generic formulation of tenofovir/emtricitabine was used for daily PrEP. Persons were followed 1 month after starting PrEP and then on 3-monthly basis. In addition to medical care, program envisages risk reduction counseling and adherence support services. Awareness rising campaign is also underway. The program represents partnership between public and community-based organizations. Analysis covered period from October 2017 through May 2018.

**Results:** A total of 97 men completed risk assessment and were tested for HIV, 63 men completed further clinical and laboratory examinations and 54 eligible persons initiated PrEP. Reasons for ineligibility included: no substantial risk for HIV (2 persons), positive tests at baseline for HIV (4 persons) and HBsAg (3 persons), and creatinine clearance  $< 60$  ml/min (1 person). The median age among enrollees was 23 (IQR: 21-27) years, 52.7% identified themselves as gay men, there were 3 transgender women. None of enrollees had anti-HCV and 12 had evidence of syphilis on

treponema pallidum hemagglutination assay (TPHA). Over the 8 months period 2 persons discontinued PrEP. There was no case of HIV seroconversion over the follow-up. One person become positive for syphilis on TPHA.

**Conclusions:** Georgia successfully launched PrEP program. Eight months of program implementation shows feasibility of implementing the program on wider scale. Increasing awareness and greater access to PrEP is needed to achieve the impact on epidemic. Particular attention should be paid to prevention and management of sexually transmitted infections.

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## The Regression of Liver Fibrosis in HCV Cirrhotic Patients Who Registered SVR after DAA Therapy

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**Background:** In Romania, interferon-free treatment with paritaprevir/ritonavir-ombitasvir-dasabuvir (PrOD) and ribavirin was approved since November 2015 for patients with advanced liver fibrosis. According to the local protocol, the assessment of the liver fibrosis was made by using Fibromax (BioPredictive).

**Methods:** This is a prospective study conducted in "Matei Bals" National Institute for Infectious Diseases – Third Department, between November 2015 and June 2018. The main objective is to evaluate the dynamics of liver fibrosis in patients with HCV compensated cirrhosis who achieved SVR after direct acting antivirals (DAA) therapy. The patients were evaluated at the beginning of the therapy, at 6 months after the end of treatment (post-EOT) and at 1 year post-EOT, using Fibromax, AST to Platelet Ratio Index (APRI) and Fibrosis-4 score (FIB-4).

**Results:** Between November 2015 and June 2018, 175 patients have received PrOD for HCV compensated cirrhosis in our Department. Using Fibromax at the initiation of therapy, 157 patients registered F4 and 18 patients had F3-F4 with a mean value of this test for all the patients of  $0.84 \pm 0.07$ . At 6 months and 12 months post-EOT, the mean value of FibroMax was  $0.67 \pm 0.15$ . The difference between baseline and these two evaluations has statistical significance (95% CI 0.13-0.2,  $p < 0.001$ ). Using different fibrosis scores, at baseline the patients registered an APRI score of  $1.68 \pm 1.43$ , at 6 months post-EOT the mean value was  $0.51 \pm 0.31$ , significantly decreased (95% CI 0.83-1.28,  $p < 0.001$ ), and at 12 months post-EOT, the mean value for APRI was almost even as the second evaluation ( $0.50 \pm 0.33$ ). This score did not correlate with FibroMax at any evaluation. Using the FIB-4 score, at the initiation of therapy, the

patients registered a mean value of  $4.22 \pm 2.99$ , at 6 months post-EOT there was a significant decrease:  $2.42 \pm 1.53$  (95% CI 1.26-2.19,  $p < 0.001$ ), and the mean value at 12 months post-EOT was of  $2.35 \pm 1.6$ , without any significant decrease. FIB-4 was proven to be statistically correlated with the liver fibrosis evaluated by FibroMax ( $r = 0.310$ ,  $p < 0.001$ ) at the initiation of interferon-free therapy and at the following visits (at 6 months post-EOT:  $r = 0.364$ ,  $p = 0.002$ ; at 12 months post-EOT:  $r = 0.355$ ,  $p = 0.025$ ). APRI and FIB-4 were highly correlated between them at every evaluation.

**Conclusion:** According to FibroMax (used by the national protocol for stratification of fibrosis), there is a statistically significant decrease between baseline and 6-12 months after the completion of antiviral therapy. The score FIB-4, highly correlated with FibroMax, proves to be a useful non-invasive tool in screening the patients and monitoring the dynamic of liver fibrosis.

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## Approaches to providing hepatitis C viremia testing to people who inject drugs in Georgia

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**Background:** In line with the WHO hepatitis C virus (HCV) elimination targets, Georgia embarked on an elimination programme in 2015. However, a large proportion of infected persons remain unaware of their infection. To expand the treatment more widely to those at high risk of HCV infection, people who inject drugs (PWID) are prioritized for test and treat strategies. Though anti-HCV screening for PWID has been implemented at point-of-service, access to confirmatory viremia testing remains a major barrier. We evaluated two novel approaches to improve access to viremia testing among PWID attending for care at harm reduction sites (HRS).

**Materials & Methods:** This is an ongoing non-randomized interventional study where HRS are assigned to one of three arms i) at four HRS, decentralized testing (Arm 1) where blood draw, viremia testing and results provision is done on-site on the same day, ii) at two HRS a centralized viremia testing approach is implemented (Arm 2) with blood draw on site and testing at a centralized lab. Test results are made available at HRS at a follow up visit, iii) at two HRS testing is done as per standard of care (Arm 3) where patients are referred to a treatment centre for testing and results provided at the treatment centre. Arm 1 and Arm 2 are using "HRS-based-approaches" as participants have blood drawn and receive test results at HRS. Participants are eligible for the study if they tested anti-HCV positive on the same day and did not have confirmed diagnosis. The proportion of participants who received their HCV viremia test result are compared across the three arms. We assess time to reporting of results.

**Results:** Between 21 May and 30 June 2018, 305 participants were enrolled [183(60%) in Arm 1, 57(19%) in Arm 2; 65(21%) in Arm 3]. Participants were predominantly male (95%), median age 42 years and 81% were currently injecting drugs. 289 (95%)

participants reported having taken an HIV test and of these 288(99.7%) self-reported being negative and one did not know their status. To date all participants enrolled in Arm 1 and 2 have had blood drawn for viremia testing and similarly all participants enrolled in Arm 3 were referred to treatment centers for testing. To date, 280 participants who had a confirmatory viremia test done and of these, 248(88.6) received their results (183 in Arm 1, 57 in Arm 2 and 8 Arm 3). Of those with results, 215(86.7%) were positive while 33(13.3%) were negative. On average participants received their results the same day (on average within 3 hours) in Arm 1, 5 days in Arm 2 and 14 days in Arm 3 from the time they had blood drawn for testing.

**Conclusions:** Providing blood draw for HCV confirmatory viremia testing at HRS where PWIDs attend for care/needle provision improves access to HCV confirmatory viremia testing. The "HRS based approaches" resulted in a larger proportion of participants receiving their confirmatory test results and the turnaround time was shortest where blood draw at HRS was combined with on-site testing.

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## Insulin-like growth factor and platelet-derived growth factor in liver cells of patients with chronic hepatitis C at different stages of fibrosis

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**Background:** Neoangiogenesis tends to be the most important process in progressing of portal hypertension and liver fibrosis in CLD, in viral hepatitis in certain. Expression of CD34 and PDGF is marker of this process and differs on different stages of liver fibrosis.

**Aims:** to study proliferative activity of Ito cells, fibroblasts, Kupffer cells, and endotheliocytes in liver tissue of patients with CHC at different stages of fibrosis.

**Materials and methods:** the repeated thin needle biopsies were performed in 180 CHC patients with different liver fibrosis stages: F0-1, F2, F3-F4 (groups A, B and C), mean age of 40.6, 41.8 and 52.6 years, M:F ratio-3.5:1, 4.1:1.0 and 6:1.2 respectively. Necro-inflammation and fibrosis were evaluated with Knodell score and immunohistochemistry. Proliferative activity of Ito cells and fibroblasts was characterized by the expression of insulin-like growth factor-1 (IGF1) and platelet-derived growth factor (PDGF), angiogenesis – by endothelial expression of CD34 and PDGF.

**Results:** the mean value of necro-inflammation activity (NIA) was  $7.5 \pm 1.1$ ,  $6.4 \pm 0.8$ , and  $6.5 \pm 1.0$  grades in groups A, B, and C respectively ( $p = 0.05$ ). Higher expression of IGF1 in liver cells and significant neoangiogenesis were presented in all groups with evident increase of IGF1 and PDGF expression in all types of cells in group C.

**Conclusions:** there is a significant expression of IGF1 in all types of liver cells that correlates with NIA of CHC that tends to be higher in severe fibrosis and cirrhosis. Obviously neoangiogenesis in the liver correlates with high expression of PDGF and CD34, increasing while liver fibrosis is being progressing to cirrhosis.

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## Access to DAAs among HCV, HCV/HIV co-infected patients in Central/Eastern Europe and the epidemiological characteristics of ESLD in this region - data from the ECEE Network Group

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**Objectives:** The investigation of the epidemiological data upon the prevalence of chronic viral hepatitis C, and viral hepatitis induced end stage liver disease (ESLD) along with the availability of HCV treatment using direct acting antivirals (DAAs) in the populations of HCV mono-infected patients, as well as among HCV/HIV co-infected in Central and Eastern European Countries could elucidate in which way our efforts should be put on in order to reduce the spread and complication of both infections. The epidemiological models of HIV and HCV infections, including the intravenous usage of psychoactive substances has been influencing the high prevalence of both blood borne infections in this area. We investigated the prevalence and the most common causes for the ESLD among patients in countries represented in the ECEE Network Group, along with the access to DAAs treatments in the region.

**Methods:** Euroguidelines in Central and Eastern Europe (ECEE) Network Group was initiated in February 2016 to compare standards of care for HIV and viral hepatitis infections in the region. Information about availability for HCV, HCV/HIV co-infection treatment options, the prevalence and causes of ESLD were collected through on-line survey. Respondents were ECEE members from 14 countries from the region.

**Results:** The number of HCV-infected patients treated with DAAs ranged from 0 to 15 500, while in four countries the data was unavailable. The number of HIV / HCV- coinfected patients treated with DAAs ranged from 0 to 500, while data was unavailable from three countries. Pan-genotypic DAAs are available only in three countries. (Table 1).

ESLD prevalence rate ranged from 0,5% to 1% and 1% to 25% in general population, and among HIV-infected, respectively. The most common cause of ESLD is viral hepatitis (43%). (Figure 1).

**Conclusion:** Our findings showed that there are gaps in epidemiological data on the number of patients treated with DAAs. In many Central and Eastern European countries access to DAA treatment is very poor. High quality healthcare, including broad access to DAAs is particularly important in the fight straggle against viral hepatitis. It should be taken into account that the most common cause of ESLD is viral hepatitis in this region.

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## Role of blood lipid spectrum determination in patients with chronic hepatitis C

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**Background:** We aimed to investigate the evaluation of lipid metabolism in patients with chronic hepatitis C (CHC), depending on their sex, age, biochemical activity of the process, viral load and genotype of the virus.

**Methods:** 45 patients with chronic hepatitis C were enrolled. There were 29 (64.4%) men and 16 (35.6%) women. The average age of the patients was  $36.26 \pm 1.65$  years. In addition to the ordinary indicators the total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) of all patients were assessed by colorimetric method on the biochemical analyzer "BioSystems" with diagnostic kits by "BioSystems" (Spain). The control group was formed with 26 healthy donors. Statistical processing of the obtained data was carried out using variational statistics methods using Student's t test and correlation coefficient  $r$ , including "small samples".

**Results:** In the clinical picture, the manifestations of asthenic-vegetative (64.4%), abdominal-pain (60%), dyspeptic (33.3%) syndromes, 91.1%, splenomegaly (46.7%) prevailed in the examined patients. The jaundice (28.9%), febrile (17.8%), arthralgia (11.1%) syndromes were less common. Decreasing in the content of TG and HDL in the serum was observed in the examined patients ( $p < 0.01$ ). The mean values of the total cholesterol, LDL and VLDL did not differ from the control figures. Wherein normal content of TG and HDL in serum was observed in 8 (17.78%) and 11 (24.44%) patients, respectively, and a significant increase in these indicators was observed in 4 (8.9%). TG, LDL and VLDL were increased in 7 (15.5%), 6 (13.3%) and 4 (8.9%), decreased in 9 (20%), 11 (24.4%) and 5 (11.1%) patients, respectively. The correlation analysis showed the presence of the following links: a feedback between maintenance of HDL and ALT activity in the blood serum ( $r = -0.51$ ,  $p < 0.01$ ), a direct link the content of LDL and the viral load ( $r = 0.47$ ,  $p < 0.05$ ), TC and LDL ( $r = 0.75$ ;  $p < 0.001$ ), TG and VLDL ( $r = 0.97$ ,  $p < 0.01$ ), TG, VLDL and

age of patients ( $r = 0.38$ ,  $p < 0.02$ ). The content of TG and VLDL in serum in patients with CHC with genotype 3a was lower than in patients with genotype 1c.

**Conclusions:** There are changes of different severity and direction in the lipid profile of the blood in the majority of patients with CHC. The most specific is the decrease in their serum TG and HDL. The study revealed the feedback between the content of HDL and the activity of ALT in the blood serum ( $p < 0.01$ ), direct correlation between LDL and viral load ( $p < 0.05$ ), TC and LDL ( $p < 0.001$ ), TG and VLDL ( $p < 0.01$ ), TG, VLDL and the age of patients ( $p < 0.02$ ).

The content of TG and VLDL in serum is significantly lower in patients with CHC with genotype 3a than in patients with genotype 1c, which probably reflects the pathogenesis of the disease in different HCV genotypes.

The determination of lipidogram marks of patients with CHC allows to reveal the extent of violations of fat metabolism in each case and approach their correction individually.

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## Liver elastography in a department of gastroenterology and hepatology - not only viral hepatitis

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**Introduction:** Non-invasive methods of liver fibrosis staging have changed diagnostics of chronic liver diseases. Advances in ultrasound based elastographical methods in particular and their expansion to clinical practice substantially decreased a need of liver biopsy. We present our experience with introduction of point-shear wave liver elastography (pSWE) to our daily practice.

**Aim/Methods:** To evaluate a spectrum of chronic liver diseases in patients examined within the first year of elastography practice in our hospital. All patients with a chronic liver disease referred to our department were examined using ultrasound machine Hitachi-Aloka Arietta 70 equipped with pSWE module. Each patient was included only once.

**Results:** We examined a total of 419 patients (age 55,8 ± 17,0 years). Aetiology was [n of patients; %; avg. age; % of patients with liver cirrhosis; avg. age of cirrhotics]: Non-alcoholic fatty liver disease – NAFLD [188 patients (45%); 58,4 years; 8% cirrhotics; 61,8 years], alcoholic liver disease [69 (16%); 59,1 years; 59%; 59,5 years], HCV [67 (16%); 49,1 years; 17,9%; 62,4 years], HBV [66 (16%); 51,9 years; 9,1%; 52,1 years], primary biliary cholangitis [11 (3%); 63,3 years; 36%; 66,9 years], autoimmune hepatitis [10 (2%); 58,4 years; 20%; 64,7 years], other 6 (1%).

**Conclusion:** NAFLD represented the most common aetiology of chronic liver disease in our patients, followed by alcoholic liver disease, HCV and HBV. ALD patients were the most advanced ones.

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## Psychosocial problems in young women with human immunodeficiency virus and hepatitis C virus coinfection in the Leningrad Region, Russia

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**Background:** Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection is an actual medical and social problem in view of the possibility of spreading the epidemics through sexual and perinatal routes. Despite the active introduction of direct-acting antivirals (DAAs) for the treatment of HCV, in Russian Federation continues to use interferon-containing treatment regimens. Among all social groups, women of childbearing age may be given preference in determining the priority of HCV treatment, there is a need to analyze the readiness of women for HCV therapy and factors that can prevent the treatment of two infections at the same time and limit its beginning. It becomes important to investigate the medical and social status of women with coinfection HIV/HCV, identifying their potential for the state of psychological health and living conditions for antiviral therapy for HCV and maintaining adherence to antiretroviral therapy (ART).

**Materials and methods:** To clarify the social and psychological status, one hundred outpatient documentation cards of women with HIV/HCV coinfection were analyzed. The majority of women were constantly observed at the Regional AIDS Center, the smaller part was sent for consultation from the cabinets of infectious diseases of the region. Fifty patients were subjected to in-depth examination with an assessment of psychosocial and narcological status and adherence to ART.

**Results:** Most women had a long history of HIV and HCV. Of these, 78% received ART and 84,6% had high

adherence to treatment. Social problems were identified in 38% cases. Work-related difficulties (34,2%) and family circumstances (26,3%) prevailed. An increase in the concentration of carbohydrate-deficient transferrin (CDT) – a marker of chronic alcohol abuse, registered in the Russian Federation - was found in three of 50 patients and in three more this figure was in the zone of unstable values. In 72% of the patients, mental disorders were detected, more than ½ (60%) previously actively used psychoactive substances, and the consequences were traced in 20% in the form of organic mental disorders. Currently, most patients were in remission for the use of psychoactive substances. The assessment of the level of depression and anxiety showed a significant spread of results, but at the same time, 54% of women expressed complaints of asthenic nature, anxiety was determined in 38% of patients, 40% had previously suicide attempts, predominantly demonstrative and blackmail character.

**Conclusions:** Considering the presence of social problems in 1/3 of patients, which may adversely affect the treatment of HCV and HIV - infection, these women need the provision of additional psychological support and assistance in solving difficulties before prescribing treatment in order to increase adherence. According to their mental health, patients need continuous observation and periodic correction of the condition. Most of them agree to start HCV antiviral therapy in the short term, but they are cautious about the proposed treatment regimens and its duration. Given the mental state of patients, it can be assumed that women with HIV/HCV coinfection for treatment of HCV are more likely to use DAAs that do not exacerbate existing disorders.

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## Factors associated with sustained viral response among HCV genotype 2 patients treated with direct acting antivirals within HCV elimination program in Georgia

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**Background:** Georgia has a high burden of HCV infection. A 2015 national serosurvey found that an estimated 5.4% of adults are currently infected with HCV. On April 28, 2015, Georgia launched the world's first National HCV Elimination Program that included free of charge treatment with DAAs for all HCV infected persons. The DAAs for the elimination program are donated by Gilead Sciences, and sofosbuvir was the first DAA available for the program. Later sofosbuvir/ledipasvir became available. Objective of this study was to assess the real-world data of treatment outcome among patients with HCV genotype 2 treated with direct acting antivirals.

**Materials and methods:** Study enrolled genotype 2 patients, enrolled in HCV elimination program in Georgia and treated at one of the leading clinics providing HCV care services. These patients were treated with sofosbuvir or sofosbuvir/ledipasvir in combination with ribavirin. We analysed demographic and clinical data of patients achieving sustained viral response (SVR) by the time of analysis. Fibrosis level of patients was measured by liver elastography or FIB4 score ( $\geq F3$  and  $>3.25$  were considered as high fibrosis level, respectively). Bivariate and logistic regression analysis was used to assess the association between SVR and several other factors.

**Results:** A total of 817 genotype 2 patients were eligible for the analysis. There were more males (88.9%). Females had higher chance of achieving SVR compared to males (98.9% vs 94.5%,  $p < 0.05$ ). Patients treated with sofosbuvir/ledipasvir and ribavirin combination were more likely to achieve SVR (97.6% as opposed to 77.8% of those treated with sofosbuvir and ribavirin).

99.4% of patients with low fibrosis level cleared the virus with 87.1% of those having high fibrosis level ( $p < 0.0001$ ). There was no statistically significant difference in cure rate of patients by the following variables: ever using injection drugs, socio-economic status, diabetes and body mass index. After adjustment, independent predictors of SVR were treatment regimen and liver fibrosis level.

**Conclusion:** Real-world experience among HCV genotype 2 patients demonstrated very high SVR rate for those treated with sofosbuvir/ledipasvir and ribavirin combination.

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## Prevalence of hepatitis B and C viruses among HIV positive patients in Georgian 2016-2017.

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**Background:** Georgia is an Eastern European country with the prevalence of HIV less than 0.3%. Co-infection of viral hepatitis remains one of the leading causes of morbidity and mortality in patients with HIV/AIDS in Georgia. Study objectives were to calculate prevalence of viral hepatitis B and C and assess their transmission routes among registered HIV patients in Georgia.

**Materials & Methods:** The retrospective study was conducted at the Infectious Diseases, AIDS and Clinical Immunology Research Center (IDACIRC). Data of HIV positive adults for 2016-2017 year were extracted from the national electronic HIV/AIDS health information system operated by the IDACIRC. Study participants satisfying inclusion criteria were categorized in the three different groups, patients: (1) with hepatitis B co-infection, (2) with hepatitis C co-infection and (3), who were co-infected with both hepatitis B and C. Data was analyzed using R statistical packages.

**Results:** A total of 1350 newly diagnosed HIV cases registered at IDACIRC were included. From them 719 were registered in 2016 year and 631 in 2017 year. From 1350 cases 44.4% were infected through heterosexual contact, 43.1% through injecting drug use, another 9.8% had infected through male to male sex and remaining patients infected through mother to child HIV transmission, blood transfusion or were undetermined. Among newly registered cases, HIV transmission through heterosexual contact decreases by 7% in the year 2017 (272) compared to year 2016 (292) and through injection drug use decreases by 32% in the year 2017 (157) compared to year 2016 (119). Same time HIV transmission through male to male sex increases by 12% in the year 2017 (111) compared to year 2016 (98). Other routes have no significant changes. Among 1350 HIV positive patients, registered during the study period 691 (51%) were co-infected by viral hepatitis B or C. Only hepatitis B co-infection was observed among 85 (12.3%) patients, only hepatitis C

co-infection among 585 (84.7%) and both HBV and HCV co-infections were registered among 21 (3%) of HIV positive patients. The majority of the first group of patients was infected through male to male sexual contact, injecting drug use was prevailed in the second group and the hepatitis B and hepatitis C infection was associated with heterosexual contact, except one case of blood transfusion.

**Conclusion:** Study results reveals that the structure of HIV transmission in Georgia has changed in 2016-2017. In particular the route of HIV transmission through injecting drug use and heterosexual contact decreases and HIV transmission through male to male sex increases. These structural changes in HIV transmission modes has its effect on the prevalence of viral hepatitis among newly registered HIV cases. Increase of HIV testing rate among patients with hepatitis B and C is strongly recommended.

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## Infection through MSM and early HIV diagnosis are associated with living in cities in Georgia

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**Background:** Estimated, more than half of HIV infected people are living in the big cities or other urban areas of world. The cities of many countries have joined or plan to join fast track cities initiative to fight against HIV on the city level. We conducted study to describe geographic distribution of HIV cases and to evaluate characteristics associated with urban and rural areas in Georgia.

**Materials & Methods:** Data of HIV patients who registered in 2008-2017 was extracted from national HIV/AIDS health information system of Georgia. Patients were divided in rural and urban groups based on their living place. Data of gender, age, transmission, test results of viral hepatitis at registration, first CD4 count and first viral load used for analyses. Descriptive statistics and chi-square test were used to compare distribution of characteristics across the groups. Binomial logistic regression models using GLM function in R language base package was used to reveal association between predictor and outcome variables.

**Results:** A total of 4206 HIV patients were included in the study with median age 41 years, 3075 (73%) of them were males. 3371 (80%) of HIV patients live in rural area including 1560 (46.3%) who live in Tbilisi, the capital of Georgia. 246 (36%) of study patients living in rural and 1105 (34%) living in urban area had positive results on anti-HCV test performed at registration. Anti-HBc test was positive for 249 (45%) of those live in rural area and 1235 (40%) in rural area. The prevalence of HBsAg+ test performed at registration was 7% for both groups of patients in rural and urban areas. 50 % of participants infected through heterosexual contact, 32 % with injection drug use and 14 % with male to male sex, the routes of HIV infection for remaining patients were combined in the category "other". Binomial logistic regression revealed statistically significant association between transmission with homosexual contact (OR 2.45, 95% CI 1.8 -3.4, P< 0.001) and living with the urban

area. First CD4 count more than 500 cells/mm<sup>3</sup> at registration (OR 1.27, 95 % CI 1.01-1.6) and positive anti-HBc (OR 1.22, 95% CI 1.1 -1.48) were also associated with living in urban area. No significant differences were identified by gender, age and other transmission routes and living in rural/urban areas.

**Discussion:** Study reveals that 80 % of HIV positive people are living in rural areas, almost half of them are lives in the capital of Georgia. More than one third has hepatitis C and almost half have antibodies on Anti-HBc antigen. Multivariate analysis revealed that people infected through homosexual contact mostly live in urban areas and have more chances to be diagnosed at the early stage of HIV infection, when CD4 count is more than 500 cells/mm<sup>3</sup>.

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## Decrease in the all-cause mortality among HLA-B5701 in HIV-positive individuals.

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**Background:** HLAB-5701 is present in approximately 5% of Caucasians, including people living with HIV/AIDS (PLWHA). On one hand, presence of this allele is linked to the abacavir hypersensitivity reaction however, HLA B5701 carriers also present with lower HIV viral load prior to the introduction of combined antiretroviral treatment (cART), and higher CD4 count at a baseline, which in turn may be linked with more favorable survival rates among PLWHA. The aim of the study was to analyze influence of the HLA B5701 allele on the all-cause mortality in the local cohort.

**Materials & methods:** Cross-sectional data of 838 patients from the Northern Poland followed up at the Department of Infectious Diseases, Regional Hospital, Szczecin were collected. Survival data were collected beginning from the date of the HIV infection confirmation as defined by (Western-Blotting or HIV-RNA) until the database closure (31.12.2017), loss to follow-up or death. 15 years mortality was calculated using Kaplan-Meier methodology. For clinical associations Chi2 or U-Mann Whitney tests were used, as appropriate.

**Results:** Examined cohort included 227(27,09%) female and 604(72,08%) males. The route of acquiring HIV were as follows: MSM (men who have sex with men) (25,54%), Hsx (heterosexual contact) (26,49%), IDU (intravenous drug users)(23,27%), unknown (24,7%). AIDS at baseline was diagnosed in 19,8%. HLA B5701 was found in 45 (5,38%) patients. Median survival time from diagnosis to end point was 94,5 months (25%-39,6; 75%-172,9), for HLA B5701 positive cases (median: 52,9; 25%-30,1; 75%-174,3), for HLA B5701 negative cases (median: 97,0; 25%-40,7; 75%-172,7), median survival time from initiating treatment to endpoint was 76,3 months (25%-33,9; 75%-137,6), for HLA B5701 positive cases (median: 53,5; 25%-34,4; 75%-92,4), for HLA B5701 negative cases (median: 78,2; 25%-33,9; 75%-138,0), median time from diagnosis till start of cART was 6,2 months (25%-0,95; 75%-48,7), for

HLA B5701 positive cases (median: 4,5; 25%-0,95; 75%-65,1), for HLA B5701 negative cases (median: 6,2; 25%-0,95; 75%-48,1).

Median HIV viral load was notably lower among HLA B5701 positive cases (median: 18845,5; 25%-1360; 75%-95887,5); compared to HLA B5701 negative ones (median: 87047; 25%-19343; 75%-344000) (p=0,001).

HLA B5701 was identified as a predictor of lower pretreatment mortality in the with cumulative mortality of 0% vs 10,67% for 60 months p= 0,03, 2,27% vs 13,20% for 120 months p=0,04, 2,27% vs 14,61% for 180 months p=0,02 and 2,27% vs 14,89% for 240 months p=0,02, as shown for HLA B5701 positive versus negative cases.

**Conclusion:** It is shown that HLA-B5701 is not only related with the lower HIV viral loads prior to introduction of cART, but is associated with better survival outcomes.

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## Prognostic factors of HCV spontaneous clearance among the HCV-infected patients in Ukraine

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**Background:** One of the variants of the natural course of HCV infection is HCV spontaneous clearance (SC) after acute hepatitis C in a part of infected patients. Unfortunately, SC following acute infection is uncommon for reasons that remain unclear, and in most studies, 50% to 85% of patients progress to chronicity and are subsequently at risk for liver-related morbidity and mortality. Recent studies have shown that HCV SC is observed in 15-45% cases of acute hepatitis C.

**Aim:** The purpose of the study is to determine the cases of HCV SC and its prognostic factors among patients living on the territory of Ukraine.

**Materials and methods:** The retrospective observational study included 203 anti-HCV-positive adult patients who were assessed for the presence of SNP in IL-28B gene. Spontaneous clearance was defined as being HCV RNA-negative at least 2 years after the estimated seroconversion date. Immunoblotting (RIBA), immuno-enzyme analysis on strips (SIA) and polymerase chain reaction reaction (PCR) have been used as conformational tests. For genetic analysis we used two basic human polymorphisms (SNP) of IL-28B gene: rs 12979860 with possible genotypes - CC, CT, TT and rs 8099917 with possible variants - TT, TG, GG. Potential factors associated with spontaneous clearance of the hepatitis C virus were identified by using multivariable logistic regression models. SPSS version 22.0 was used for statistical analysis.

**Results:** Among 203 patients the median age was 37 years, 112 (55%) were women. Patients with HCV SC makes up 16%. Female gender (OR=3.23; 95% CI [1.47-

7.11]), young age (OR= 2.39; 95% CI [1.12- 7.34]), icteric form of acute hepatitis C in the anamnesis (OR=3,44; 95% CI [1.14-11.67]), coinfection with hepatitis B virus (OR= 2.39; 95% CI [1.21- 9.34]), genotypes CC rs 12979860 (OR=1,6; 95% CI [1,11-3,7]) and TT rs 8099917 (OR=1,8; 95% CI [1,21-7,8]) of IL-28B gene have been identified as the factors that contribute to HCV SC in patients.

**Conclusion:** This study suggests association between the presence of genotypes CC rs 12979860 and TT rs 8099917 of IL-28B gene and spontaneous clearance of the hepatitis C virus in HCV – infected patients in Ukraine.

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## Toll-like receptor 4 polymorphism influence on the opportunistic infections in HIV-positive patients

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**Objectives:** Toll-like receptors (TLRs) play an important role in the innate immune response. The TLR4 is an essential component of the innate immune response to various microorganisms. We investigated the impact of TLR4 polymorphism on rapid CD4 decline and development of AIDS defining illness.

**Methods:** The presence of TLR4 Asp299Gly single nucleotide polymorphisms was determined in a cohort of 194 antiretroviral treatment-naive HIV-1 infected patients. TLR4 genotyping was performed by real-time PCR. We used survival analysis (Cox regression). Two outcome measures related to faster HIV progression were considered – decline CD4 cells to <350/ml and occurrence of AIDS defining illness.

**Results:** One hundred seventy-six patients were homozygous for the wild-type genotype (AA); 18 patients (9,3%) were heterozygous for the Asp299Gly (AG).

Faster development of AIDS was associated with Asp299Gly TLR4 polymorphism (HR= 3.45; 95% CI [1.22-8.25]), nadir CD4 count<350/ml (HR= 4.15; 95% CI [2.25-9.38]) and duration HIV-infection>3 years. Faster decline of CD4 count to <350/ml was associated with age>35 years (HR=4.15; 95% CI [2.16-7.16]), intravenous drugs abuse (HR= 2.23; 95% CI [1.05-9.22]) and Asp299Gly TLR4 polymorphism (HR= 2.23; 95% CI [1.05-9.22])

AG polymorphism was associated with more frequent development of the opportunistic infections, such as active tuberculosis (OR= 5.71; 95% CI [3.92-12.44]), herpes zoster (OR= 2.83; 95% CI [1.11-5.19]) and toxoplasmosis (OR= 6.23; 95% CI [1.19-18.67]) compared with genotype AA.

In addition, TLR4 SNP was associated with development of opportunistic diseases among individuals with CD4

cell count >100 cells/mm<sup>3</sup>, compared with homozygous HIV-infected patients (OR, 5.25; 95% CI [2.28-10.47]).

**Conclusion:** This study suggests a greater risk of developing of faster HIV-progression in patients with the Asp299Gly TLR4 polymorphism.

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## Impact of antiretroviral resistance on the HIV-related neurocognitive impairment

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**Background:** HIV-associated neurocognitive disorders (HAND) negatively affect the quality of life, morbidity and mortality of HIV+ patients on antiretroviral therapy. HIV drug resistance can lead to treatment failure and could be a risk factor for HAND. Our study evaluates the prevalence of neurocognitive impairment (NCI) and its association with HIV drug resistance in a cohort of ART experienced Romanian patients, parenterally infected with HIV since early childhood.

**Materials & Methods:** 180 HIV+ subjects (median age: 24 years, males: 48.86%) with a median duration on cART of 12 years were included. Pol gene sequencing was performed using the ViroSeq HIV-1 Genotyping System (Abbott Laboratories, USA) on plasma and available CSF samples (72/180) with a viral load > 1,000 copies HIV RNA/mL. All participants underwent neurocognitive testing using a comprehensive neuropsychological test battery covering 7 cognitive domains. Neurocognitive impairment was assessed using the global deficit score (GDS), calculated as the average of deficit scores across all neuropsychological tests (cut-off  $\geq 0.5$ ). Demographically-corrected (age, education, gender) dysfunction scores (mean of 50, standard deviation of 10) were developed based upon an age-matched control group.

**Results:** 53% of the participants have achieved viral suppression and 43.8% showed no sign of immunosuppression (CD4 count >500 cells/ul). Of the 51 patients with HIV plasma viral load  $\geq 1,000$  copies/mL, 50.9% had HIV drug resistance. Mutations related to reverse-transcriptase inhibitors were predominant, followed by PIs resistance mutations. HIV-associated neurocognitive impairment were present in 33% of the participants. No correlation was recorded between neurocognitive dysfunction and demographically data, immunological and virological

status. The rate of drug resistance was higher in the group of impaired patients vs. unimpaired ones, but did not reach statistical significance (63.2% vs. 50%;  $p=0.36$ ). In univariate analysis, subjects harboring resistant viruses had higher global deficit score (GDS) ( $p=0.05$ ) and worse verbal ( $p=0.007$ ) and working/memory ( $p=0.03$ ) dysfunction scores when compared with participants harboring wild-type HIV. However, multivariate analysis showed no association between HIV drug resistance and neurocognitive performance. In CSF, the prevalence of HIV drug resistance was 4.7%; none of the patients infected with HIV resistant viruses were cognitively impaired. No signs of virologic compartmentalization were observed: CSF HIV-1 RNA was positively correlated with plasma viral load and HIV-1 pol sequences from both plasma and CSF had identical drug-resistance profiles.

**Conclusion:** We report a moderate rate of NCI and a low rate of antiretroviral resistance in a cohort of heavily-treated HIV-positive Romanian patients, with life-long infection. Our data suggest that HIV drug resistance do not influence neurocognitive impairment; a longitudinal follow-up of these patients is needed in order to assess its impact on the progression of NCI.

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## Differences in genotype 1b HCV NS5A variant patterns related to the clinical characteristics.

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**Introduction:** In the era of HCV treatment with directly acting antiviral (DAA) regimens presence of drug resistant variants (RAVs) negatively affecting treatment efficacy remains a concern. In this study Polish multicentre pretreatment genotype 1b (G1) NS5A sequence data were associated with transmission patterns.

**Methods:** NS5A RAVs were identified by population sequencing in 333 directly acting antiviral (DAA) treatment naive G1b-infected individuals. Clinical data on the HCV transmission route (iatrogenic/unknown, men-who-have-sex-with-men (MSM), injection drug use (IDU), gender, history of HBV coinfection were collected. For associations between RAVs and clinical characteristics statistics Chi2 or two-sided Fisher's exact tests were used.

**Results:** NS5A RAVs were found in 31/333 (9.31%) G1b cases. Presence of NS5A RAVs was associated with unknown/iatrogenic HCV transmission route [12.15% (30/247) compared to 1.16% (1/86) for other infection routes,  $p=0.0097$ ]. Also, these variants were notably less common among HIV coinfecting subjects [1.22% (1/82) vs. 11.95% (30/251) for HCV mono-infected,  $p=0.0036$ ], and not present among patients with diagnosed AHC (0/36 cases), compared to 10.54% (31/294) for CHC cases ( $p=0.034$ ). No association between overall NS5A G1b RAVs frequency and gender, presence of HBs antigen or HBcore antibody or prior pegylated interferon/ribavirin treatment was found. Y93H tended to associate with female gender [10/145 (6.9%) vs. 7/242 (2.89%) for men,  $p=0.06$ ], but was slightly less common among patients with the history of HBV infection (HBc antibody negative) - 5.6% (14/250) vs. 1.16% (1/86) for HBc antibody positive ( $p=0.08$ ).

**Conclusions:** In G1b presence of NS5A RAVs correlated with iatrogenic HCV mono-infection which may indicate presence of the selection pressure in these cases, absent in HIV/HCV coinfecting cases. Most likely, the increased NS5A RAVs prevalence is linked to the longer time of infection among HCV mono-infected individuals.

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## Resource utilization health care indices in HIV/HCV co-infected patients in Ukraine

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**Background:** HIV/HCV co-infection has placed an increasing burden on the health care delivery system. Accurate estimates of resource utilization attributable to HIV/HCV co-infection are needed to inform resource allocation. This study aimed to compare health care utilization indices among HIV/HCV co-infected and HIV mono-infected patients in Ukraine.

**Methods:** Participants with known HIV and HIV/HCV positive status were randomly selected from the list of in-patient services for people living with HIV in Sumy region (Sumy, Ukraine) between 2014 and 2017. All subjects provided written informed consent. The data from medical documentation including the number of nights spent in the hospital (NSH) and the number of visits for in-patient medical assistance (VMA) per current year were analyzed. The relative risk (RR) of high resource utilization indices in patients with HIV/HCV co-infection and HIV mono-infection was observed. We also estimated adjusted index of relative risk (aRR) stratified by gender, age, current CD4 cells count, injecting drug use and experience of ART. High resource utilization indices were defined as  $\geq 10$  NSH and  $\geq 2$  VMA per current year.

**Results:** One hundred and sixty-seven persons were enrolled in the study: 111 HIV/HCV co-infected (64 % males, age (30 $\pm$ 6.0) years), 56 HIV mono-infected (50 % males, age (31 $\pm$ 7.3) years). The 2 study populations were well matched except for the route of HIV transmission: people who inject drugs reached 81 % in HIV/HCV co-infected vs 32 % for HIV mono-infected ( $p < 0.001$ ). The median CD4 cells count did not differ between groups (HIV/HCV co-infected – (323 $\pm$ 27.65), HIV mono-infected – (251 $\pm$ 24.65) cells/ $\mu$ L). There was no significant difference in receiving ART in both study populations.

The relative risk of  $\geq 10$  hospital nights for patients with co-infection was 1.6 (95% CI, 1.1-2.5,  $p=0.043$ ). For co-

infected subjects the relative risk of  $\geq 2$  visits for in-patient medical assistance consisted 3.2 (95% CI, 1.4-7.1,  $p=0.004$ ).

In adjusted analyses in HIV/HCV co-infected vs HIV mono-infected persons, CD4 count  $\leq 200$  cells/ $\mu$ L, experience of ART and age over 40 were significantly associated with high indices of NSH (aRR=1.4, 95% CI, 1.1-1.8,  $p=0.038$ ; aRR=1.2, 95% CI, 1.1-1.7,  $p=0.046$ ; aRR=1.39, 95% CI, 1.2-2.4,  $p=0.04$ , respectively). Adjusted index of relative risk for high VMA rate was significant in stratum of co-infected persons on ART and with CD4 count  $\leq 200$  cells/ $\mu$ L (aRR=1.8, 95% CI, 1.1-2.5,  $p=0.03$ ; aRR=1.2, 95% CI, 1.1-1.9,  $p=0.044$ , respectively). Gender and a history of injection drug use were not associated with high indices of NSH/VMA in co-infected vs mono-infected group.

**Conclusions:** HIV/HCV co-infection in Ukraine remains associated with higher resource utilization health care indices, especially at lower CD4 counts and in patients who receive ART. These policy makers could use for planning of adequate budgets for medical care for this category of population in a context of limited resources and decentralized distribution of financial revenues.

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## Susceptibility to HIV/HCV co-infection and IL-10 (C-592A) polymorphism among people who inject drugs in Ukraine

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**Background:** IL-10 regulates the immune response and remains intrinsically related to HIV/AIDS pathogenesis. Several lines of evidence suggest important roles for IL-10 gene single nucleotide polymorphisms (SNP) in variations in susceptibility to infections in different population groups. The aim of this study was to determine the association of IL-10 gene allele variants with HIV/HCV co-infection in Caucasian Ukrainians.

**Methods:** We conducted cross-sectional comparison of IL-10 (rs 1800872) promoter SNP frequencies among randomly selected 44 HIV/HCV co-infected European Ukrainians who inject drugs (71 % males, age at diagnosis (33,41±0,64) years), 88 HIV/HCV non-infected injecting drug users and 100 blood donors using PCR-RFLP at Sumy State University Hospital (Sumy, Ukraine) from August 2014 to June 2017. Statistical analysis was performed using SPSS software.

**Results:** The dominant cytokine gene variants among HIV/HCV co-infected Ukrainians who inject drugs were major allele homozygotes (C/C IL-10 - 54.55 %) that corresponded to blood donors (64.0 %) and non-infected drug users group (77.27 %) and reflected regularities of genotype distribution among Caucasian population. IL-10 minor allele spread showed the difference among study groups: A/A variant was associated with co-infection in men (A/A IL-10 - 12.9 % vs 0 % in non-infected drug users and 2.7 % in blood donors,  $p < 0.05$ ). We found protector effect of IL-10 homozygous major allele genotype on risk of HIV/HCV co-infection among negative male population from the high risk infection group (C/C IL-10 - 81.25 % vs 51.61 % in HIV/HCV co-infected drug users and 64.0 % in blood donors,  $p < 0.05$ ).

**Conclusions:** The analysis of frequencies of IL-10 (C-592A) SNP in Ukrainian drug users shows gender-related association with susceptibility to HIV/HCV co-

infection: minor allele homozygote could be considered as a disease risk factor in male population.

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## Challenges of Drug-to-Drug Interactions in the Clinical Management of HCV Infection

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**Background:** Patients infected with hepatitis C virus (HCV) often need multiple concomitant medications to manage other comorbidities. Awareness and knowledge of drug-to-drug (DDI) interactions have become a major point in the clinical management of HCV infection. Our objective was to evaluate drug-to-drug interactions in a cohort of patients treated with ombitasvir + paritaprevir + ritonavir and dasabuvir.

**Materials and methods:** Data from patients monitored in the "Prof. Dr. Matei Bals" National Institute of Infectious Diseases between June 2017 and April 2018, who had started an interferon free regimen with a combination of dasabuvir and ombitasvir + paritaprevir + ritonavir for 12 weeks were retrospectively evaluated. All significant comedications were recorded and the DDIs were assigned according to HepC Drug Interactions (<https://www.hep-druginteractions.org>).

**Results and discussion:** We enrolled 62 patients, with a mean age of 59.8 years (33.8% over 65 years of age), of which 70.9 % were female and 29.1 % male. One or more comorbidities were identified in 39 patients (62.9%) and the most frequent were: arterial hypertension – 41.9%, diabetes mellitus – 17.7%, dyslipidemia – 12.9%, chronic obstructive pulmonary disease – 9.6%, thyroid dysfunction – 4.8%, congestive heart failure – 3.2%, psychiatric disorders – 4.8%, atrial fibrillation – 1.6%. We had to replace the current treatment for 9 out of 26 patients with arterial hypertension (34.6%), 3 out of 8 patients with dyslipidemia (37.5%), 3 out of 6 patients with chronic obstructive pulmonary disease (50%), 1 out of 3 patients with psychiatric disorders (33.35) and for the patient with atrial fibrillation. The only comorbidities that did not required changes in medication were diabetes mellitus and thyroid dysfunction. For some patients with dyslipidemia statins were interrupted

during the 12 weeks of interferon-free regimen, but for others it was necessary to choose a drug that did not have interactions with the hepatitis treatment. On the other hand, for comorbidities like arterial hypertension, atrial fibrillation, chronic obstructive pulmonary disease, congestive heart failure or psychiatric disorders, the medication could not be interrupted and, in the case of drug-to-drug interactions, dose adjustments and close monitoring were undertaken.

**Conclusions:** The management of drug-to-drug interactions in patients with significant comorbidities treated with an interferon free regimen is challenging but can be managed without interrupting the treatment with dasabuvir and ombitasvir + paritaprevir + ritonavir or the other concomitant medications. To interrupt the interferon free treatment would cause virologic failure, whilst interrupting the medications for the comorbidities would alter the underlying diseases.

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## Characteristics of intravenous drug users in Bucharest, Romania

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**Background:** The increasing incidence of HIV infection among intravenous drug users (IVDUs) in Romania began in 2011, approximately one year after the introduction of the new psychoactive substances (NPS) on the market. In 2012-2013, approximately 30% of the new HIV cases were diagnosed among IVDUs, with a drop at about 20% by 2014-2015 and 15% in 2016 (1).

**Objective:** Describe the epidemiological and clinical characteristics of IVDUs newly diagnosed with HIV infection.

**Methods:** We prospectively studied adult patients, notified in our institution between October 2015 and September 2017, including 56 out of 135 newly diagnosed IVDUs in Romania.

**Results:** The study group included 56 IVDUs, 50(89%) men, with the median age of 33 years (IQR 28-37). Twenty-five (45%) were late presenters (LP) and 12(21%) were IVDUs with advanced HIV disease. 48(96%) were in stage A and only 2(4%) presented with an AIDS-defining event. The median CD4 count was 354 cells/mm<sup>3</sup>(IQR 220-4509) and the median HIV viral load was 90900 copies/ml(IQR 26300-245000). Two predominant HIV strains were identified in IVDUs: subtype F1 (70%) and the newly endemic CRF14\_BG (7%).

Heroin and NPS alone were the main drug of abuse in both 13(23%) IVDUs, and the two combined in 30(54%) IVDUs. The median duration of drug use was 10 years (IQR 5-15). Only 25% (14) ever attended opioid agonist therapy. Fifty-four (96%) IVDUs were coinfecting with HCV virus, with a median duration of infection of 5 years (IQR 2-8).

**Conclusions:** More than half of IVDUs are using NPS as the main drug of abuse. Most of our patients were young with a low proportion of LP, that could be explained by a higher proportion of HIV screening tests.

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## Hiv-1 in Belarus: domination of subtype A6

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**Introduction:** More than 7,100 HIV-infected patients have been registered in the country over the past 3 years. As of April 1-st, 2018, there were 25,275 cases of HIV infection in Belarus. More than 62% of infections occur in the sexual way of transmission.

**Materials and methods:** 1,064 serum / plasma samples obtained from different regions of country from patients with HIV infection. All samples were ELISA and Western blot positive. In all samples, the viral load was determined. Of the 1064 samples in 963 cases, RNA was isolated and RT-PCR, PCR, sequencing PCR were performed and the nucleotide sequences of HIV-1 were obtained from the gag-pol generegion.

**Results:** Out of 1064 samples taken to work, 546 (51.3%) were from males, 414 (38.9%) were from women. 104 plasma samples were obtained from children aged 0-14 years born to HIV-infected mothers, Of the 963 sequenced and analyzed samples, 449 (46.6%) were obtained from patients infected with hetero-homosexual contacts, 372 (38.7%) - from IDUs, 104 (10.7%) from children, born of HIV-infected mothers, 2 (0.2%) - recipients of blood components and in 36 (3.8%) cases it was not possible to establish the source of infection. In 906 (94%) cases subtype A6 was determined, in 25 (2.7%) - B, 4 (0.5%) - C, 3 (0.3%) - G, in 13 (1.3%) - recombinant form of CRF03\_AB, in 8 (0.8%) - CRF02\_AG, in 2 (0.2%) - CRF06\_cpx, and in one (0.1%) case CRF01\_AE / B and URF. Subtype B, which dominated the country until 1996, was imported into the territory of the Republic of Belarus from the United States, Ukraine and the Russian Federation and dominated among MSM. Recombinant form of HIV CRF03\_AB formed several clusters with samples from Lithuania and Russia, and 4 samples formed independent clusters, which indicates the "local" origin of the virus. The recombinant form of CRF02\_AG formed several clusters with samples from Uzbekistan, Russia, the USA and Cameroon, which indicates repeated drifts of this variant of HIV into the country. The recombinant form of CRF06\_cpx detected in the

brother and sister drug users formed a cluster with samples from Estonia and Russia. For the first time in 2018, we identified a recombinant form CRF01\_AE\_B, which forms a cluster with samples from the China. More than 94% of all HIV infections in the Republic of Belarus are associated with the A6 subtype (formerly A1FSU). The epidemic process on the territory of the Republic of Belarus is supported by a large number of local outbreaks associated with the A6 HIV-1 subtype, which forms independent clusters in different regions of the country.

**Conclusion:** We tracked the structure of the HIV-1 genotypes detected in the territory of the Republic of Belarus during 1995 - 2018. It was found that if before 1996 the epidemic process was supported by drifts of different variants of subtypes (B, G). At present the epidemic process in the country is supported by different variants of subtype A6, which accounts for more than 94% of cases of infection.

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## Molecular-genetic characteristic of HBV: domination of D2 subgenotype

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**Introduction:** After the introduction of vaccinations against hepatitis B into the vaccination schedule in the 1990s, the spread of the disease in the country stabilized. At the same time, in the Republic of Belarus about 1000 new cases of chronic form of hepatitis B virus are registered annually. HBV cases are registered in different age groups of patients. The reasons for this situation are likely to be many and related both to the quality of vaccination - people were not vaccinated, received incomplete vaccination course, etc., and with the virus itself, for example, the appearance of mutant strains of HBV. In this connection, carrying out molecular genetic studies that allow determining HBV genotypes subgenotypes, as well as mutations in different regions of the virus genome, acquire a new meaning and provide an opportunity to conduct both preventive measures to prevent the spread of infection, to change the therapy schedule, to evaluate the quality of diagnostic kits and so on.

**Materials and methods:** 738 serum / plasma samples. All samples were HBsAg positive. Sequencing PCR was performed on S and P genes region. Multiple alignment of nucleotide sequences was performed using the ClustalW algorithm. Phylogenetic trees were constructed using the ML (maximum likelihood) algorithm in the PHYML (Phylogenetic maximum likelihood) and GARLI (Genetic Algorithm for Rapid Likelihood Inference) programs, with the nucleotide substitution model GTR + I + G (I - the proportion of invariable sites, G - Gamma shape parameter). Optimization of tree topology - Best of NNIs and SPRs. To calculate the statistical reliability of clusters, the SH-aLRT test was used. Clusters of a phylogenetic tree were considered reliable, the root branch of which had a value of >0.9.

**Results:** Of the 738 serum / plasma samples, 516 (69.8%) were obtained from patients from Minsk and the Minsk region, 86 (11.7%) from Vitebsk, 71 (9.6%)

from Gomel, 33 (4, 5%) - from Mogilev, 24 (3,3%) - Brest and 8 (1,1%) - from the Grodno region. 404 (54.7%) of the patients were male, 250 (33.9%), and 84 (11.4%) had no data. For the age group 26-45 and over 45, there were 82.9% (542) of all the analyzed cases. At the same time, 112 (17.1%) patients were in the group from 0 to 25 years old. Of the 738 sequenced HBV DNA samples, 292 (39.6%) belonged to the D2 subgenotype, 178 (24.1%) to D3, 125 (16.9%) to D1, 136 (18.5%) to A2.3 0.4%) - C2, 1 (0.1%) - B4 and D4, 2 (0.3%) - RF. We described about 40 cases of hepatitis B virus resistance to antiretroviral drugs. The mutations M204V, L180M, 80I, V173L and I233V were most often detected.

**Conclusion:** We have given the molecular genetic characteristics of the hepatitis B virus detected in the territory of the Republic of Belarus in different age groups of patients, the dominant HBV genotypes have been determined and resistance mutations in the P region of the HBV genome isolated from patients on antiretroviral therapy have been described.

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## NS5A RASs among HCV RF1\_2k/1b patient failed on ledipasvir/sofosbuvir/ribavirin therapy within Georgian hepatitis C elimination program

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**Background:** Georgia has one of the highest HCV prevalence as well as highest frequency of recombinant strain RF1\_2k/1b in the world. Effectiveness of different DAAs among RF1\_2k/1b patients was evaluated in a study conducted in 2015 in Georgia. Which reported significantly higher cure rates among RF1\_2k/1b patients treated with sofosbuvir/ribavirin in combination with interferon and especially ledipasvir/sofosbuvir/ribavirin compared to standard HCV genotype 2 treatments with 12 or 20 weeks of sofosbuvir/ribavirin. Even though SVR rates among RF1\_2k/1b patients are high within Georgia's national hepatitis C elimination program, virologic failure still occurs and failing patients are subjected to re-treatment with alternative DAA regimens. Most data on the clinical impact of NS5A RASs concern HCV genotype 1 and 3 infections. However, the clinical role of NS5A RASs among HCV genotype 2 patients is still debatable. Moreover, no information is currently available on development and clinical significance of NS5A RASs among RF1\_2k/1b patients. Taking into account the sharing of HCV genotype 1 and genotype 2 sequences in RF1\_2k/1b genome, as well as low genetic barrier for developing NS5A RASs among HCV genotype 1 NS5A sequence, emergence of NS5A RASs can be responsible for treatment failure among RF1\_2k/1b patients.

**Materials and Methods:** We report occurrence of NS5A RASs among HCV infected 70 years old male patient, who was enrolled in hepatitis C elimination program in 2017. Patient has F3 liver fibrosis by metavir (kPa-11.1) and hepatocellular carcinoma. Baseline HCV viral load was 4 280 000 IU/ml and was infected with HCV G2 by based on conventional 5'UTR/Core genotyping assay.

Patient received 12 week of ledipasvir/sofosbuvir/ribavirin therapy and relapsed after treatment completion. NS5A sequencing was performed using home based semi nested sequencing assay with the following primers: HCV-NS5a\_6082\_F1: ARTGGATGAACCGRTRATAGCSTT (6082-6106), HCV-NS5a\_6652\_R: CCCGWBAYGTARTGGAARTC (6652-6633) and HCV-NS5a\_6120\_F2: AACCAAGTYTCCCYACRCACTA (6120-6142). HCV NS5A sequence was analyzed by Geno2pheno [HCV] tool available at <http://hcv.geno2pheno.org/index.php>.

**Results:** 520 basepair long NS5A sequence was obtained. Base on the Geno2pheno [HCV] tool, NS5A sequence had similarity to reference D90208 at 90.1% and subtype was 1b. Following polymorphisms were identified: K6R, S17T, L31M, L34IV, T56AT, A92V, Y93H, D126V, F127G, H128V, of which 31M and 93H causing either resistance or reduced susceptibility to all NS5A drugs (Daclatasvir, Elbasvir, Ledipasvir, Ombitasvir, Velpatasvir) except Pibrentasvir.

**Conclusions:** In conclusion, this case study demonstrates, for the first time, occurrence of NS5A RASs L31M and Y93H RASs among RF1\_2k/1b patients failing on ledipasvir/sofosbuvir/ribavirin therapy. Which indicates that emergence of these mutations among RF1\_2k/1b patients could cause antiviral treatment failure. Therefore, performing NS5A sequencing on RF1\_2k/1b patients failing on ledipasvir/sofosbuvir/ribavirin before re treatment could be extremely important for achieving individual and public health benefit.

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## Galactose functionalized mesoporous silica nanoparticles as a delivery vehicle in the treatment of Hepatitis C infection

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In the last decade, silica nanoparticles have drawn massive interest by researchers as an excellent carrier to treat numerous viral diseases due its distinguished physical and morphological properties. Higher biocompatibility, large surface to volume ratio, easy surface modifications, high stability and tunable pore sizes along with low cost and easy preparation methods make it more promising towards drug/nucleic acid delivery subsequently followed by larger encapsulation of drug molecules for real-life applications. Gene therapy has become a potential tool in the medical cooperation of genetically caused diseases. DNA or RNA based antiviral strategy showed better potential application over the viral media due to the less chances of gene recombination and immunogenicity. Hence, in this work mesoporous silica nanoparticle (MSN) based carrier system has been synthesized by simple chemical route, for the targeted delivery of DNA molecule against the conserved 5 prime-untranslated region of a viral RNA molecule to inhibit viral replications as The MSNs have been characterised by Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM), Brunauer Emmet Teller (BET) model and Fourier Transform Infrared Spectroscopy (FTIR) studies. The as synthesized MSNs have a diameter in range of 200-300 nm with an average pore size of 8-10 nm and possess very high specific surface area of ~2206 m<sup>2</sup>/gm. Additionally the synthesized refined MSNs have been conjugated with suitable functional groups to make it a controlled drug delivery system. In vitro cytotoxicity assay in human hepatocyte carcinoma (Huh7) cells exhibits excellent cell viability in presence of these MSNs carriers. Noticeable reducing of viral RNA levels has been achieved compared with other anti-viral agents in HCV JFH1 infectious cell culture indicating that this nanoparticle based system can be used as an

efficient candidate for the effective delivery of DNA molecule for gene silencing.

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## The management of HBV infection in patients with haematological malignancies

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**Background:** The risk of hepatitis B virus (HBV) reactivation in patients with haematological malignancies under chemotherapies or immunosuppressive therapies is very high. All the patients who need immunosuppressive therapy have to be tested not only for HBs antigen but also for anti-HBc antibodies and anti-HBs antibodies, in order to decide which patients need HBV reactivation prophylaxis. The most used antiviral therapies in these patients are nucleotide/nucleoside analogues.

**Objective:** to analyse the patients with HBV infection reactivation during the immunosuppressive therapy for haematological malignancies.

**Materials/methods:** We performed a cross-sectional study using the database of the National Institute for Infectious Diseases "Prof. Dr. Matei Balș". We analysed all the patients who needed immunosuppressive treatment for haematological malignancies and who were infected with HBV. The inclusion criteria were: age  $\geq 18$  years, documented haematological disease, recommendation for chemotherapy or immunosuppressive treatment, positive HBe antibodies with or without positive HBs antigen and HBs antibodies  $\leq 10$  IU/ml.

**Results:** In our HBV-infected patients database we have over 800 patients under treatment with nucleoside/nucleotide analogues (NA). Twenty-five patients were included, 11 were treated for HBV reactivation and 14 received prophylactic treatment. The median age was 62 years (IQR 48-67) and the sex ratio male:female was 1.08:1. 16 subjects have non-Hodgkin lymphoma, 3 have chronic myeloid leukaemia, 4 have chronic lymphocytic leukaemia and 2 have Hodgkin lymphoma. 23 patients (92%) had HBV reactivation, with positive HBsAg and 2 patients (8%) had occult HBV infection (negative HBsAg with positive anti HBe antibodies and negative anti HBs antibodies).

The median HBV viral load in patients with reactivated HBV infection was 94000000 IU/ml. 14 patients had elevated alanine aminotransferase levels with a median of 398 IU/dL. Four patients had positive HBe antigen at baseline. 22 patients (88%) received entecavir therapy and 4 of them became HBsAg negative during the treatment. Only one patient registered HBs seroconversion during the treatment, after 120 weeks of therapy. From 16 patients with detectable viral load, 13 had undetectable viral load at the moment of the study. The median duration until undetectability of HBV viral load was 46 weeks.

**Conclusions:** All haematological patients who need immunosuppressive treatment for haematological malignancies should be tested for HBV infection. It is not enough to test for HBs antigen only, all of these patients will be tested also for HBe antibodies before starting immunosuppressive therapy.

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## Hepatitis B vaccination response among HIV-infected adults

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**Background:** In the Antiretroviral treatment era life expectancy of HIV positive people is close to the life expectancy of the general population. Because of ARV availability mortality rate of HIV strongly decreased and in a first stage got ahead other chronic diseases like non-AIDS-related Diseases, TB and Viral Hepatitis. Immunization against Hepatitis B using Hepatitis B vaccine is the most effective preventive ways to avoid co-infection of HIV-positive patients with Hepatitis B. However, the immune response to hepatitis B vaccine is less effective in HIV-infected persons.

**Materials and methods:** Data analyses were performed to find out response rate of Hepatitis B vaccination and identify factors which increase response rate in HIV positives. Demographic, clinical and immunological factors of 102 adult HIV positive patients, who were negative on HBsAg were vaccinated with 3 doses of Hepatitis B vaccine in 2016 at Tbilisi AIDS Center, Georgia, were analyzed to find associations with development of a protective antibody (Ab) response following vaccination.

**Results:** Out of 132 HIV-infected patients, 102 patients (77.2%) completed vaccine series and followed-up by serology testing. Mean age of 102 study participants was 35 year. Among those 102 participants, 78 were male (76.5%) and 24 were female (23.5%). By root of HIV transmission 54 (53%) were infected by heterosexual contact, 38 (37%) men became positive by having unprotected sex with man, and 9 (10%) were infected by drug use. Anti-HBs response was measured after 3-12 month of last vaccination (mean time 6 month). Positive Respond has considered if anti-HBs titer was >10 IU/L.

In total, 57 (55.9%) HIV positive patients had a positive protective Ab response against Hepatitis B. Compare to male HIV positives, female have 7 times more chance to develop protective Ab against Hepatitis B compare to male HIV positives (adj. OR 7,4; 95% CI; 1.78- 30.93; P=0.006). Older age was negatively associated with the

development of protective Ab against Hepatitis B (adj. OR 0.9; 95% CI; 0.84 - 0.97) P= 0.004)

Among male responders mean CD4 T cell count was 577 cells/ $\mu$ L (346 cells/ $\mu$ L -920 cells/ $\mu$ L) and among non – responder male 702 cells/ $\mu$ L (338 cells/ $\mu$ L -1041 cells/ $\mu$ L). In both sexes, mean CD4 T cell count in responders was 595cells/ $\mu$ L compared to non-responders 689 cells/ $\mu$ L. On multivariate analyses, only age and sex were factors which were associated with positive Ab response.

The lowest number of CD4 T cell count among patients who received vaccination against Hepatitis B was 233cells/ $\mu$ L. CD4 T cell counts (< 250 cells/ $\mu$ L) and as well as viral load was not associated with Anti HBs Ab Response.

**Conclusions:** Female sex and young age were positively associated for development of protected Ab to HBV after 3 dose Hepatitis B vaccination in HIV positive patients. CD4 T cell count, as well as the viral load at the time of vaccination, do not play a significant role to predict the positive response to HBV vaccination among HIV positive patients. Non- significant results can be the result of small sample size.

Keywords: HIV, hepatitis B, vaccination, CD4

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## Cascade of care for patients with chronic hepatitis C in the Dnipropetrovsk region (Ukraine)

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**Background:** Implementation of WHO strategy of the elimination of viral hepatitis until 2030 is the main goal for Ukraine as well as for most countries. According to estimates, the prevalence of HCV infection in Ukraine is about 5%. Dnipropetrovsk region has a population about 3,227,100 people. Therefore, in the Dnipropetrovsk region the number patients is about 161,355. Despite of the expansion of access to treatment, the coverage of patients with antiviral therapy remains insufficient. The study is aims to analyze the effectiveness of the implementation of the cascade service of patients with HCV.

**Materials & Methods:** The HCV prevalence and incidence rate in Dnipropetrovsk region during 2015 - 2017 was studied using the epidemiological and descriptive statistical methods. Based on these investigations the Register of patients with chronic hepatitis C in the region has been created. This Register included the electronic database of patients. Then the range of medical services, cascade care of patients in the region was assessed and analysed using Excel and Statistica V.6.1.

**Results:** 519,970 people were screened serologically for anti-HCV antibodies for the last three years. The rate of positive results was 4.98%. The prevalence of HCV in the general population ranged from 3.94% to 6.73% in different years. The incidence rate of acute viral hepatitis C in Dnipropetrovsk region gradually decreased from 2015 to 2017 and amounted to 2.05; 1.90 and 1.63 in comparison with rate of chronic hepatitis C - 12.72; 17,25 and 17,18 per 100 thousand population respectively. The level of the coverage of HCV diagnostic and the medical care of patients, the dynamic monitoring has been increased every year, and amounted to 30.02% in 2015, 37.34% in 2016, and 42.36% in 2017. In cascade of care for patients, the achievement of a sustained virological response (SVR)

was noted in from 96.69% of the entire cohort of patients. The rate of SVR in DAAs was the highest - 100% (interferon-free regimens - ledipasvir /sofosbuvir /ribavirin (LDV/SOF/RBV) and the 3D regimen (ritonavir boosted paritaprevir /ombitasvir /dasabuvir)). The failure of antiviral treatment was noted in patients with Peg-IFN/RBV regimens: non response - 1,23%, partial response - 1,97%, relapse - 2,7% patients.

**Conclusions:** The cascade of services and care for patients with HCV in Ukraine of patients is improving every year, but the coverage of patients with antiviral therapy remains insufficient. Systematic monitoring and expansion of HCV screening and diagnostics with subsequent creation of a national patient registry is an important tool for optimizing the cascade services to provide effective care of HCV-infected patients. Such approach can provide a more rational planning of State financial support to achieving the goal of elimination of HCV in Ukraine.

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## The virological response to antiviral therapy among HBV/HIV co-infected patients

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**Introduction:** Chronic hepatitis B (CHB) is associated with considerably morbidity and mortality, in HIV co-infected patients. The prevalence of HBV co-infection among HIV infected patients in Serbia is 5.6%. All HIV/HBV co-infected patients in Serbia have been treated with HAART containing an anti-HBV drug, irrespective of CD4-cell count and HBV disease status in order to prevent more active liver disease. The successful therapy implicates the loss of HBs and HBe antigens and even seroconversion to anti HBe anti HBs antibodies, which was shown to be possible. Guidelines recommend tenofovir as the first line treatment. This selection of first line treatment is based on the safety and efficacy of the drug and risk of resistance. However, lamivudine was the only antiviral drug available for the treatment of HBV infection, since 2010, in Serbia. Therefore all HBV/HIV co-infected patients initiated lamivudine containing HAART, which was switched to tenofovir based one, after HBV developed resistance to lamivudine.

**Methods:** A cross sectional cohort study was conducted to analyse the treatment response to lamivudine and tenofovir containing HAART after lamivudine failure, among subjects with CHB, from the Belgrade cohort of HIV infected patients. The study included ... HAART treated HIV infected patients with CHB, who initiated lamivudine containing HAART between 2000 and 2011.

**Results:** Patient population included 54 (87%) HBe Ag positive patients while severe liver fibrosis was present in only ten patients (16.1%). Patients were mostly young men with the mean age of 36.1±10.3 years. The mean duration of lamivudine therapy, within HAART, was 4.3±3.2 years (ranged 1-12 years). Lamivudine failure was recorded in 40 patients (64.5%). Out of twenty-two remaining subjects with favourable virologic response

to lamivudine, all achieved HBs Ag loss, of which 2 patients developed anti-HBs antibodies, after 4.1±3.1 years (ranged 1-11 years), and 9±2.8 years (7-11 years), respectively. The mean HBV viral load at the time of switching to tenofovir based HAART was 6.0±1.5 log<sub>10</sub> IU/mL HBV DNA. After additional 1.7±1.0 years of tenofovir containing HAART, hepatitis B viral load was 1.5±1.1 log<sub>10</sub> IU/mL HBV DNA. Undetectable viremia was recorded in seven patients, while additional ten patients achieved HBV DNA of less than 20 IU/mL at the end of observed period, which gave the overall rate of optimal virologic response of 42.5%. However, none of the tenofovir treated patients achieved HBs seroconversion, while HBsAg loss occurred in one subject. The overall virologic response of CHB to HBV active drug containing HAART was rather good since after mean 5.3 years of treatment over 40% achieved good virologic response, including either undetectable HBV viremia, or HBsAg loss.

**Conclusion:** The benefit of tenofovir containing HAART among HBV/HIV co-infected patients, who previously failed HBV therapy with lamivudine containing HAART, was rather modest after approximately a year and a half of treatment, which suggested that the prolonged TDF therapy is mandatory to achieve the favourable response.

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## Noninvasive method of liver fibrosis evaluation in patients with chronic hepatitis C

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**Background:** Assessment of liver fibrosis in chronic hepatitis C (CHC) is important for disease prognosis, management plan and choose of adequate scheme of antiviral treatment. Although liver biopsy has been considered the gold standard it is an invasive procedure that has contraindications. Not so long ago several noninvasive markers became available for liver fibrosis detection but their expensiveness makes continuous search for the new cost effective methods of noninvasive assessment of liver parenchyma the priority area. Ultrasound method with the use of three-dimensional imaging in combination with power Doppler gives an opportunity to receive information on the distribution of areas of fibrosis and fatty infiltration in the whole organ, evaluate the state of perivascular spaces, changes in the parameters of microcirculation of the liver parenchyma.

The aim of our work was to improve the diagnostics of liver fibrosis in patients with CHC using ultrasound method with three-dimensional reconstruction combined with power Doppler mode (3D + PD).

**Materials & Methods:** We examined 79 patients with CHC. All patients have undergone complete clinical and laboratory examination and morphological evaluation of liver fibrosis based on METAVIR score. Abdominal ultrasound was performed on Voluson 730 Expert ultrasound diagnostic device using convective sensors for two- and three-dimensional images. After conducting a standard two-dimensional survey using an ultrasound sensor for 3D visualization and a mode of energy dopplerography a 3D image was obtained with the visualization of small vessels. Then using the VOCAL (Virtual Organ Computer Aided Analysis) function 3D-histograms with the evaluation of the following indices were constructed: Mean Gray Value of liver parenchyma (MG), indicators of peripheral blood flow – VI which reflects the percentage of vascular elements in the volume of liver tissue; FI which reflects the number of cells transported at the time of the study, ie, the

intensity of the blood flow; VFI which reflects the amount of blood passing through this volume.

**Results:** According to results of liver biopsy F1 fibrosis was observed in 17 (21.5%) patients, F2 – in 21 (26.5%), F3 – in 23 (29.1%) and F4 – in 18 (22.7%) patients. We observed a significant reduction in the microcirculation indexes in liver parenchyma as well as a significant increase in the mean acoustic density of the liver parenchyma in the gray scale in all patients. The degree of severity of these changes correlated with the progression of fibrosis. The most significant changes in all groups were seen in VI:  $10.2 \pm 1.5$  in F1 fibrosis;  $6.2 \pm 1.4$  in F2;  $2.3 \pm 0.3$  in F3 and  $0.4 \pm 0.03$  in F4 and VFI:  $2.5 \pm 0.07$ ;  $1.9 \pm 0.04$ ;  $1.0 \pm 0.05$  and  $0.29 \pm 0.007$  for F1-F4 respectively.

**Conclusions:** The use of 3D + PD regimen of ultrasound is quite informative for assessing the liver parenchyma, evaluation of peripheral blood flow, determination of the presence of liver fibrosis and its score in patients with CHC. The combination of such features as a decrease in VI, FI and VFI and MG can be used as criteria for diagnostic of liver fibrosis in patients with CHC especially when other noninvasive methods are not available.

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## Analysis of HCV treatment in a cohort of HIV/HCV co-infected persons in Lithuanian University Hospital

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**Background:** Due to the high effectiveness of direct-acting antivirals (DAA) against hepatitis C virus (HCV), their use is increasing significantly worldwide. From 2015 treatment with DAA for HCV genotype 1 is available in Lithuania. We aimed to identify the rate of HCV treatment uptake among HIV/HCV co-infected persons and the factors associated with use of DAA treatment.

**Methods:** In this study we included patients co-infected with chronic HCV (defined as being HCV-Ab positive) who were under follow-up in Infectious Diseases Centre of Vilnius University Hospital from January 2015 to November 2017. Comparison of clinical characteristics between HCV treated and untreated patients was made. The proportion of HCV-RNA positive patients with fibrosis METAVIR  $\geq$ F3 and fibrosis METAVIR  $<$ F3 was compared. Fibrosis  $\geq$ 3 was defined by the result of liver biopsy  $\geq$ 3 (METAVIR) or FibroScan  $\geq$ 9kPa. p value  $<$ 0.05 considered as significant.

**Results:** A total of 167 individuals with HIV/HCV coinfection were included in the study and most of them had acquired HIV/HCV coinfection with intravenous drug using (149 (89.2%)). 14(8.4%) patients died during follow-up. HCV-RNA test was done for 147 (88%) patients. Among them spontaneous clearance was observed in 23 (15.6%) individuals. The median age was similar of both treated and untreated individuals. HCV treated patients were more likely to have cirrhosis, be HIV virally suppressed, had higher median of CD4 cell count compared with untreated ( $p<$ 0.05). Fibrosis level was identified for 57 (46%) individuals. Among them with fibrosis  $\geq$ 3 (19 (33.3 %), intravenous drug using, HCV-RNA $>$ 500,000 IU/ml were identified for 16 (84.2%) and 15 (78.9%) persons respectively. Patients with fibrosis  $<$ 3 and with fibrosis  $\geq$ 3 had similar HIV related

characteristics ( $p>$ 0.05). HCV treatment was started for 29 (23.4%) individuals and the majority (24 (93.1%)) received DAA. Patients who received DAA-based treatment and IFN-based treatment did not differ significantly per gender, HIV undetectability ( $p>$ 0.05).

**Conclusions:** Uptake of DAA treatment is increasing but still remains in modest level. HIV undetectability, higher CD4 count, cirrhosis were factors associated with HCV treatment start.

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## The efficacy of antiviral therapy for HBV hepatitis - a cross-sectional study of a Romanian cohort of patients

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**Background:** Patients with chronic hepatitis B require life-long treatment with nucleoside/nucleotide analogues (NNA). The aim of the study was to analyse the antiviral regimens used in a tertiary hospital in Romania for HBV infected patients and the outcome of these patients.

**Materials/methods:** This is a cross-sectional study of all the patients with HBV who received antiviral therapy in our hospital and who were evaluated between April 2017 and November 2017. In Romania, the recommendations for HBV infection are made according to European guidelines.

**Results:** A total of 510 patients were included in the study, 490 with HBV (96.07%) and 20 with HBV+HDV (3.92%), with a mean age of 49.18 years and a M:F ratio of 1.04:1. Only patients with HBV infection were analysed. A quarter of these patients needed the initiation of treatment and the other 75.72% the continuation of the antiviral regimen. The therapy was needed for HBV treatment (in 94.3% of cases) and for the prophylaxis of HBV reactivation in 5.7% of patients. The used regimens were: Entecavir 0.5mg/day (84.08%), Entecavir 1mg/day (4.69%), Tenofovir (5.51%), PegInterferon alfa2a (3.26%) and Lamivudine (1.83%). Analysing the HBeAg status, 13.67% were positive and only 11.94% experienced HBe seroconversion after a mean period of 96 weeks. According to HBsAg status at the beginning of therapy, 5 patients were negative (HBV reactivation prophylaxis). Four patients have cleared the HBsAg during therapy and only one patient had HBs seroconversion. The mean viral load at baseline was 7.9 log IU/mL. The mean period of therapy with NNA was 134.72 weeks. Under treatment, after a mean duration of 46.12 weeks, the viral load became undetectable. During therapy, 87.56% of patients registered

undetectable viral load and at the moment of the study, 17.34% of patients still had detectable viral load, most of them around low limit of quantification (LLQ) with a mean period of treatment of 103 weeks.

**Conclusions:** Entecavir was the most frequently used therapy in our cohort and after the first year of treatment most of these patients registered undetectable viral load. The patients with detectable viral load after 1 year of treatment had persistent HBV DNA around LLQ.

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## THE TREATMENT OF HCV INFECTION WITH DIRECT-ACTING ANTIVIRALS MEDICINE IN 12-YEAR OLD GIRL WITH HIV/HCV CO-INFECTION.

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**Background:** The estimating level of co-infections HCV/HIV among people who lived with HIV-infection in Ukraine is near 23 %. Direct-acting antivirals medicine (DAA) treatment, particularly treatment with ledipasvir/sofosbuvir is available now in Ukraine. HCV treatment with DAA in pediatric population is allowed since 12 years old. At the same time there are lack of data of using this regimen in HIV-positive pediatric population.

The first case of treatment child with co-infection HIV/HCV with ledipasvir/sofosbuvir in the Infectious Diseases Center «Clinic for treatment children with HIV/AIDS» at the National Specialized Children's Hospital «OKHMATDYT» Kiev, Ukraine are presented.

**Clinical case:** 12 year girl was admitted in our hospital in January 2018 with complain on the fatigue, nasal bleeding in the morning, pain in legs (since September 2017), which increased during physical activity.

She was vertically HIV infected, on ART since 2006 zidovudine/ lamivudine/lopinavir /ritonavir (AZT/3TC/LPV/r), was switched on tenofovir disoproxil fumarate/emtricitabine/ (TDF/FTC)/LPVr in 2016 because of myelotoxicity.

She was diagnosed with HCV genotype 1b at 4 years old and in 2017 fibrosis 3 stage was found. HCV viral load was  $4,38 \times 10^5$  IU/ml. Total bilirubin was 23 mmol/l and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was slightly increased.

Treatment with ledipasvir/sofosbuvir was prescribed at December 2017. Since that time the pain in legs increased.

CD4 cells- 32%- 760 cell/ml, PCR RNA HIV was less 40 RNA copies/ml

The densitometric diagnostic was made: osteopenia was found.

N-Acetyl-b-D-Glucosaminidase (NAG) of urine was made -15,1 (N range 1.64-9.8). TDF was switched on Abacavir(ABC).The patient condition was improved.

**Conclusions:** Ledipasvir/sofosbuvir increased tenofovir exposure, especially when used together with a pharmacokinetic enhancer (ritonavir).

Patients receiving TDF and a boosted HIV protease inhibitor should be strictly monitored for tenofovir-associated adverse reactions.

The question about changing ART regimen and preferable ART regimen for patient on HCV treatment is still open.

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## Risk Factors for Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome in Patients Coinfected With HIV, Tuberculosis and Chronic Hepatitis C

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**Background:** Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) is an immunopathological reaction occurring in 4-54 % patients who start antiretroviral therapy (ART) while on treatment for tuberculosis (TB). Mortality directly caused by TB-IRIS is not frequent, however, it causes substantial morbidity, necessitating hospitalisation and health care utilisation for diagnostic and therapeutic procedures. We conducted this study to determine the incidence and risk factors for TB-IRIS in patients coinfected with HIV, tuberculosis and chronic hepatitis C (CHC).

**Methods:** The study was conducted at the ID Department of O.O.Bogomolets National Medical University and included 86 patients coinfected with HIV, tuberculosis and CHC: 25 women (29.1%) and 61 men (70.9%), mean age was 36,3±3,8 years. HIV infection was diagnosed with the detection of HIV antibodies (ELISA and Western blot) and HIV viral load (PCR). CHC was confirmed by detection of HCV RNA (PCR) and antibodies (ELISA). Diagnosis of pulmonary and extra-pulmonary TB was confirmed according to medical history, clinical data, results of X-ray or CT scan, bacteriological tests and histological examination of biopsy samples of lymphatic nodes. Descriptive statistics of frequency distributions, summary measurements and variability measurements was used. Multivariate analysis was used to assess the association of each factor with the development of TB-IRIS.

**Results:** TB-IRIS was observed in 18 patients (20.9%) after administration of ART. In the majority of cases (in 11 patients - 61.1%) TB-IRIS developed within the first month after starting ART, in 5 patients (27.8%) - during 5-8 weeks after its initiation and in 2 patients (11.1%) -

after 8 weeks of ART. Early ART initiation was the only risk factor for TB-IRIS ( $\chi^2=4.982$ ,  $p<0.05$ ). The other factors that were assessed in the study (extrapulmonary tuberculosis -  $\chi^2=0.510$ , bacterioexcretion and/or pulmonary destruction -  $\chi^2=0.073$ , other severe opportunistic infections -  $\chi^2=0.427$ , low CD4+< 200/ $\mu$ l at the baseline -  $\chi^2=0.902$ ) did not increase the risk for TB-IRIS ( $p>0.05$ ).

**Conclusions:** TB-IRIS was observed in 20.9% patients coinfected with HIV, TB and CHC and in most cases (61.1%) it developed within the first month after starting ART. Early ART initiation was the only risk factor for TB-IRIS ( $\chi^2=4.982$ ,  $p<0.05$ ). The other factors that were assessed in the study (presence of extrapulmonary tuberculosis, bacterioexcretion and/or pulmonary destruction, other severe opportunistic infections and low CD4+< 200/ $\mu$ l at the baseline) did not increase the risk for TB-IRIS.

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## Outcomes of hepatitis C antiviral treatment among PWIDs in Georgia

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**Introduction:** PWIDs are vulnerable and stigmatized population and treatment adherence is a challenge in this target group. Some physicians consider that the treatment of hepatitis C in this group is not reasonable due to poor adherence and non-compliance to treatment regimens that have negative impact on treatment outcome. The goal of our study was to evaluate the adherence and outcomes of HCV antiviral treatment with direct acting antivirals (DAA) among PWIDs.

**Methods:** The study subjects were selected from clinic NEOLAB - one of the major treatment providers of HCV elimination program in Georgia. The random sample of HCV patients having recorded injection drug use as a mode of HCV transmission in medical chart was selected. Totally 160 individuals were enrolled in the study. The study instrument was medical chart review, where socio-demographic, clinical and treatment monitoring data are recorded. The treatment adherence was measured by HCV viral load at week 4 and timely show ups at appointments. The treatment data of 200 patients with no history of injection drug use were taken for comparison.

**Results:** Among 160 study subjects 159 (99.3%) were males. Average age was 44.5 years (range 22-62 years). 17 (10.6%) individuals were on methadone substitution therapy. According to the quantitative PCR-test conducted at week 4 of treatment 95.6% % of study subjects (153 individuals) had undetectable level of HCV RNA. Among 6 individuals RNA was decreased at least by 2log. As for control group, 97% had cleared the virus at week 4. No statistically significant difference was observed. 91% of study subjects timely showed up at clinical appointments. This indicator was 88% among controls.

**Conclusion:** Our study revealed that PWIDs have high level of treatment adherence and accordingly, PWIDs

should be enrolled in HCV treatment programs without any hesitation.

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## Tuberculosis, hepatitis C and hepatitis B co-infections among people living with HIV in Armenia

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**Background:** Tuberculosis (TB), hepatitis C (HCV) and hepatitis B (HBV) are common co-infections of HIV. World Health Organization estimates, that HCV affects 2-15% and chronic HBV affects 5-20% of people living with HIV (PLHIV). PLHIV co-infected with viral hepatitis have a more rapid fibrosis progression than HCV and HBV mono-infected patients. More than a third of the estimated 34 million PLHIV worldwide are also infected with TB. TB is the most common presenting illness and cause of death among PLHIV. We aimed to understand the situation concerning co-infections among PLHIV in Armenia and develop recommendations to prevent their further spread and progression.

**Methods:** The International Review Board of the American University of Armenia approved the study protocol. We interviewed 180 beneficiaries of the “Positive People Armenian Network” NGO using quantitative cross-sectional survey design with structured self-administered questionnaire. We used convenience-sampling approach. Descriptive statistics was run using SPSS 16 software.

**Results:** The mean age of participants was 40.6 (SD, Standard Deviation, 8.3). Males comprised 61.1% of the sample. Twenty five percent of the respondents reported having at least one co-infection (HCV, HBV or TB). The most prevalent co-infection was HCV (17.8%). About 14% of the respondents reported having only HCV, one percent of the study participants mentioned having only HBV and about 6% of them reported having only TB. About 2% of the respondents reported having both HCV and HBC co-infections. Having HCV and TB was mentioned by 1.7% of the respondents.

**Conclusions:** The study results showed that the prevalence of co-infections among PLHIV is high. There is need to do educational programs aiming to increase the knowledge on prevention of co-infections and to increase the adherence to TB treatment. Programs aiming early detection and treatment of HCV and HBV

among PLHIV should be widely implemented in Armenia.

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## Efficacy of Sofosbuvir-containing regimens in patients with chronic hepatitis C

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**Background:** Estimated rate of HCV-infected patients in Belarus consistent of 1.5-2.5% of population. The introduction of directly acting antiviral agents (DAA) for treatment of HCV-infection into clinical practice makes it possible to hope for eradication of HCV infection in the future.

**Aim of the study:** to evaluate the efficacy of Sofosbuvir-containing regimens for treatment of HCV-infected patients living in Grodno region of Belarus

**Material and methods:** Clinical and laboratory data of 69 HCV-infected patients living in the Grodno region of the Republic of Belarus, who received DAA therapy, were analyzed. Patients infected with genotypes 1 and 3 of the HCV have received the scheme Sofosbuvir and Daklatosvir. Patients infected with the 2 genotype - Sofosbuvir and Ribavirin in standard dosages. The duration of the regimens was 12 weeks for most patients in the group, in patients with advanced fibrosis and liver cirrhosis the course of treatment was extended to 16 weeks. Patients with HBV co-infection were excluded from the group, co-infection of HIV / HCV occurred in 2 patients. "Statistica" 10,0 was used. The data are presented in Me (Q25; Q75).

**Results:** Among the patients there were 39 (56.5%) women and 30 (43.5%) men. The age of the patients was 48 (35, 57) years. The duration of observation for HCV infection in patients of group was 1 (3-8) year. The experience of disease more than 10 years was established in 12 (17,4%). According to genotypes of HCV, the patients were distributed as follows: the genotype 1 of HCV was in 48 (69.6%), the genotype 2 - in 10 (14.5%), genotype 3 - in 9 (13.0%); In 2 cases, a mixed infection of 1 and 2 genotype was established. The viral load of the HCV prior to initiation of therapy was 610 298.0 (300 500.0; 3 972 015) IU/ml. AlAT was 64 (39.6, 115.0) U/L, AsAT - 67.2 (14; 375) U/L. Advanced fibrosis (3-4 stages by Metavir), including liver cirrhosis of class A, was in 5 patients.

Preliminary therapy with interferon alpha in combination with ribavirin was performed in 30 (43.5%) patients.

Comorbidity occurred in more than 50% of patients. At the same time, 5 patients had malignant tumors of different localization, including 1 case of hepatocellular carcinoma (HCC).

All patients in the group achieved a virological response (VR) proven by negative result of HCV RNA in serum detection on end of therapy. None of the patients indicated significant side effects. Late relapse of HCV-infection was fixed in 3 patients (4,3%), so sustained virological response at 24 weeks (SVR24) was documented in 95,7% cases. Among 3 patients without SVR24 two patients had genotype 2 and one had genotype 1, HIV infection was in 1 case, liver cirrhosis – in 1 case.

**Conclusion:** The DAA therapy demonstrated 95,7% of SVR24 in the analyzed group of patients, despite the presence in the group of so-called difficult patients infected with the 1st HCV genotype, who had advanced liver fibrosis and did not respond to previous interferon containing regimens.

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## Antiretroviral therapy adverse reactions in a recently diagnosed HIV patient - case presentation

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**Background:** Since the discovery of combination antiretroviral treatment (cART), HIV infection has become a chronic disease, patients having the same life expectancy as the general population. Unfortunately, despite the considerable body of evidence advocating for its efficiency, cART can have important adverse reactions and drug-to-drug interactions if not properly tailored for each patient.

**Case presentation:** This case is about a 37 year-old male who was admitted into our hospital and diagnosed with cytomegalovirus (CMV) retinitis and HIV infection (HIV viral load 729.566 c/ml, CD4+ count 11/mm<sup>3</sup>). He was treated for the CMV retinitis with Ganciclovir as induction therapy and then given Valganciclovir as maintenance therapy. After 2 weeks of CMV treatment we started him on cART. We opted for Darunavir (DRVr), Zidovudine (AZT), Lamivudine(3TC) in spite of a possible AZT associated hematological toxicity, because a combination of Abacavir and Lamivudine was not efficient given the high HIV viral load, and also as to avoid an additional renal toxicity due to Tenofovir and in combination with Valganciclovir. His anemia slightly worsened to a threshold of 10,3g/dl. Two weeks from antiretroviral treatment initiation, the patient started complaining of bilateral knee pain radiating to the lower legs with limited mobility. His acid-base balance showed an elevated lactate value (4 mmol/L) with a tendency for metabolic acidosis. All drugs that could promote mitochondrial toxicity were stopped, also, the NRTI drugs were switched to Raltegravir (RAL) and Etravirine (ETR) with rapid remission of symptoms.

Several months later, the patient presented to the hospital with elevated lipid profile markers (total lipids 1212 mg/dL, triglycerides >500 mg/dL, cholesterol 235 mg/dL). Since he denied any change in his diet, we assumed that the hyperlipidemia was an adverse reaction of cART so we adjusted the treatment by

stopping RAL and ETR, with improvement of lipid markers during the next months.

**Conclusion:** Physicians should always keep in mind and closely monitor each patient for possible cART related adverse reactions and promptly adjust treatment each time it is necessary.

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## HIV case profile in Lithuania, 2016

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**Background:** The spread of HIV infection in different periods of time in Lithuania has had different predominant mode of transmission, male/female ratio, age of HIV infected people, place of residence, which are directly related to the HIV case profile. To know national HIV case profile is important in HIV response planning process. The objective of the study - to describe the HIV case profile in Lithuania.

**Methods:** HIV epidemic review is based on retrospective analysis of the national HIV surveillance database (1988 - 2016) and published reports.

**Results:** Totally 2749 new HIV cases (2182 males (79.4 %) and 567 (20.6 %) women) were reported in Lithuania during period of 1988 - 2016. Male to female ratio M / F 3.8. The average age of HIV infected person is 34 years. By mode of HIV transmission, almost 60% were infected through injecting drug use, one third is infected through sexual intercourse. According to the place of residence, in all municipalities of Lithuania (except Neringa) HIV cases have been identified, but the distribution is uneven. Nearly every second (49.3%) HIV infected person lives in one of two counties - Vilnius or Klaipėda (port city). According social PLHIV aspects: every second has secondary education, and one in ten - a university degree and almost two in ten - primary or basic. 43% - four out of ten - infected people have imprisonment experience - most man. Two thirds are socially insured and one third unemployed. 32 percent receive ART, of which every second were infected through sexual way of HIV transmission. The mean age of patients who received ART in 2016 was 42 years (in men - 42.6, in women - 40.4).

**Conclusions:** HIV case profile in Lithuania in 2016 - a young (34 years old) man living in Vilnius or Klaipėda district, who has a secondary or higher education, has been infected with HIV through injecting drug use, had imprisonment experience and not receiving ART.

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## Vitamin D level in patients with Chronic Viral Hepatitis C

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**Relevance:** Treatment of patients with chronic viral hepatitis C (HVC) is a serious problem of modern infectology. Despite significant successes in this field, many questions remain unresolved and require further research.

The main purpose in the treatment of patients HVC is the cessation of the processes of fibrous degeneration of the liver, elimination of virus and achievement of prolonged therapeutic efficiency.

Another important issue of antiviral therapy at HVC is the frequency and quality of side effects from medicament therapy.

The search for measures which enhance antiviral effect of the drugs and reduce their negative effects or predictor responses to antiviral therapy is conducted almost from the beginning of the introduction of specific therapy HVC.

Several studies showed an important immunomodelling role of vitamin D with various infectious pathology, including at HVC.

**Objective:** To investigate the level of vitamin D (25-OH-DZ) in patients with chronic viral hepatitis C , which were on treatment in the CZ "Dnipropetrovsk City Clinical Hospital № 21".

**Materials and methods:** We have been examined 30 patients, from 31 to 63 years old.

The diagnosis was established on the basis of a set of clinical and laboratory data, according to local protocols.

The control group comprised 30 almost healthy people, most of them were between 40-43 years old.

The level of 25-OH-DZ was determined by the method of hemimunal of magnetic immunianalysis on Analyzer Architect i2000, test Systems ABBOT Diagnostics (USA). Vitamin D-Status evaluation was carried out in accordance with classification of M.F. Holick (2011 y.). Statistical data processing method of variational statistics was conducted. The probability

factor was determined by the Student's t-test. The difference between the values compared has been considered likely by the  $p < 0.05$ .

**Results and discussions:** The results of research of active form of vitamin D3 (25-OH DZ) in patients CVHC showed absolute ( $p < 0.5$ ) or relative ( $P = 0.5$ ) Deficiency of vitamin D3 in half of patients ( $n = 16$ ).

Deficit 25-OH DZ found in-23% ( $n = 7$ ). This group of patients was observed to reduce the vitamin D3 in 2-3 times from the norm ( $p < 0.5$ ).

The relative deficiency of vitamin 25-OH DZ is found in the proportion of patients-27% ( $n = 8$ ).

In such patients decreased 25-OH DZ observed in the boundary limits (1.2-1.3 times from the norm) or was on the lower limits of the norm.

Normal level 25-OH DZ ( $> 20 \text{ ng/ml}$  or  $> 50 \text{ nmol/L}$ ) was celebrated in the rest of the patients, which amounted to almost half of the studied from the CVHC - 50% ( $n = 15$ ).

**Conclusions:** The content of the active form of vitamin D3 in patients with the disease has different meanings.

In the half of patients with a disease there is an absolute or relative deficit of content of 25-OH DZ, which allows to propose application of the active forms of vitamin D in the complex antiviral therapy CVHC, taking into account various positive influence of this Vitamin on metabolism and given its immunomodelling effect.

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## First experience with treatment of co-infection HIV / HCV in Slovakia

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The prevalence of anti-HCV antibodies in general population of Slovakia older than 15 years in 2002 was 1.52 %; chronic HCV infection is 0.67 %.

The rapid development and implementation of curative HCV therapy with direct-acting antivirals (DAA) is dramatically changing management for treating HIV / HCV co-infected patients. Prior to the approval of DAA, HCV treatment was low, especially for co-infected patients. Overall sustained virologic response (SVR) rates were lower for co-infected patients, particularly in the case of HCV genotype 1 infection. DAA therapy offers > 95% SVR for the vast majority of HCV-infected patients, regardless of HIV infection. Importantly, this equal opportunity for HCV cure among mono-infected and HIV / HCV co-infected patients is independent of previous treatment experience and presence of cirrhosis.

HIV may still be a factor when treating people with multiple predictors of poor response, such as genotype 1a prior null responders with cirrhosis. This may be a concern especially when pushing a regimen to its limits, for example shortening treatment to 8 weeks or less.

In addition, most hepatitis C treatment trials which have included people with co-infection, have enrolled people on ART with suppressed HIV and high CD4 counts may fare well, but more cautious we have to focus in those with less well-controlled HIV status.

We want to better understand how the availability of DAA has changed the management of treating patients with HCV, and specifically those co-infected with HIV. Elucidating the challenges and successes in treating HIV / HCV co-infected patients in the DAA era is urgently needed in order to strategize and advocate for optimized care delivery and outcomes for this special population.

We retrospectively recorded 34 infected HIV / HCV patients (31 men, 3 women) in Slovakia until 31st of Dec. 2017, (Bratislava 30 patients, Banská Bystrica 3 patients, Kosice 1 patient, Nitra and Martin 0 patients).

One patient died during 3K treatment (at week 36, F4) in 2012 due to hepatorenal failure. We recorded 1 death after 2K treatment - suicide and 2 deaths in cured by DAA patients (1 traffic accident, 1 stroke and cardiorespiratory failure). Without treatment 4 men spontaneously achieved HCV PCR RNA negative. Three men and two women were successfully treated with 2K treatment.

Relapses after 2K treatment - 4 men were subsequently treated by DAA with sustained virologic response (SVR12). Other 7 men (no previous treatment) were treated by DAA with achievement of sustained virological response (SVR12). Because of debts in health insurance or IDU we have not still treated 11 men and 1 woman due to national rules.

In the IFN-free DAA era, HIV/HCV co-infected patients in our data achieved a high rate of SVR. These data add to our treatment experience, and growing body of literature reporting that all-oral direct-acting antivirals (DAAs) for chronic hepatitis C virus (HCV) infection reported high response rates in HCV/HIV coinfection, similar to those obtained in HCV mono-infection.

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