Background document

Romania hepatitis meeting

Elimination of Viral Hepatitis in Romania: lessons learnt and the way forward

BUCHAREST, ROMANIA

17 May 2018

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VHPB Secretariat

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Content

This pre-meeting document contains general background information on Romania and the current hepatitis situation. Furthermore a list of selected abstracts/ references from a Pubmed MEDLINE search on different search terms.
This document should guide you in the preparation of the meeting, it should not be considered as complete literature review, but hopefully it will give an overview of what has been published on the topics of the meeting

1. General background

1.1 Romania – General information

(Source World factbook https://www.cia.gov/library/publications/resources/the-world-factbook/geos/en.html) and Wikipedia http://en.wikipedia.org/wiki)

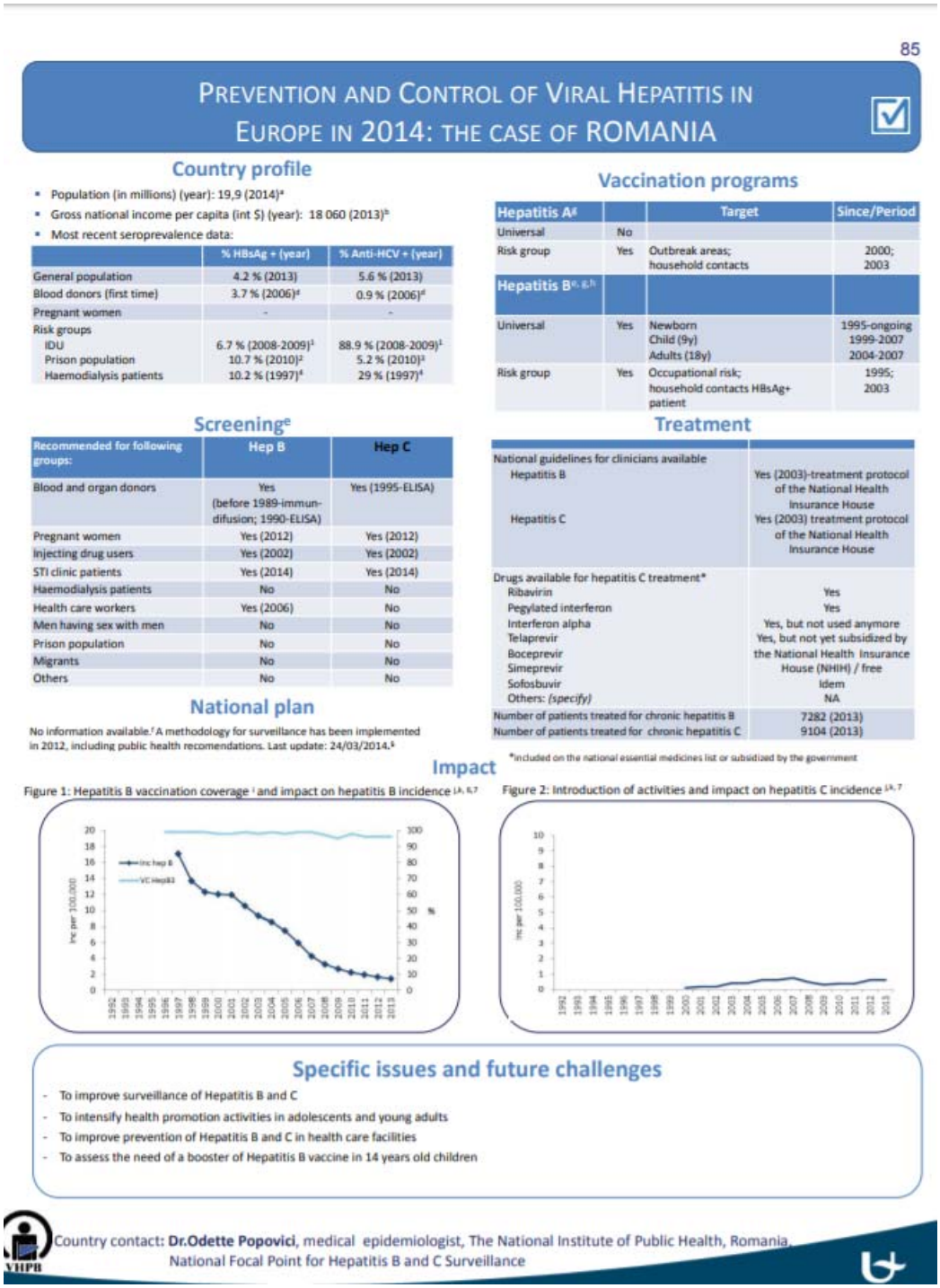
Romanian: is a sovereign state located at the crossroads of Central, Eastern, and Southeastern Europe. It borders the Black Sea, Bulgaria, Ukraine, Hungary, Serbia, and Moldova. It has an area of 238,397 square kilometres (92,046 sq mi) and a temperate-continental climate. With almost 20 million inhabitants, the country is the seventh most populous member state of the European Union. Its capital and largest city, Bucharest, is the sixth-largest city in the EU, with 2,106,144 inhabitants as of 2016

	Demographics data
Population	21,529,967 (July 2017 est.)
GDP (PPP) per capita	$24,000 (2017 est.)
GDP	$474 billion (2017 est.)
Unemployment rate	5.3% (2017 est.)
Population growth	-0.33% (2017 est.)
Birth rate:	8.9 births/1,000 population (2017 est.)
Death rate:	12 deaths/1,000 population (2017 est.)
Net migration rate	-0.2 migrant(s)/1,000 population (2017 est.)
Health expenditures	5.6% of GDP (2014)
Physicians density:	2.67 physicians/1,000 population (2013
Life expectancy at birth	total population: 75.4 years

1.2 Hepatitis in Romania

1.2.1 VHPB survey

VHPB survey on prevention and control of viral hepatitis in 53 European countries in 2014 – November 2014
((http://www.vhpb.org/files/html/Meetings_and_publications/Other_VHPB_documents/SURVEY2014.pdf)



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PREVENTION AND CONTROL OF VIRAL HEPATITIS IN EUROPE IN 2014: THE CASE OF ROMANIA

Country profile

- Population (in millions) (year): 19,9 (2014)[a]
- Gross national income per capita (int $) (year): 18 060 (2013)[b]
- Most recent seroprevalence data:

	% HBsAg + (year)	% Anti-HCV + (year)
General population	4.2 % (2013)	5.6 % (2013)
Blood donors (first time)	3.7 % (2006)[d]	0.9 % (2006)[d]
Pregnant women	-	-
Risk groups		
IDU	6.7 % (2008-2009)[1]	88.9 % (2008-2009)[1]
Prison population	10.7 % (2010)[2]	5.2 % (2010)[3]
Haemodialysis patients	10.2 % (1997)[4]	29 % (1997)[4]

Vaccination programs

Hepatitis A[g]		Target	Since/Period
Universal	No		
Risk group	Yes	Outbreak areas; household contacts	2000; 2003
Hepatitis B[e, g, h]			
Universal	Yes	Newborn Child (9y) Adults (18y)	1995-ongoing 1999-2007 2004-2007
Risk group	Yes	Occupational risk; household contacts HBsAg+ patient	1995; 2003

Screening[e]

Recommended for following groups:	Hep B	Hep C
Blood and organ donors	Yes (before 1989-immun-difusion; 1990-ELISA)	Yes (1995-ELISA)
Pregnant women	Yes (2012)	Yes (2012)
Injecting drug users	Yes (2002)	Yes (2002)
STI clinic patients	Yes (2014)	Yes (2014)
Haemodialysis patients	No	No
Health care workers	Yes (2006)	No
Men having sex with men	No	No
Prison population	No	No
Migrants	No	No
Others	No	No

Treatment

National guidelines for clinicians available	
Hepatitis B	Yes (2003)-treatment protocol of the National Health Insurance House
Hepatitis C	Yes (2003) treatment protocol of the National Health Insurance House
Drugs available for hepatitis C treatment*	
Ribavirin	Yes
Pegylated interferon	Yes
Interferon alpha	Yes, but not used anymore
Telaprevir	Yes, but not yet subsidized by the National Health Insurance House (NHIH) / free
Boceprevir	Idem
Simeprevir	NA
Sofosbuvir	
Others: *(specify)*	
Number of patients treated for chronic hepatitis B	7282 (2013)
Number of patients treated for chronic hepatitis C	9104 (2013)

*included on the national essential medicines list or subsidized by the government

National plan

No information available.[f] A methodology for surveillance has been implemented in 2012, including public health recomendations. Last update: 24/03/2014.[k]

Impact

Figure 1: Hepatitis B vaccination coverage [i] and impact on hepatitis B incidence [i,k,l,7]

Figure 2: Introduction of activities and impact on hepatitis C incidence [k,l,7]

Specific issues and future challenges

- To improve surveillance of Hepatitis B and C
- To intensify health promotion activities in adolescents and young adults
- To improve prevention of Hepatitis B and C in health care facilities
- To assess the need of a booster of Hepatitis B vaccine in 14 years old children

Country contact: **Dr.Odette Popovici**, medical epidemiologist, The National Institute of Public Health, Romania, National Focal Point for Hepatitis B and C Surveillance

1.2.2 WHO data

(source: http://www.who.int/gho/countries/rou.pdf?ua=1)

World Health Organization

Romania: WHO statistical profile

Basic statistics

Indicators	Statistics	Year
Population (thousands)	21699	2013
Population aged under 15 (%)	15	2013
Population aged over 60 (%)	21	2013
Median age (years)	39	2013
Population living in urban areas (%)	54	2013
Total fertility rate (per woman)	1.4	2013
Number of live births (thousands)	223.1	2013
Number of deaths (thousands)	255.5	2013
Birth registration coverage (%)	>90	2013
Cause-of-death registration coverage (%)	100	2010-2012
Gross national income per capita (PPP int $)	18060	2013
WHO region	European	2013
World Bank income classification	Upper middle	2013

Source:
Country statistics and global health estimates
by WHO and UN partners

For more information visit the Global Health Observatory
(http://www.who.int/gho/en/)

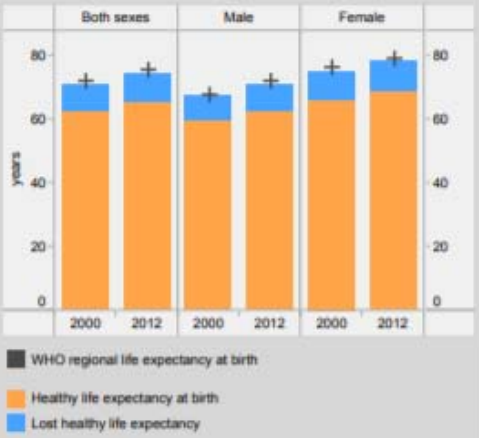
Last updated: January 2015

Life expectancy (years), 2012

		Country	WHO region	World Bank income group
Life expectancy	At birth	74	76	74
	At age 60	20	22	20
Healthy life expectancy	At birth	66	67	66

Life expectancy at birth for both sexes increased by 3 year(s) over the period of 2000-2012; the WHO region average increased by 4 year(s) in the same period.

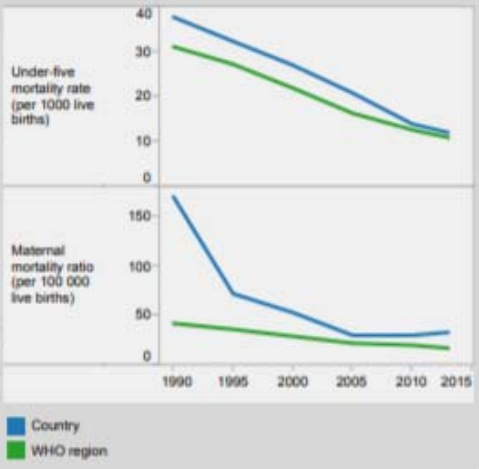
In 2012, healthy expectancy in both sexes was 9 year(s) lower than overall life expectancy at birth. This lost healthy life expetancy represents 9 equivalent year(s) of full health lost through years lived with morbidity and disability.



Millennium Development Goals (MDGs)

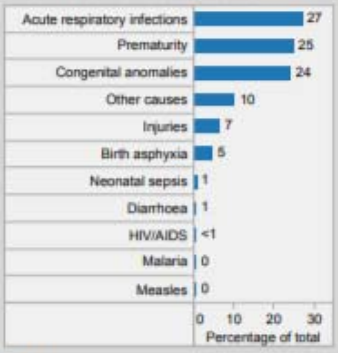
Indicators	Statistics Baseline*	Statistics Latest**
Under-five mortality rate (per 1000 live births)	38	12
Maternal mortality ratio (per 100 000 live births)	170	33
Deaths due to HIV/AIDS (per 100 000 population)	2.3	1.1
Deaths due to malaria (per 100 000 population)	0.0	0.0
Deaths due to tuberculosis among HIV-negative people (per 100 000 population)	9.5	5.4

*1990 for under-five mortality and maternal mortality; 2000 for other indicators
**2012 for deaths due to HIV/AIDS and malaria ; 2013 for other indicators

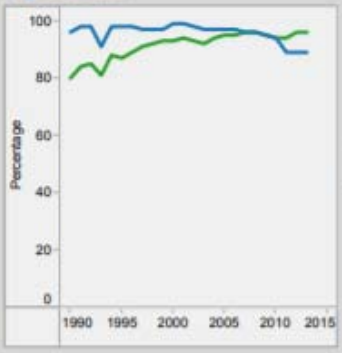


Romania: WHO statistical profile

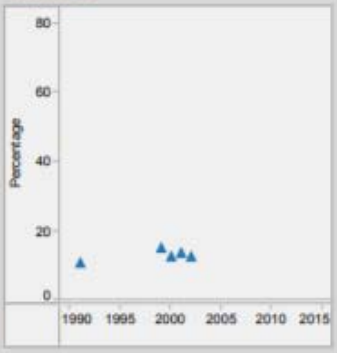
Distribution of causes of deaths in children under-5, 2013



DTP3 immunization among 1-year-olds



Children aged under-5 stunted

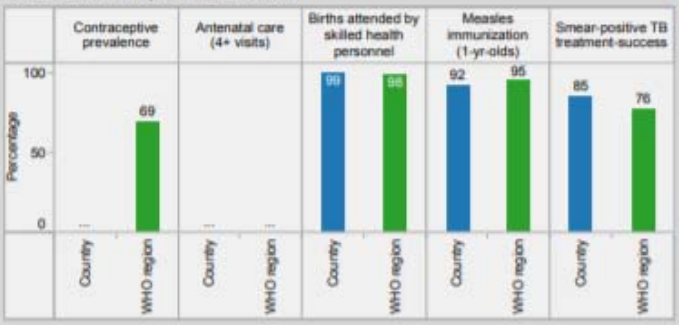


Country
WHO region

Source: Country statistics and global health estimates by WHO and UN partners
For more information visit the Global Health Observatory (http://www.who.int/gho/en/)
Last updated: January 2015

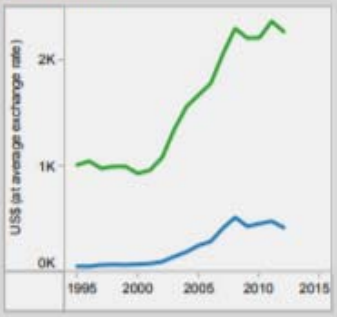
Utilisation of health services*

*Data refer to the latest year available from 2007.

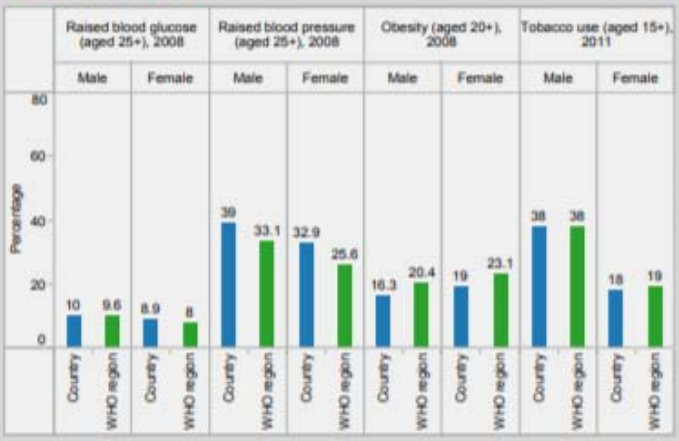


... Data not available or applicable.

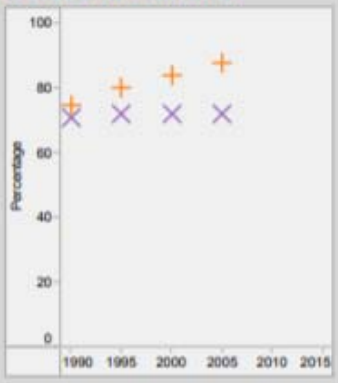
Per capita total expenditure on health



Adult risk factors



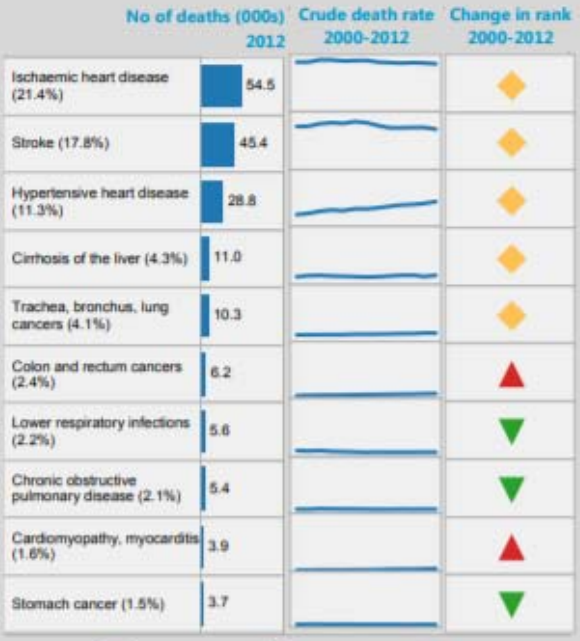
Population using improved water and sanitation



Romania: WHO statistical profile

Top 10 causes of death

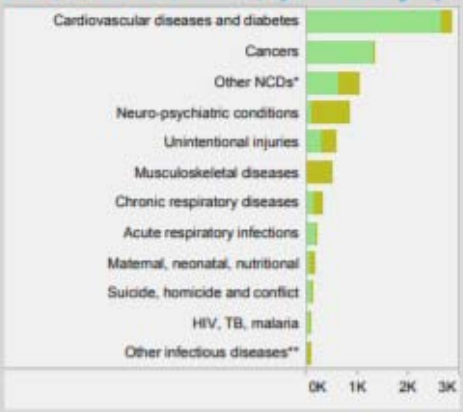
Ischaemic heart disease was the leading cause of death, killing 54.5 thousand people in 2012



Burden of disease, 2012

Disability-adjusted life years (DALYs) are the sum of years of life lost due to premature mortality (YLL) and years of healthy life lost due to disability (YLD).

DALYs, YLL and YLD (thousands) by broad cause group

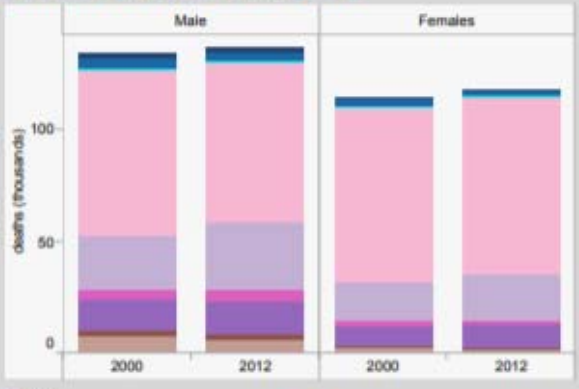


*Other noncommunicable diseases (NCDs) including non-malignant neoplasms; endocrine, blood and immune disorders; sense organ, digestive, genitourinary, and skin diseases; oral conditions; and congenital anomalies.

** Infectious diseases other than acute respiratory diseases, HIV, TB and malaria.

YLL YLD

Deaths by broad cause group



Causes

- HIV, TB, malaria
- Acute respiratory infections
- Other infectious diseases
- Maternal, neonatal, nutritional
- Cardiovascular diseases and diabetes
- Cancers
- Chronic respiratory diseases
- Other NCDs
- Suicide, homicide and conflict
- Unintentional injuries

Probability of dying, 2012

Probability of dying between relevant exact ages, for a person experiencing the 2012 age-specific mortality risks throughout their life.

Before age 15, all causes	Male	6%
	Female	5%
Before age 70, all causes	Male	57%
	Female	33%
Between ages 15 and 49, from maternal causes	Female	0%
Between ages 30 and 70, from 4 major noncommunicable diseases (NCDs)~	Both sexes	23%

~Cancers, cardiovascular diseases, chronic respiratory diseases and diabetes

Source: Country statistics and global health estimates by WHO and UN partners
For more information visit the Global Health Observatory (http://who.int/gho/mortality_burden_disease/en/)
Last updated: January 2015

WHO CISID database info (http://data.euro.who.int/cisid/?TabID=399572)

Hepatitis A

6011 - Hepatitis A - Number of cases											
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Romania	4982	3145		3487							

Hepatitis B Incidence (cases per 100 000 population)

9009 - Hepatitis B - Incidence (cases per 100 000 population)											
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Romania	4.29	3.4		2.35	2	1.59	1.33				

6011 - Hepatitis A - Number of cases											
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Romania	4982	3145		3487							

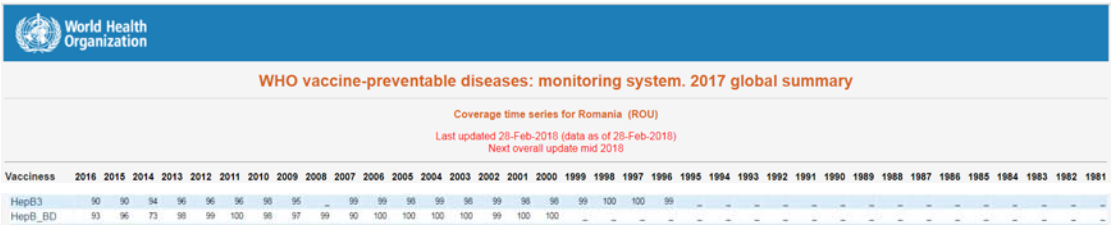
Hepatitis C Incidence (Cases per 100 000 population)

6015 - Hepatitis C - Incidence (cases per 100 000 population)											
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Romania	0.41	0.33		0.34							

6014 - Hepatitis C - Number of cases											
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Romania	88	72		72							

Immunization coverage

Source: http://apps.who.int/immunization_monitoring/globalsummary/coverages?c=ROU


World Health Organization

WHO vaccine-preventable diseases: monitoring system. 2017 global summary

Coverage time series for Romania (ROU)

Last updated 28-Feb-2018 (data as of 28-Feb-2018)
Next overall update mid 2018

Vacciness	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000	1999	1998	1997	1996	1995	1994	1993	1992	1991	1990	1989	1988	1987	1986	1985	1984	1983	1982	1981
HepB3	90	90	94	96	96	96	98	95	_	99	99	98	99	98	99	98	98	99	100	100	99	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_
HepB_BD	93	96	73	98	99	100	98	97	99	90	100	100	100	100	99	100	100	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_

1.2.3 ECDC

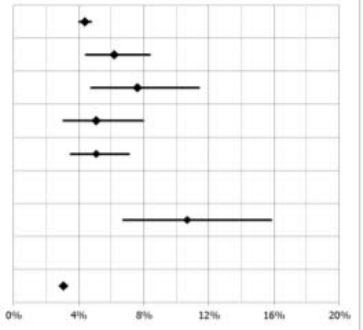
source: ECDC Systematic review on hepatitis Band C prevalence in the EU/EEA 2016. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/systematic-review-hepatitis-B-C-prevalence.pdf

3.25 Romania

HbsAg prevalence

Author (year of publication)	Population	Sampling period	Risk of bias score	Sample size	Sampling method	Sampling description	Age range
Gheorghe et al. (2013)	General population	2006–2008	6	13,127	Random	National cross-sectional population survey	18 to 69
Nardone et al. (2009)	General population	2002	3	629	Convenience	Residual lab samples representative of location and gender	16 to >40
Nardone et al. (2009)	General population	2002	3	276	Convenience	Residual lab samples representative of location and gender	16 to 39
Nardone et al. (2009)	General population	2002	3	353	Convenience	Residual lab samples representative of location and gender	>40
Nardone et al. (2009)	General population	2002	3	630	Convenience	Residual lab samples representative of location and gender	1 to 15
Nazare (2011)	Prisoners	2007–2010	1	197	Convenience	Single prison screening study	N/R
Council of Europe	First-time blood donors	2011	N/A	88,066	N/A	N/A	N/A

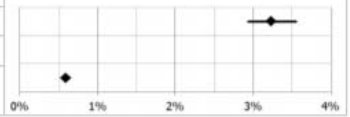
Author (year of publication)	Sampling period	Estimate (95% CI)	Sample size	Forest plot of estimates and 95% CI
General population				
Gheorghe et al. (2013)	2006–2008	4.4% (4.0–4.8)	13,127	
Nardone et al. (2009)	2002	6.2% (4.5–8.4)	629	
Nardone et al. (2009)	2002	7.6% (4.8-11.4)	276	
Nardone et al. (2009)	2002	5.1% (3.1–7.9)	353	
Nardone et al. (2009)	2002	5.1% (3.5–7.1)	630	
Prisoners				
Nazare (2011)	2007–2010	10.7% (6.7-15.8)	197	
First-time blood donors				
Council of Europe	2011	3.08% (2.97–3.19)	88,066	



Anti-HCV prevalence

Author (year of publication)	Population	Sampling period	Risk of bias score	Sample size	Sampling method	Sampling description	Age range
Gheorghe et al. (2010)	General population	2006–2008	6	13,146	Random (75% response)	National cross-sectional population survey	18 to 69
Council of Europe	First-time blood donors	2011	N/A	88,066	N/A	N/A	N/A

Author (year of publication)	Sampling period	Estimate (95% CI)	Sample size	Forest plot of estimates and 95% CI
General population				
Gheorghe et al. (2010)	2006–2008	3.2% (2.9–3.6)	13,146	
First-time blood donors				
Council of Europe	2011	0.59% (0.54–0.64)	88,066	



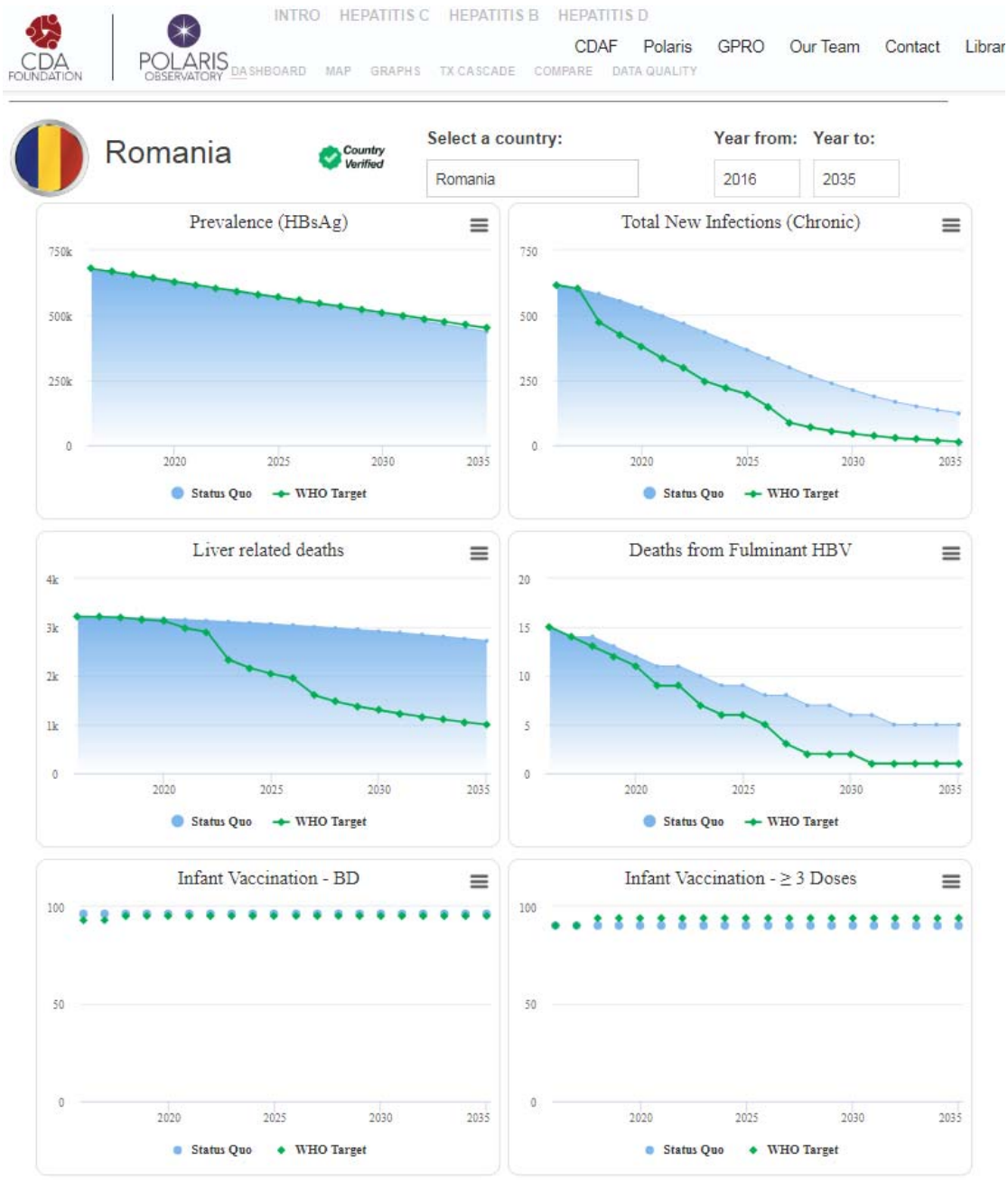
HBsAg and anti-HCV prevalence: PWID

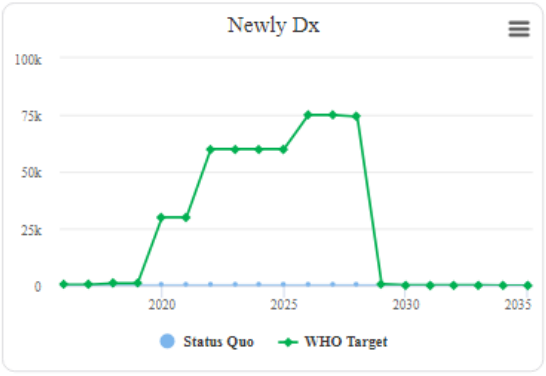
Source	Sampling period	Virological marker	Testing settings and sample size (if available)	Estimate (CI not available)
EMCDDA	2009	HBsAg	Street-based testing (one site) in Bucharest N=N/A	4.7%
EMCDDA	2009	Anti-HCV	Street-based testing (one site) in Bucharest N=N/A	82.9%

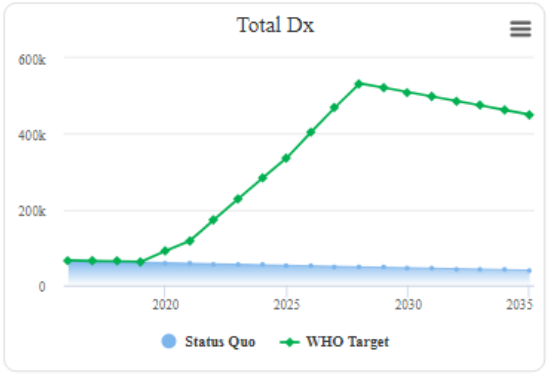
1.2.4 Centre of disease control - Polaris observatory

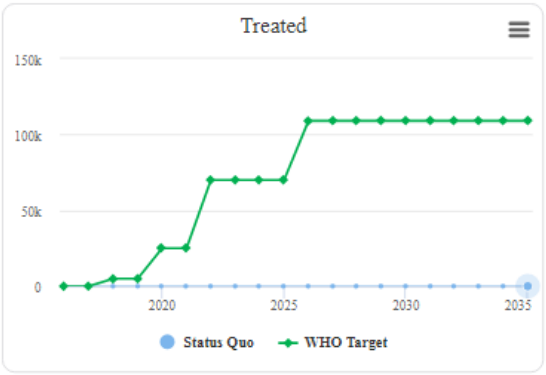
http://cdafound.org/polaris-hepB-dashboard/

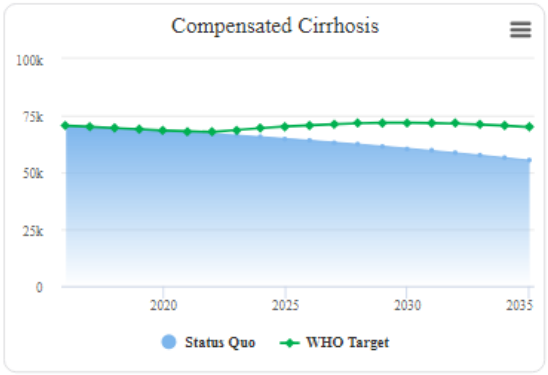
Hepatitis B

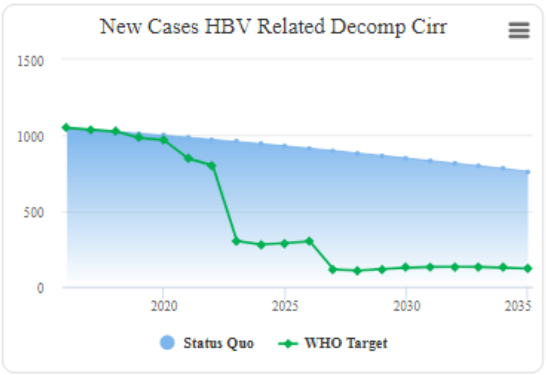


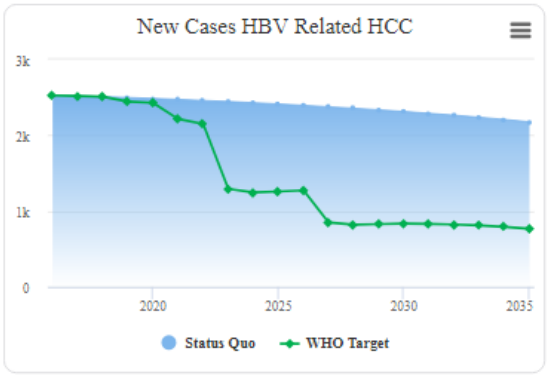

Newly Dx
100k
75k
50k
25k
0
2020
2025
2030
2035
Status Quo
WHO Target

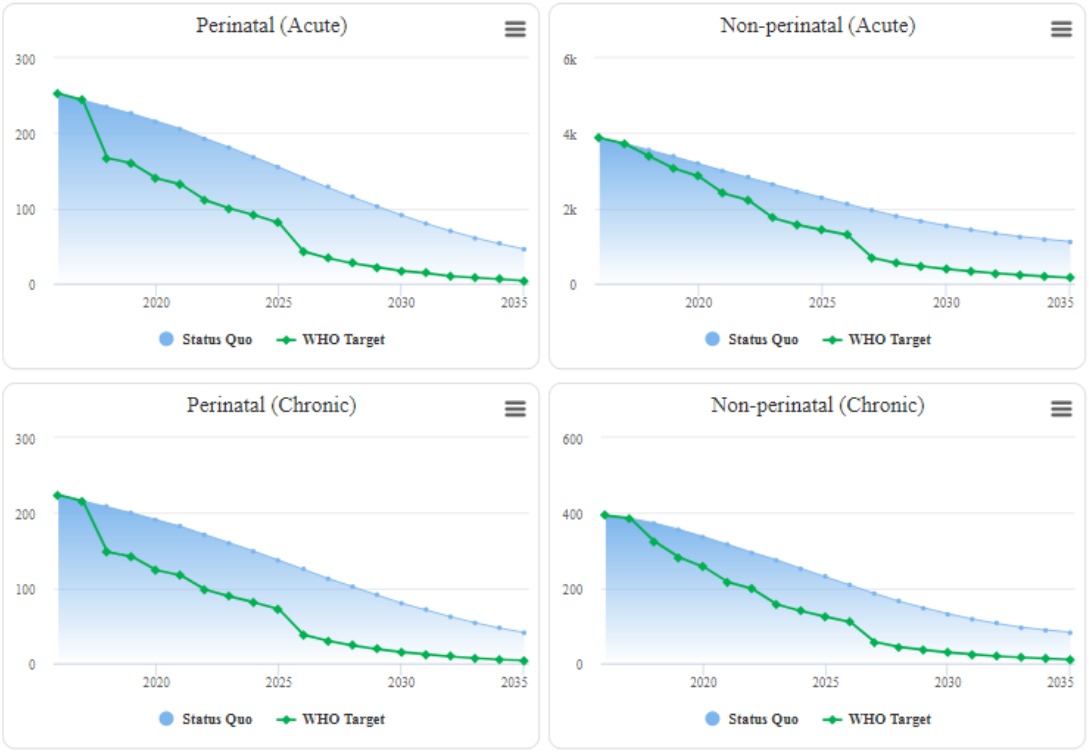

Total Dx
600k
400k
200k
0
2020
2025
2030
2035
Status Quo
WHO Target


Treated
150k
100k
50k
0
2020
2025
2030
2035
Status Quo
WHO Target


Compensated Cirrhosis
100k
75k
50k
25k
0
2020
2025
2030
2035
Status Quo
WHO Target


New Cases HBV Related Decomp Cirr
1500
1000
500
0
2020
2025
2030
2035
Status Quo
WHO Target


New Cases HBV Related HCC
3k
2k
1k
0
2020
2025
2030
2035
Status Quo
WHO Target



HBeAg+ rate = *9.70%*

Perinatal Prophylaxes Protocol

• Birth-dose is defined as first dose being administered ≤24 hours of birth. However, this definition is not universal but reported data on verified countries can be relied upon.

In the table below, vaccination rates in 2016 of reported data are shown (most recent figure shown)

	Birth Dose	≥ 3 Dose	HBIG	Treated
Infants born to HBsAg+ Mothers	*93%*	*90%*	*0%*	
Infants born to HBsAg- Mothers	*93%*	*90%*		
HVL/HBeAg+ Mothers	*93%*	*90%*	*0%*	*0%*

- *The Status Quo scenario describes the disease burden at the time of country meetings.*
- *The WHO Target scenario describes the integrated healthcare strategy proposed by World Health Organization which includes: a) 90% reduce in new infections, b) 90% increase in diagnosis rate c) 80% treatment eligibility and d) 65% reduction in HCV mortality in 2030, compared to status quo in 2030 [(1)].*

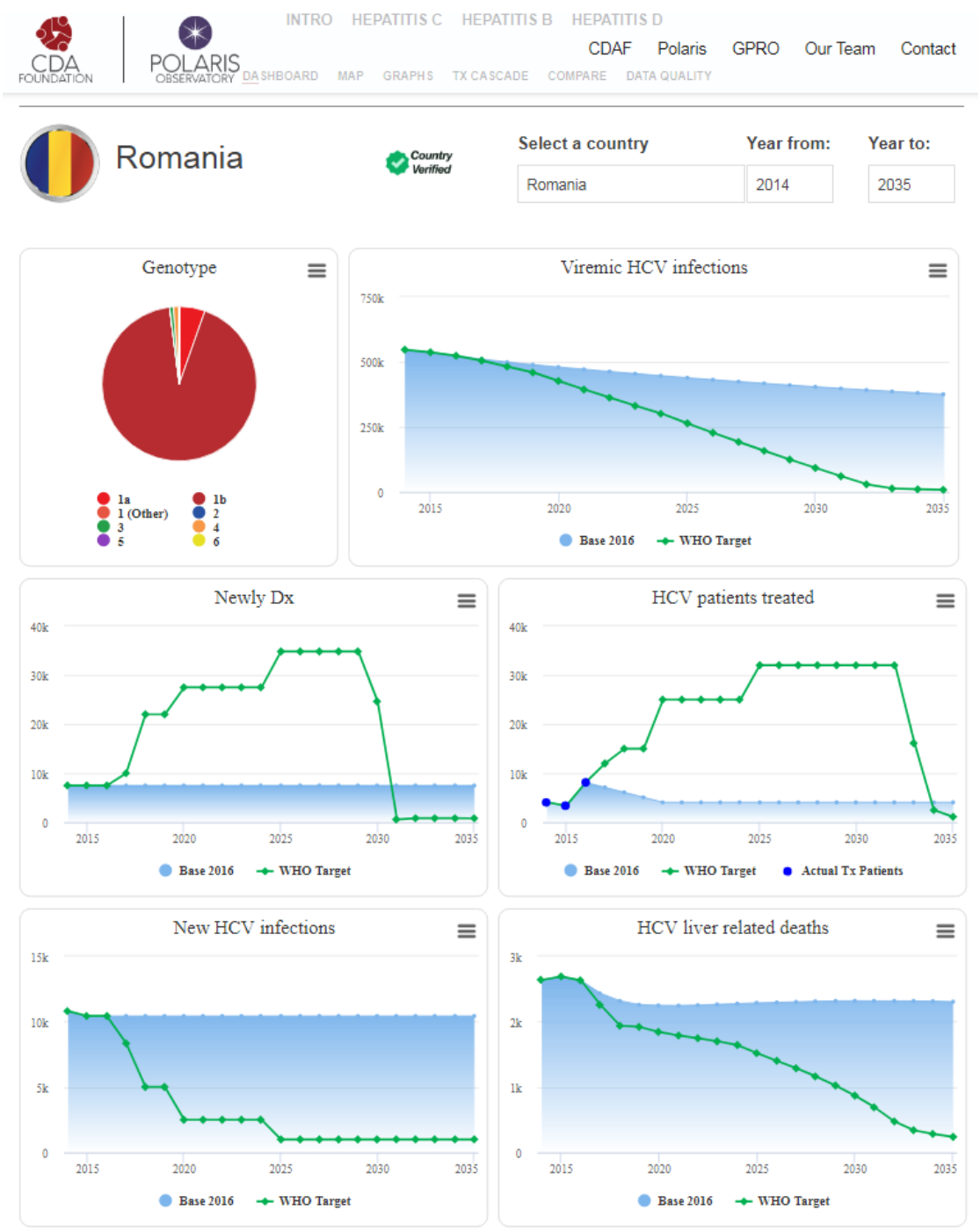
References:

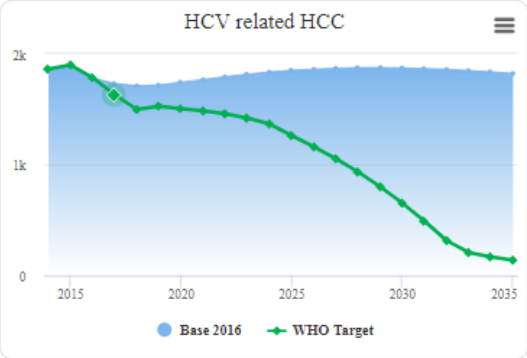
[(1)] WHO. Global Health Sector Strategies for Viral Hepatitis, 2016-2021, 22 April 2016.

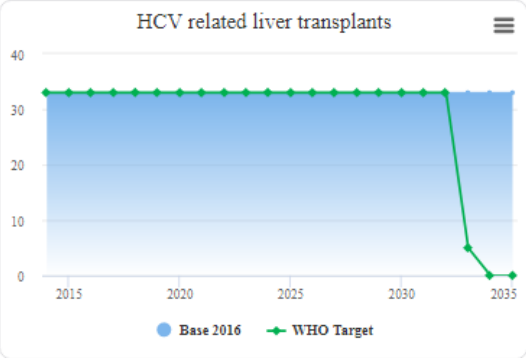
- *World Health Organization. Global Health Observatory Data Repository:Hepatitis B (HepB3). Accessed: 7/30/2017.*
- *World Health Organization. Global Health Observatory Data Repository:Hepatitis B (HepB1). Accessed 7/30/2017.*
- *World Health Organization. Global policy report on the prevention and control of viral hepatitis in WHO member states. 2013.*
- *PAHO. Comprehensive Family Immunization Unit. Annual country reports via PAHO-WHO/UNICEF Joint Reporting Forms; 2015*

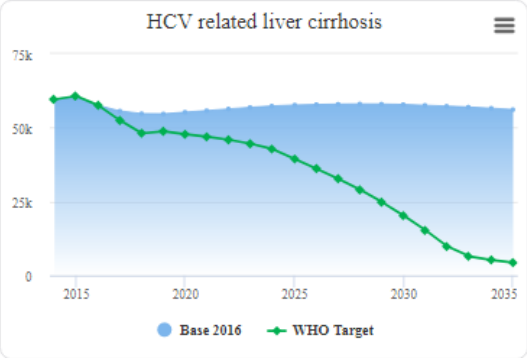
http://cdafound.org/polaris-hepC-dashboard/

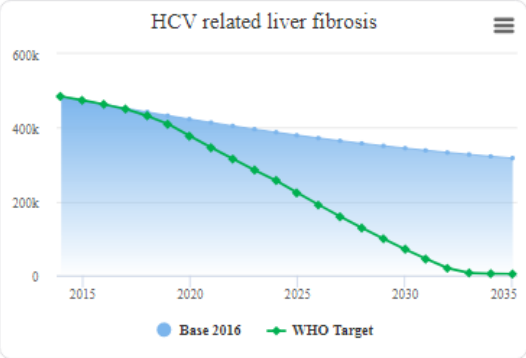
Hepatitis C











(1) WHO. Global Health Sector Strategies for Viral Hepatitis, 2016-2021, 22 April 2016.

2. Presentation related Information

Pubmed MEDLINE search on {(Hepatitis) AND (Romania*) } in all [Abstract/title]
and filter:'last 10 years' on was performed.
The references were manually sorted in the different subject in an EndNote database.
The references are listed by publication year (recent first).

2.1 Session 3 Hepatitis Situation in Romania

Session 3: Current hepatitis situation	
09:10 - 09:30	Overview of surveillance system and the epidemiology of hepatitis B & C ***Odette Popovici***

Prevalence and epidemiology

Hepatitis B

Dinu S, Tardei G, Ceausu E, Motoc A, Oprea C, Ungureanu E, . . . Oprisan G. **GENOMIC ANALYSIS OF HEPATITIS B VIRUS STRAINS INFECTING ROMANIAN PATIENTS**. Roumanian archives of microbiology and immunology. 2015;74(1-2):18-25.
Chronic hepatitis B is widespread and represents an important cause of morbidity and mortality due to the evolution to cirrhosis and hepatocellular carcinoma. This study was designed to improve the national laboratory surveillance of hepatitis B virus (HBV) infection, focusing on genomic analysis of isolates from Romanian patients. Sera from ten patients with HBV were collected and analyzed. Phylogenetic analysis was conducted on a DNA fragment spanning almost the entire genome. The occurrence of mutations was assessed for each open reading frame in the viral genome. Phylogenetic analysis revealed five isolates belonging to genotype A (subgenotype A2) and other five clustering with genotype D strains (subgenotype D1). Two patients treated with lamivudine were found to carry isolates harboring rtM204V lamivudine resistance mutation. An HBV isolate displaying a lamivudine complex resistance pattern, rtM204I in conjunction with rtL180M and rtA200V, was found in a lamivudine naive patient. All samples harbored sA105P substitution, usually found in HBIg therapy escape isolates. Three of the studied strains were simultaneously displaying T1753, T1762 and A1764 mutations which in vitro induce enhanced genome replication and reduction of HBeAg expression. The sequence obtained from a patient with decompensated liver cirrhosis presents a novel type of insertion consisting of nine nucleotides between positions 260 and 261 in the X gene. Despite the small number of samples, our findings suggest the need to determine the drug resistance pattern for each patient before taking a therapeutic decision and also highlight the necessity of knowing the real level of drug resistance among HBV strains circulating in Romania.

Gheorghe L, Csiki IE, Iacob S, Gheorghe C. **The prevalence and risk factors of hepatitis B virus infection in an adult population in Romania: a nationwide survey**. European journal of gastroenterology & hepatology. 2013;25(1):56-64.

AIM: The prevalence and risk factors of hepatitis B virus (HBV) infection in the general population in Romania are still largely unknown. METHODS: A nationwide cross-sectional survey among a Romanian adult population (18-69 years) was conducted during 2006-2008 using a stratified, multistage sampling design. A total of 17 600 individuals were enrolled randomly into the study; the prevalence of chronic HBV infection (HBsAg-positive and anti-HBcAb-positive samples) was assessed on 13 127 individuals (74.6%) and a history of previous HBV infection (anti-HBcAb-positive, but HBsAg-negative samples) was assessed on 12 470 individuals (70.5%). A questionnaire was used to collect information on the sociodemographic characteristics of the participants and the potential risk factors for HBV transmission. RESULTS: The overall prevalence rate of HBV chronic infection among all the participants tested was 4.4% (confidence interval: 4.0-4.8%), with significant differences (P=0.0001) between participants from the main geographical regions of residence (Moldavia 4.5%, Muntenia and Dobrogea 5.4%, and Transylvania and Banat 3.1%). The total prevalence of previous HBV infection of all participants was 27.0% (confidence interval: 26.2-27.8%). The proportion of individuals with previous HBV infection, as well as with chronic HBV infection, showed a statistically significant increasing trend with age. The personal history of blood or blood product transfusion, surgical interventions, tattooing, and alcohol consumption greater than 60 g/day were risk factors associated with both anti-HBcAb and HBsAg seropositivity. CONCLUSION: A prevalence rate of 4.4 and 27.0% for HBsAg and anti-HBcAb, respectively, represents a high figure within the European Union and a strong motivation for developing adequate strategies for prevention, active detection, and treatment of HBV infection in Romania.

Voiculescu M, Iliescu L, Ionescu C, Micu L, Ismail G, Zilisteanu D, . . . Pertache I. **A cross-sectional epidemiological study of HBV, HCV, HDV and HEV prevalence in the SubCarpathian and South-Eastern regions of Romania**. Journal of gastrointestinal and liver diseases : JGLD. 2010;19(1):43-8.
AIM: To evaluate the prevalence of HBV, HCV, HDV and HEV infections in populations with different categories of risk and the seroprevalence of HBV and HCV infections in subjects asking for a medical examination. METHOD: We conducted a cross-sectional, epidemiological study in 2,851 subjects from the SubCarpathian and South-Eastern Romania (including 17 counties, 34% of the country area and 42% of the population). The subjects were divided into four groups: controls (n=2,540, i.e. consecutive subjects asking for a medical examination), subjects with very low risk (students; n=44), with low risk (doctors and nurses; n=93) and with high risk for viral hepatitis (hemodialysis patients; n=174). All subjects were screened for HBsAg, antiHCV and ALT level. In populations at risk, antiHBs, HBeAg, antiHBe, antiHBc (IgG), HBV-DNA, HCV-RNA, antiHDV(IgG) and antiHEV(IgG) were also assessed. RESULTS: In controls, HBV seroprevalence was 5.59% and HCV seroprevalence 4.56%. The risk factors for HBV infection were: age, male gender and South-East region of Romania. The risk factors for HCV infection were: age, female gender, elevated ALT level and the South-East region of Romania. In the very low risk population HBV, HCV, HDV and HEV seroprevalence was: 2.27%, 0%, 0% and 12.5%, respectively. In low risk population the seroprevalence was 2.15%, 1.07%, 0% and 13.98%. In hemodialysis patients, HBV and HCV seroprevalence were 7.91%, respectively 39.26%. HCV-RNA was detectable in 20.69% cases. CONCLUSION: In the South and South-Eastern Romania the seroprevalence of viral hepatitis infections is intermediate, similar to other Romanian regions or the Balkans.

Nardone A, Anastassopoulou CG, Theeten H, Kriz B, Davidkin I, Thierfelder W, . . . Hatzakis A. **A comparison of hepatitis B seroepidemiology in ten European countries**. Epidemiology and infection. 2009;137(7):961-9.
To inform current and future vaccination strategies, we describe the seroepidemiology of hepatitis B virus (HBV) infection in ten representative European countries using standardized serology that allowed international comparisons. Between 1996 and 2003, national serum banks were compiled by collecting residual sera or by community sampling; sera were then tested by each country using its preferred enzyme immunoassays and testing algorithm, and assay results were standardized. Information on current and past HBV vaccination programmes in each country was also collected. Of the ten countries, six reported low levels (<3%) of antibodies against HBV core antigen (anti-HBc). Of the eight countries testing for HBV surface antigen (HBsAg), the highest prevalence was reported in Romania (5.6%) and in the remaining seven countries prevalence was <1%. Universal HBV vaccination programmes had been established in seven countries as recommended by the World Health Organization, but the seroprevalence of antibodies against HBsAg (anti-HBs) was lower than the reported vaccine coverage in three countries. Regular serological surveys to ascertain HBV status within a population, such as reported here, provide important data to assess the need for and to evaluate universal HBV vaccination

programmes.

Hepatitis C

Manuc M, Preda CM, Popescu CP, Baicus C, Voiosu T, Pop CS, . . . Oproiu A. **New Epidemiologic Data Regarding Hepatitis C Virus Infection in Romania**. Journal of gastrointestinal and liver diseases : JGLD. 2017;26(4):381-6.
BACKGROUND AND AIMS: Literature data suggest that HCV genotype-1b is present in 93-99% of the Romanian patients infected with hepatitis C virus (HCV). We present the genotyping tests recently performed on patients with HCV and advanced fibrosis eligible for the Direct-Acting Antiviral (DAA) therapy, as well as the prevalence of these cases across Romania. METHODS: The genotyping method was performed on 7,421 HCV patients with advanced fibrosis. The detection method was automatic real time PCR platform M2000 (Abbott). Every subject was introduced into a database including age, sex, county and address. RESULTS: Genotype 1b was almost exclusively present: 7,392/7,421 (99.6%). Genotype 1b patients were 19.6% from Bucharest, 49% were males, with a median age of 60 years. Genotype non-1b was encountered in 29/7,421 subjects (0.4%), 62% were males, 69% from Bucharest and the median age was 52 years. Most of the subjects (75%) were in the 6th and 7th age decade. The prevalence of these cases varied significantly across Romanian counties: the highest was in Bucharest (61.3/105), Bihor (47/105), Iasi (46/105) and Constanta (43/105), and the lowest in Ilfov (2.8/105), Harghita (3.7/105), Covasna (5.4/105) and Maramures (8.8/105) ($p<0.001$). CONCLUSIONS: Genotype 1b is encountered in 99.6% of patients with chronic hepatitis C and advanced fibrosis from Romania. The presence of genotypes non-1b is more common in Bucharest, in males and at a younger age. There are significant differences regarding the distribution of these cases across Romania: the highest rates are in Bucharest, Bihor, Iasi and Constanta.

Madalinski K, Zakrzewska K, Kolakowska A, Godzik P. **Epidemiology of HCV infection in Central and Eastern Europe**. Przeglad epidemiologiczny. 2015;69(3):459-64, 581-4.
AIM OF STUDY: is the estimation of prevalence of HCV infection in fourteen Central and Eastern European countries (CEEC). MATERIAL AND METHODS: This review describes the comparative data of persons possessing anti-HCV antibodies and persons with HCV viremia (% of population and number) in fourteen Central and Eastern European countries (CEEC). The study was performed according to data on the >/=15 years of age populations obtained from the Statistical Offices of the countries. RESULTS: The prevalence of anti-HCV in populations varied between 0.27 and 3.5%. The lowest values were reported from Kosovo, Hungary, Germany and the Czech Republic; 0.3-0.6%. The highest values of anti-HCV antibodies were noted in Latvia, Lithuania and Romania; 2.4, 2.85 and 3.5%, respectively. From eight countries the percentages of persons with HCV viremia were available (0.2-3.5%). CONCLUSIONS: The paper gives an estimate of the number of people infected with HCV in the general population of 8 countries from the CSEEC region. This number is approximately ~1.16 million.

Sultana C, Oprisan G, Szmal C, Vagu C, Temereanca A, Dinu S, . . . Ruta S. **Molecular epidemiology of hepatitis C virus strains from Romania**. Journal of gastrointestinal and liver diseases : JGLD. 2011;20(3):261-6.
BACKGROUND AND AIMS: A high seroprevalence of Hepatitis C Virus (HCV) infection has been reported in Romania, with limited data on the viral subtypes' distribution. In order to detect any changes in the genetic composition of the epidemic, a survey on the recent profile of circulating HCV genotypes was conducted. METHODS: 241 hepatitis C infected patients with active viral replication diagnosed between September 2004 - October 2008 were included in a retrospective study. Genotyping using commercial Line Probe Assay (Innogenetics) was confirmed by sequencing of Core PCR products followed by phylogenetic analysis. RESULTS: HCV subtype 1b was found in 92.6% of the samples, subtype 1a in 5.4 % of the samples, subtype 4a in 1.2%, and subtype 3a in 0.8% of the samples. Chronic hepatitis C infections with subtype 1b were found in women aged 40-60 years old with a history of blood transfusions received during surgical/obstetrical interventions. No geographical clustering was evident for HCV 1b sequences. The new emerging non-1b genotypes were detected mainly in younger patients with a history of intravenous drug use. The genetic distances among the HCV 1a strains are very homogeneous and small, with a high sequence identity with other European strains, suggesting the recent entrance of

this subtype in Romania from singular or limited sources of infection. CONCLUSION: The introduction of new HCV genotypes in Romania stimulates a continuous epidemiological surveillance, suggesting shifts in the transmission pathways and risk factors, with the possible emergence of recombinant strains in patients with multiple infections.

Cornberg M, Razavi HA, Alberti A, Bernasconi E, Buti M, Cooper C, . . . Zeuzem S. **A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel**. Liver international : official journal of the International Association for the Study of the Liver. 2011;31 Suppl 2:30-60.
BACKGROUND AND AIM: Decisions on public health issues are dependent on reliable epidemiological data. A comprehensive review of the literature was used to gather country-specific data on risk factors, prevalence, number of diagnosed individuals and genotype distribution of the hepatitis C virus (HCV) infection in selected European countries, Canada and Israel. METHODOLOGY: Data references were identified through indexed journals and non-indexed sources. In this work, 13,000 articles were reviewed and 860 were selected based on their relevance. RESULTS: Differences in prevalence were explained by local and regional variances in transmission routes or different public health measures. The lowest HCV prevalence (</= 0.5%) estimates were from northern European countries and the highest (>/= 3%) were from Romania and rural areas in Greece, Italy and Russia. The main risk for HCV transmission in countries with well-established HCV screening programmes and lower HCV prevalence was injection drug use, which was associated with younger age at the time of infection and a higher infection rate among males. In other regions, contaminated glass syringes and nosocomial infections continue to play an important role in new infections. Immigration from endemic countries was another factor impacting the total number of infections and the genotype distribution. Approximately 70% of cases in Israel, 37% in Germany and 33% in Switzerland were not born in the country. In summary, HCV epidemiology shows a high variability across Europe, Canada and Israel. CONCLUSION: Despite the eradication of transmission by blood products, HCV infection continues to be one of the leading blood-borne infections in the region.

Gheorghe L, Csiki IE, Iacob S, Gheorghe C, Smira G, Regep L. **The prevalence and risk factors of hepatitis C virus infection in adult population in Romania: a nationwide survey 2006 - 2008**. Journal of gastrointestinal and liver diseases : JGLD. 2010;19(4):373-9.
AIMS: This study was aimed at determining the seroprevalence of hepatitis C virus (HCV) infection in Romania and the possible risk factors and modality of HCV transmission. METHODS: A nationwide cross-sectional survey among the adult population was conducted between 2006-2008 in Romania through a population multicenter stratified random cluster sampling. Serum samples from 13,460 subjects were tested with a 3rd generation ELISA and a standardized questionnaire concerning the socio-demographic characteristics and potential risk factors was used. RESULTS: The prevalence rate of HCV infection in Romanian adult population was 3.23% with significant differences between the main geographical regions (Moldavia 4.25%, Wallachia & Dobrogea 3.35% and Transylvania & Banat 2.63%), as well as between different counties (maximum 7.19%, minimum 0.56%). Overall participation rate to the survey of the selected subjects was 74.69%. Risk factors for HCV infection were: blood/blood products transfusions (p=0.0001), previous surgery (elective and emergency, p=0.0001 and p=0.043, respectively), frequent hospitalizations (p=0.0001), injections at home (p=0.0001), accidents/trauma (p=0.0001), occupational hazard related to blood exposure (p=0.025), intravenous drug administration (p=0.002), a partner chronically infected with HCV/hepatitis B virus (HBV) (p=0.046), first sexual intercourse <18 years (p=0.019), familial exposure to HCV/HBV infection (p=0.001) or to chronic HBV/HCV liver disease (p=0.001), personal history of chronic HBV infection (p=0.001). HCV RNA positivity was detected in 91% of the anti HCV positive subjects. CONCLUSIONS: Overall HCV prevalence in Romania is 3.23%. Both nosocomial and non-nosocomial routes are implicated as risk factors for HCV infection.

Oprisan G, Szmal C, Dinu S, Oprisoreanu AM, Thiers V, Panait M, . . . Claici C. **Comparative methods for genotyping hepatitis C virus isolates from Romania**. Roumanian archives of microbiology and immunology. 2009;68(3):151-7.
Accurate genotyping of hepatitis C virus (HCV) has clinical implications for treatment orientation and epidemiological impact in tracing the contamination sources. The aim of the study was to compare a genotyping assay by restriction fragment length polymorphism (RFLP) in the HCV 5'untranslated region (5'UTR) with sequencing in the 5'untranslated and NS5B regions. One hundred and three samples, collected between 2004 and 2006 from chronically infected patients with HCV, were tested with the

5'UTR and NS5B protocols. Of the total number of the samples tested by the 5'UTR-RFLP assay (n=103) the HCV subtype could be inferred by this method for 92 samples, by 5'UTR sequencing for 16 samples out of 23 tested (n=23) and by using the NS5B sequencing for all the samples tested (n=34). Our results showed that the HCV genotype distribution in Romania is: 1b--86.4%, 1a--10.7% and 4a--2.9%. In conclusion, RFLP screening in the 5'UTR is a convenient method for HCV genotyping and discrimination between 1b and non-1b genotypes but has a poor resolving power for subtyping and evaluation of the transmission routes. Sequencing in NS5B region is more adapted than RFLP and sequencing in 5'UTR for subtyping and epidemiological investigation.

Grigorescu M. **HCV genotype 1 is almost exclusively present in Romanian patients with chronic hepatitis C**. Journal of gastrointestinal and liver diseases : JGLD. 2009;18(1):45-50.
AIM: To investigate the HCV genotype distribution in Romania in the first national study, to establish the correlations with epidemiological, biochemical, virological and histological features and to compare our results with those from neighboring countries. PATIENTS AND METHODS: Two distinct groups of patients and two methods were used: 153 patients in the frame of ACHIEVE study with genotyping and subtypes determination (Versant HCV genotype 2.0 assay) and 461 patients in the frame of an Epidemiological National Multicenter Study having only genotype determination with a commercial kit (Roche Molecular System). Epidemiological, biochemical, virological and histological features were investigated only in the ENMS group. RESULTS: Genotype 1b was found in 93.46% (ACHIEVE study) and genotype 1 (without subtype identification) in 99.13% of patients (ENMS study). Percutaneous routes of transmission were found in 85.9% of cases. The prevalence of HCV infection increased with age. A high viral load (> or = 600,000 IU/ml) was found in 67.9% of patients, especially those older than 40 years. Significant fibrosis > or = F2 was present in patients older than 40 years (70.9%). There were no correlations between HCV-RNA levels and histological features or between ALT levels and METAVIR activity or fibrosis scores. A similar homogeneity of HCV genotype distribution has been reported for Moldavia (96%) and Hungary (94.5%). CONCLUSIONS: Type 1 HCV genotype was found almost exclusively in Romanian patients with chronic hepatitis C by two different methods of investigation. The pattern showed by this distribution in Romania and some neighboring countries suggests an epidemic profile of HCV infection.

Gheorghe L, Iacob S, Csiki IE. **Prevalence of hepatitis C in Romania: different from European rates?** Journal of hepatology. 2008;49(4):661-2; author reply 3.

Hepatitis B & C

Popovici O, Molnar GB, Popovici F, Janta D, Pistol A, Azoicai D. **A Seroprevalence Study of Hepatitis B and C Virus Infections in a Hospitalized Population in Romania, an Opportunity for a Better National Prevention and Control Strategy**. Journal of gastrointestinal and liver diseases : JGLD. 2016;25(1):25-32.
BACKGROUND AND AIMS: The most recent prevalence data for hepatitis B virus (HBV) infection in Romania came from an ESEN 2 study (2002), and from a Romanian population-based study performed in 2008. Most of the previous studies were regional and performed in specific groups (blood donors, pregnant women, institutionalized people, etc) and had limited representativeness at the national level, both for HBV and hepatitis C virus (HCV) infection. The scarcity of prevalence data for HBV and HCV infection coming from the routine surveillance was also considered. The aim of our study was to obtain overall and age group specific estimates of the prevalence of HBV and HCV infections markers in Romania, in order to recommend evidence-based public health interventions. The main outcome was the proportion of persons with HBV, HCV and HBV+HCV infection markers, overall and by age group and gender. METHODS: Our seroprevalence study ensured national representativeness for the targeted hospitalized population. A prospective collection of serum samples in hospital laboratories was completed between September and November 2013, using a systematic sampling. The study respected the confidentiality of personal data. We calculated the sample size using EpiInfo7 and used Z test - Two-tailed probability for statistical significance. RESULTS: The overall prevalence data estimated in our study were HBc Ab 28%, HBs Ag 4.2%, HBs Ab regardless of titer 64.1%, HBs Ab in titer of at least 10 mUI/ml and negative HBc Ab 17.5%; HCV Ab 5.6%; HBc Ab and HCV Ab 2.8%, as markers of double infection. CONCLUSION: The overall prevalence data estimated in our study for HBs Ag (4.2%) and HCV Ab (5.6%)

correspond to a medium endemicity based on the WHO criteria. The estimated prevalence of HBV and HCV infection markers in the study population should represent an opportunity for a better national prevention and control strategy.

Azoicai AN, Moraru E, Duca E, Azoicai D. **[Trends in epidemiological evolution of viral hepatitis B and C , in children , Romania and Iasi county between 1990-2009]**. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2010;114(3):731-7.
UNLABELLED: Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the frequent causes of acute and chronic hepatitis worldwide and the leading causes for hepatic cirrhosis and liver cancer. There is a distinct geographical variation in VHB and VHC incidence in adult and child. AIM: To assess the evolution trend of VHB and VHC incidence in child, in Romania and Iasi County, during the last two decades. MATERIAL AND METHODS: Data were obtained using information from the Reporting National System for acute viral hepatitis A, B, and C, from various geographical areas of Romania. Some systematical errors of information were identified, without significant influence of results and conclusions. RESULTS: Results highlighted an incidence peak of VHB in Romania, in 1989, and in Iasi county, in 1991 (43.1, respectively 41.2 per thousand inhabitants). The VHB incidence trend decreased after the implementation of vaccination programme, especially in children < 4 years old. CONCLUSIONS: The study remarked the necessity of viral hepatitis surveillance programme continuity in Romania and the importance of prevention measures including, for VHB, an optimal vaccination.

Session 3: Current hepatitis situation

09:30 - 09:50 Disease Burden in Romania: chronic viral hepatitis and liver disease in Romania

Adrian Streinu Cercel

Burden of disease

Luca AS, Dorobat C, Ursu RG, Luca MC, Vata A, Iancu LS. **Epidemiological and laboratory features of chronic hepatitis B cases in the interval 2010-2013**. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2014;118(2):479-84.
UNLABELLED: HBV virus infection is an important public health problem because of its huge transmission potential, and severe evolution to cirrhosis or liver cancer. AIM: Analysis of the epidemiological and laboratory features of chronic hepatitis B virus infection. MATERIAL AND METHODS: The patients with chronic hepatitis B admitted to the "Sf. Parascheva" University Hospital for Infectious Diseases in the interval: January 1st, 2010 - December 31st were analyzed. RESULTS: Patients age was 18 to 66 years with a prevalence of middle-aged males. Most patients came from urban areas. Alanine aminotransferase (ALAT) levels were elevated, without significant differences between HBeAg-positive and HBeAg-negative patients, the elevated ALAT levels being associated with the increased prevalence of fibrosis. HBeAg-positive patients had viral loads above the threshold of 2,000/l in 34 cases (89.5%), and below 2,000 IU/l in only 10.5% of cases, and the majority (88%) of HBeAg-negative patients presented high viral load levels. The prevalence of stage F2-F4 liver fibrosis was 63.4% in the HBeAg-negative patients with viremia > 25,000 IU/l compared to 55.2% in the HBeAg-positive patients. The correlation between the level of viral load and fibrosis shows that there are significant differences between viremia and the status of HBeAg-positive or negative patients. Increased viral load was correlated with increasing prevalence of fibrosis, significant in HBeAg-negative patients, and the increasing fibrosis prevalence was correlated with low viral load. CONCLUSIONS: The correlation between viral load and fibrosis shows that there are significant differences between viral load and the status of HBAg-positive or negative patients.
Pascu O, Gheorghe L, Voiculescu M, Ceausu E, Mateescu B. **How severe is chronic hepatitis with HCV genotype 1b? A study of 1,220 cases on the waiting list for antiviral therapy in Romania**. Journal of gastrointestinal and liver diseases : JGLD. 2011;20(1):51-5.

INTRODUCTION: Chronic HCV infection represents a public health problem in Romania, with a prevalence of 3.23-4.56%, and more than 5,000 patients on the waiting lists for antiviral therapy. AIM: To perform an evaluation of the severity of chronic HCV infection genotype 1b, and a quantification of patients with a low viral load, in order to quantify the number of patients who may be considered for shortened treatment duration. MATERIAL: Histological assessment and viral load were performed in 1,220 consecutive patients from the waiting list for antiviral therapy in 2009. The severity of chronic hepatitis was assessed by histological evaluation (the necrotic-inflammatory index - Metavir and the fibrosis score - Metavir). Viral load was measured by PCR and 400,000 UI/ml and 600,000 UI/ml were defined as thresholds for low versus high viral load We assessed the influence of age, sex, and viral load on necro-inflammatory activity and fibrosis. RESULTS: The mean age of the patients included was 48 +/- 10.69 years and females predominated (58%). Many of them (60%) were in stage F3, with a high potential for disease progression in the next 10 years (necro-inflammatory activity was moderate to severe in over 90%). Almost half of the patients had low viral load, below 600,000 copies/ml. The viral load was significantly associated with the age ($p < 0.001$) and sex ($p < 0.001$) of the patients. CONCLUSION: Chronic HCV hepatitis in patients on the waiting lists for antiviral therapy in Romania has a high severity with important predictable consequences on the duration of life, complications and treatment costs. The strategy of shortening the duration of treatment would be beneficial for almost 50% of the patients.

Constantin CV, Streba CT, Rogoveanu I, Nita-Stefanescu L, Ionescu AG. **Cirrhosis and Chronic Viral Hepatitis as Risk Factors for Hepatocellular Carcinoma: Romanian Single-clinic Experience**. Maedica. 2010;5(4):265-70.
INTRODUCTION: Hepatocellular carcinoma (HCC) represents the fifth most common cancer worldwide, while being the third leading cause of death by cancer. The primary risk factor for HCC seems to be liver cirrhosis. A large majority of these patients have a history of viral hepatitis. MATERIALS AND METHODS: We selected a study lot consisting of 244 patients diagnosed with HCC, admitted between 2006 and October 2009 in the Emergency County Hospital of Craiova, Romania along with an age and gender matched control group, consisting of patients with no history of HCC or other malignancies. We interviewed all subjects regarding their alcohol consumption and background environment. All subjects underwent hepatitis B surface antigen (Hbs Ag) and anti-HCV antibodies (Anti-HCV Atb) serological determinations. RESULTS: The study group consisted of 148 males and 96 females. Liver cirrhosis (LC) was present in 84% of the study lot, 10% associated viral B hepatitis (HBV) and 6% viral C hepatitis (HCV), with no signs of LC. We found LC to be an important risk factor for HCC (RR 6.53, CI 95% 3.18-13.38). The RR and 95% CI of HCC were 4.51 (2.48-8.21) for HbsAg positivity. We noticed a strong correlation (Chi-square test, $p<0.001$) between the rural environment and the association with LC. HVB was also more present in patients coming from rural areas ($p < 0.01$). Alcohol intake was present in 89% of the whole lot, being more correlated with the presence of LC as well as with HbsAg positivity (RR 9.165, CI 95% 4.43-18.92). CONCLUSION: Cirrhosis proved to be the primary risk factors for HCC. We underline the fact that HCC was found to be directly associated with viral hepatitis, without evident LC. Further studies are needed in order to establish if intensified HCC screening, especially in rural areas, is required in patients with newly diagnosed viral hepatitis. The increased prevalence of HBV infections might encourage HBV vaccinations as an efficient tool to prevent HCC.

Session 3: Current hepatitis situation

09:50– 10:10	Hepatitis case finding – Screening programmes and cascade of care in Romania ***Anca Trifan***

Screening and case finding:

Schweitzer AM, Bogdan M, Corduneanu A, Ciocea I. **Role of pretest counseling sessions on increasing subjective knowledge about HIV and hepatitis transmission among the beneficiaries of a free of charge, voluntary counseling and testing program in Constanta, Romania**. HIV medicine. 2018;19 Suppl 1:66-70.
OBJECTIVES: To describe the characteristics of clients who enrolled into of an opt-in, HIV, HBV & HCV Voluntary Counseling and Testing Program in Dobrogea Region, Romania (VCT) and to identify the utility of the pre-test counseling sessions in increasing subjective perception regarding transmission knowledge for the clients attending the VCT program. METHODS: Cross sectional data collection, between August 2015 and September 2016. Sociodemographic and behavioral information were collected for the clients who enrolled at two Baylor centers. Counselors were trained regarding the delivery of standardized information during the session, to reduce variation. After the pre-test session clients evaluated the subjective level of knowledge (SK) increase regarding viral transmission. RESULTS: 3065 clients were screened at the two centers and completed the SK increase assessment after the pre-test session. About 9% of all persons tested had reactive results to any of the infections in the context of high exposure risks for 62% and low hepatitis B vaccination rates (8%). 78% of attendees perceived that their knowledge regarding HIV and viral hepatitis transmission increasing with more than 60% as the result of the pretest counselling; more information was gained about hepatitis transmission compared with HIV. CONCLUSION: Cumulative prevalence in Dobrogea community is high. The NGO-run VCT program is helping the healthcare system to efficiently screen for undiagnosed HIV and hepatitis cases. Pre-test counselling is directly contributing to increasing SK among attendees. Routine HIV and hepatitis integrated pre-test counseling should be considered as a good-practice even in settings where it is not compulsory by law.

Hatu G, Brumboiu MI, Gorgan IN, Bocsan IS. **Romanian blood donors screening: is it really necessary and/or mandatory?** Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2013;117(3):741-6.
Blood services are required to provide the safest possible products, but no transfusion can ever be totally free of the risk of transfusion transmissible infections (TTI). Over the past decade, the risk of TTI through transfusion has been reduced (e.g. 1 in 300 000 for HBV to 1 in 2 million for HIV). With the introduction in 1999 of sensitive and expensive nucleic acid testing (NAT) technology in some countries, the disease transmission rate and the window period have been significantly reduced, but a remaining concern is the chance that a blood donor will be infected and not detected by such tests. To obtain safe blood and blood components it is important to ensure that the donors are healthy and free from TTI by using a donor selection procedure meticulously made, using a donor questionnaire to assess donor health and safety and for reducing the risk of transmission of infection, in particular for infections for which no suitable screening tests are available. In Romania the prevalence of TTI among donor population is high in comparison with other European Union (EU) countries. This may require significant improvements in the screening process of both donors and donations to minimize the infectious risk.

Diagnostics

Ricco G, Popa DC, Cavallone D, Iacob S, Salvati A, Tabacelia D, . . . Brunetto MR. **Quantification of serum markers of hepatitis B (HBV) and Delta virus (HDV) infections in patients with chronic HDV infection**. Journal of viral hepatitis. 2018.
The interplay between hepatitis B (HBV) and Delta (HDV) viruses is complex and not always characterized during chronic HDV infection. We assessed the clinical usefulness of new quantitative assays for HBV and HDV serum markers in a retrospective cross-sectional study. Sera obtained from 122 HDV-genotype-1 and HBV-genotype-D co-infected, anti-HIV-negative patients [71 males; median age 49.8 (21.7-66.9) years], recruited consecutively in two geographic areas (Italy 69 patients, Romania 53) with different HBV and HDV epidemiology, were tested for HBsAg, HBV-DNA, HBcrAg, total anti-HBc, HDV-RNA, IgM and total anti-HDV using quantitative assays. Cirrhosis, that showed comparable prevalence in the two cohorts, was diagnosed in 97 of 122 (79.5%) patients. At multivariate analysis, cirrhosis was associated

with lower total anti-HBc/IgM-anti-HDV ratio (OR 0.990, 95%CI 0.981-0.999, P=0.038), whereas disease activity was associated with higher total anti-HDV (OR 10.105, 95% CI 1.671-61.107, P=0.012) and HDV-RNA levels (OR 2.366, 95% CI 1.456-3.844, P=0.001). HDV-RNA serum levels showed a positive correlation with HBV-DNA (rho=0.276, P=0.005), HBsAg (rho=0.404, P<0.001) and HBcrAg (rho=0.332, P<0.001). The combined quantitative profiling of HBV and HDV serum markers identifies specific patterns associated with activity and stage of chronic hepatitis D (CHD). HDV pathogenicity depends on the underlying active HBV infection in spite of the inhibition of its replication. HDV-RNA, IgM anti-HDV, total anti-HDV, total anti-HBc, HBsAg and HBcrAg serum levels qualify for prospective studies to predict progressive CHD and identify candidates to antiviral therapy.

Oprisan G, Szmal C, Dinu S, Oprisoreanu AM, Thiers V, Panait M, . . . Claici C. **Comparative methods for genotyping hepatitis C virus isolates from Romania**. Roumanian archives of microbiology and immunology. 2009;68(3):151-7.
Accurate genotyping of hepatitis C virus (HCV) has clinical implications for treatment orientation and epidemiological impact in tracing the contamination sources. The aim of the study was to compare a genotyping assay by restriction fragment length polymorphism (RFLP) in the HCV 5'untranslated region (5'UTR) with sequencing in the 5'untranslated and NS5B regions. One hundred and three samples, collected between 2004 and 2006 from chronically infected patients with HCV, were tested with the 5'UTR and NS5B protocols. Of the total number of the samples tested by the 5'UTR-RFLP assay (n=103) the HCV subtype could be inferred by this method for 92 samples, by 5'UTR sequencing for 16 samples out of 23 tested (n=23) and by using the NS5B sequencing for all the samples tested (n=34). Our results showed that the HCV genotype distribution in Romania is: 1b--86.4%, 1a--10.7% and 4a--2.9%. In conclusion, RFLP screening in the 5'UTR is a convenient method for HCV genotyping and discrimination between 1b and non-1b genotypes but has a poor resolving power for subtyping and evaluation of the transmission routes. Sequencing in NS5B region is more adapted than RFLP and sequencing in 5'UTR for subtyping and epidemiological investigation.

Session 3: Current hepatitis situation

10:10 – 10:30 Hepatitis in Risk groups

Simona Ruta

Risk behavior

Nazare C, Girleanu I, Cojocariu-Salloum C, Trifan A. **[Prevalence of chronic hepatitis B virus (HBV) infection in closed communities and risk behaviour]**. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2011;115(2):325-30.
AIM: To determine the prevalence of chronic hepatitis B virus infection in closed communities and the relations between the risk behavior and VHB infection. MATERIAL AND METHODS: In this study we included persons deprived of personal freedom at Bacau Correctional Facility. The subjects filled out a questionnaire, which contained identification and epidemiologic data (detention history, evaluation of the risk factors), as well as an informed consent. All subjects were tested for HBsAg. RESULTS: According to the performed tests, the general prevalence of hepatitis B and C in this correctional facility was 15.34%, with a prevalence of hepatitis B of 10.74%. Although these figures show a higher prevalence in this population than within the general population, they are lower than the figures reported in correctional facilities from other countries. CONCLUSIONS: The results confirm the fact that the population in correctional facilities is at high risk for hepatitis B infection, the ways of disease transmission being already known (infected blood, injected drugs, tattooing, homosexual relationships).

Nazare C, Girleanu I, Cojocariu-Salloum C, Trifan A. **[Characteristics of hepatitis C virus (HCV) infection in closed communities]**. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2011;115(3):736-41.
AIM: To determine the prevalence of HCV in closed communities and the relations between risk behavior and HCV infection. MATERIAL AND METHODS: The persons deprived of personal freedom selected for this study have filled out an epidemio logical questionnaire including identity and epidemiological data (detention history, evaluation of the risk factors), as well as a written consent. All the subjects were tested for the presence of anti-HCV antibodies. RESULTS: This study included 326 of the total of 500 persons deprived of personal freedoms at the Bacau Correctional Facility The prevalence of hepatitis B and C was 15.34 %, and that of HCV 5.21%, higher than in the general population. Risk factors associated with HCV in closed communities were injected drugs, homosexuality, and tattooing. CONCLUSIONS: The results confirm that the population in correctional facilities is at high risk for infection with hepatitis viruses (both B and C), the modes of disease transmission being already known.

Gheorghe L, Csiki IE, Iacob S, Gheorghe C, Smira G, Regep L. **The prevalence and risk factors of hepatitis C virus infection in adult population in Romania: a nationwide survey 2006 - 2008**. Journal of gastrointestinal and liver diseases : JGLD. 2010;19(4):373-9.
AIMS: This study was aimed at determining the seroprevalence of hepatitis C virus (HCV) infection in Romania and the possible risk factors and modality of HCV transmission. METHODS: A nationwide cross-sectional survey among the adult population was conducted between 2006-2008 in Romania through a population multicenter stratified random cluster sampling. Serum samples from 13,460 subjects were tested with a 3rd generation ELISA and a standardized questionnaire concerning the socio-demographic characteristics and potential risk factors was used. RESULTS: The prevalence rate of HCV infection in Romanian adult population was 3.23% with significant differences between the main geographical regions (Moldavia 4.25%, Wallachia & Dobrogea 3.35% and Transylvania & Banat 2.63%), as well as between different counties (maximum 7.19%, minimum 0.56%). Overall participation rate to the survey of the selected subjects was 74.69%. Risk factors for HCV infection were: blood/blood products transfusions (p=0.0001), previous surgery (elective and emergency, p=0.0001 and p=0.043, respectively), frequent hospitalizations (p=0.0001), injections at home (p=0.0001), accidents/trauma (p=0.0001), occupational hazard related to blood exposure (p=0.025), intravenous drug administration (p=0.002), a partner chronically infected with HCV/hepatitis B virus (HBV) (p=0.046), first sexual intercourse <18 years (p=0.019), familial exposure to HCV/HBV infection (p=0.001) or to chronic HBV/HCV liver disease (p=0.001), personal history of chronic HBV infection (p=0.001). HCV RNA positivity was detected in 91% of the anti HCV positive subjects. CONCLUSIONS: Overall HCV prevalence in Romania is 3.23%. Both nosocomial and non-nosocomial routes are implicated as risk factors

PWID (People Who Inject Drugs)

Wiessing L, Ferri M, Belackova V, Carrieri P, Friedman SR, Folch C, . . . Griffiths P. **Monitoring quality and coverage of harm reduction services for people who use drugs: a consensus study**. Harm reduction journal. 2017;14(1):19.
BACKGROUND AND AIMS: Despite advances in our knowledge of effective services for people who use drugs over the last decades globally, coverage remains poor in most countries, while quality is often unknown. This paper aims to discuss the historical development of successful epidemiological indicators and to present a framework for extending them with additional indicators of coverage and quality of harm reduction services, for monitoring and evaluation at international, national or subnational levels. The ultimate aim is to improve these services in order to reduce health and social problems among people who use drugs, such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection, crime and legal problems, overdose (death) and other morbidity and mortality. METHODS AND RESULTS: The framework was developed collaboratively using consensus methods involving nominal group meetings, review of existing quality standards, repeated email commenting rounds and qualitative analysis of opinions/experiences from a broad range of professionals/experts, including

members of civil society and organisations representing people who use drugs. Twelve priority candidate indicators are proposed for opioid agonist therapy (OAT), needle and syringe programmes (NSP) and generic cross-cutting aspects of harm reduction (and potentially other drug) services. Under the specific OAT indicators, priority indicators included 'coverage', 'waiting list time', 'dosage' and 'availability in prisons'. For the specific NSP indicators, the priority indicators included 'coverage', 'number of needles/syringes distributed/collected', 'provision of other drug use paraphernalia' and 'availability in prisons'. Among the generic or cross-cutting indicators the priority indicators were 'infectious diseases counselling and care', 'take away naloxone', 'information on safe use/sex' and 'condoms'. We discuss conditions for the successful development of the suggested indicators and constraints (e.g. funding, ideology). We propose conducting a pilot study to test the feasibility and applicability of the proposed indicators before their scaling up and routine implementation, to evaluate their effectiveness in comparing service coverage and quality across countries. CONCLUSIONS: The establishment of an improved set of validated and internationally agreed upon best practice indicators for monitoring harm reduction service will provide a structural basis for public health and epidemiological studies and support evidence and human rights-based health policies, services and interventions.

Paraschiv S, Banica L, Nicolae I, Niculescu I, Abagiu A, Jipa R, . . . Abecasis A. **Epidemic dispersion of HIV and HCV in a population of co-infected Romanian injecting drug users**. PloS one. 2017;12(10):e0185866.
Co-infections with HIV and HCV are very frequent among people who inject drugs (PWID). However, very few studies comparatively reconstructed the transmission patterns of both viruses in the same population. We have recruited 117 co-infected PWID during a recent HIV outbreak in Romania. Phylogenetic analyses were performed on HIV and HCV sequences in order to characterize and compare transmission dynamics of the two viruses. Three large HIV clusters (2 subtype F1 and one CRF14_BG) and thirteen smaller HCV transmission networks (genotypes 1a, 1b, 3a, 4a and 4d) were identified. Eighty (65%) patients were both in HIV and HCV transmission chains and 70 of those shared the same HIV and HCV cluster with at least one other patient. Molecular clock analysis indicated that all identified HIV clusters originated around 2006, while the origin of the different HCV clusters ranged between 1980 (genotype 1b) and 2011 (genotypes 3a and 4d). HCV infection preceded HIV infection in 80.3% of cases. Coincidental transmission of HIV and HCV was estimated to be rather low (19.65%) and associated with an outbreak among PWID during detention in the same penitentiary. This study has reconstructed and compared the dispersion of these two viruses in a PWID population.

Ruta S, Sultana C, Oprea C, Vagu C, Ceausu E, Cernescu C. **HCV non-1b genotypes in injecting drug users from Romania**. Journal of infection in developing countries. 2016;10(5):523-7.
INTRODUCTION: Chronic hepatitis C cases diagnosed in Romania were mostly related to unsafe parenteral treatments and blood transfusions; HCV genotype 1b was prevalent. During the last decade, an increasing number of HCV infections was reported among people who inject drugs (PWID). The aim of the current study was to test if this epidemiological shift triggered a diversification of the circulating viral strains. METHODOLOGY: HCV genotypes were determined by reverse hybridization in 130 HCV-infected PWID (87.7% males; mean age 27.9 +/- 6.7 years, injecting drugs for 8.1 +/- 4.8 years). RESULTS: HIV-HCV co-infection was diagnosed in 80.8% of the subjects and 26.9% were HIV-HCV-HBV triple infected. Active HCV viral replication was present in 104 PWID (80%), more frequently in those HIV-co-infected (91.4% vs. 52% in HCV mono-infected, and 77.148.5% in HIV-HCV-HBV triple-infected, p = 0.0001). Non-1b genotypes were prevalent (54.8%), with subtype 1a the most commonly detected (24%), followed by genotypes 3a (14.4%) and 4 (7.7%). Mixed infections with genotypes 1a and 1b were found in nine subjects (8.7%). There was no difference in the genotypes frequencies based on HIV or HBV co-infection status, length of drug usage, or associated risk factors (tattoos, piercing, detention). CONCLUSION: The continuous surveillance of HCV genotypes in PWID from Romania will add valuable information to the overall European epidemiological picture, with important therapeutic implications.

Ruta S, Cernescu C. **Injecting drug use: A vector for the introduction of new hepatitis C virus genotypes**. World journal of gastroenterology. 2015;21(38):10811-23.
Hepatitis C virus (HCV) genotypes' monitoring allows real-time insight into the dynamic changes that occur in the global epidemiological picture of HCV infection. Intravenous drug use is currently the primary driver for HCV transmission in developed and developing countries. The distribution of HCV genotypes/subtypes differs significantly between people who inject drugs (PWID) and the general

population. HCV genotypes that previously exhibited a limited geographical distribution (3a, 4) are becoming more prevalent in this high-risk group. Immigration from HCV-endemic countries and the evolving networks of HCV transmission in PWID influence HCV genotypes distribution in Europe. Social vulnerabilities (e.g., unemployment, homelessness, and limited access to social and healthcare insurances systems) are important triggers for illicit drug use, which increases the associated risks of HCV infection and the frequent emergence of less prevalent genotypes. Genotype/subtype determination bears important clinical consequences in the progression of liver disease, susceptibility to antiviral therapies and the emergence of resistance-associated variants. An estimated half of the chronically HCV-infected PWID are unaware of their infection, and only one in ten of those diagnosed enter treatment. Nevertheless, PWID exhibit high response rates to new antiviral regimens, and the level of HCV reinfection is unexpectedly low. The focus of the healthcare system must be on the early detection and treatment of infection, to avoid late presentations that are associated with high levels of viremia and liver fibrosis, which may diminish the therapeutic success rate.

Oprea C, Ianache I, Radoi R, Erscoiu S, Tardei G, Nicolaescu O, . . . Ceausu E. **Alarming increase in tuberculosis and hepatitis C virus (HCV) among HIV infected intravenous drug users**. Journal of the International AIDS Society. 2014;17(4 Suppl 3):19625.
INTRODUCTION: In the last years, we observed an alarming increase in the number of newly diagnosed HIV infected intravenous drug users (IDUs) co-infected with hepatitis viruses or with severe bacterial infections. The aim of our study was to assess the incidence, the demographic and clinical characteristics of IDUs diagnosed with HIV, HCV and tuberculosis (TB). MATERIALS AND METHODS: Prospective study on HIV infected IDUs with HCV and TB admitted in a single centre between January 2009 and April 2014. Data were compared to a group of HIV infected IDUs without TB. Statistical analysis was performed using Graphpad Prism 4.01. RESULTS: Out of 450 HIV infected IDUs, 134 (29.7%) were diagnosed with HIV, HCV and TB. TB incidence among IDUs increases from 0% in 2009 to 30.2% in 2013. The TB coinfected patients had a mean age at diagnosis of 30 [15-56] years; were in majority males, 106 (84.4%); from urban areas, 120 (89.5%); and had significantly lower education level (85% vs 68.3%, $p<0.0001$) and higher rates of unemployment (80% vs 55%, $p<0.0001$) than those without TB. The median CD4 cell count was lower in the TB versus non TB IDUs (143 vs 472/mm(3), $p<0.0001$). TB infected IDUs tend to be more frequently late presenters (59.7 vs 24.6, $p<0.0001$) and to have advanced HIV disease (47.7 vs 7.59%, $p<0.0001$) than those without TB. TB cultures were positive in 64 (47.7%) patients, 3 (2.2%) had multidrug resistant TB and 2 (1.5%) had extended drug resistance. Disseminated and/or extrapulmonary TB was diagnosed in 51 patients (38%). The overall mortality rate was higher in TB compared to non TB IDUs (19.4% vs 8.2%, $p=0.0007$), disseminated TB being associated with the most severe immunosuppression (median CD4 cell count 42/mm(3)) and the highest mortality rate (27.4%). CONCLUSIONS: The incidence of TB in HIV/HCV coinfected IDUs was high and rose over the time. TB infection was more frequent in patients with severe immunosuppression and the mortality rate was higher in IDUs with disseminated and/or extrapulmonary disease. IDUs are important candidates for acquiring and transmitting HIV infection, viral hepatitis and TB, being difficult to control due to their high-risk behaviours. Strengthening of HIV transmission prevention strategies, particularly in identified risk groups, is mandatory.

Manea E, Jipa R, Niculescu I, Benea S, Benea O, Arama V, Hristea A. **Co-infections and co-morbidities among injecting drug users versus sexually infected patients in Bucharest**. Journal of the International AIDS Society. 2014;17(4 Suppl 3):19665.
INTRODUCTION: After the 2008 introduction of new psychoactive substances (NPS) in Romania, the number of newly diagnosed HIV infections showed significant increase among injecting drug users (IDUs). Our objective was to analyze the differences between co-infections related to the HIV infection, based on the way of transmission (IDUs versus sexually infected). MATERIALS AND METHODS: A retrospective transversal study was carried out, analyzing 245 adult HIV-positive patients, diagnosed between January 2013 and December 2013 in our hospital. We collected socio-demographic, epidemiological and laboratory data at the diagnosis and analyzed them using SPSS version 20. RESULTS: Most patients (71%, 174/245) were men and the median age was 32 years (IQR: 26-38). 91 patients (37%) were former/active IDUs (most of them injecting both opioids and NPS), while 154 patients (63%) were sexually infected, with 84% being heterosexuals and 16% men having sex with men (MSM). The median CD4 count, at the moment of diagnosis, was 294 cells/mm(3) (IQR: 119-483). CONCLUSION: Heterosexual transmission was the most common way of HIV transmission in 2013 in

contrast with EU/CEE, where MSM accounted for the majority of cases of HIV epidemics in 2012 [1]. Sexually transmitted HIV infection was associated with late presentation, stage C and syphilis. We noted a high percentage of IDU transmission, which was associated with stage A and hepatitis C infection.
Oprea C, Ceausu E, Ruta S. **Ongoing outbreak of multiple blood-borne infections in injecting drug users in Romania**. Public health. 2013;127(11):1048-50.

Sultana C, Vagu C, Temereanca A, Grancea C, Slobozeanu J, Ruta S. **HEPATITIS C VIRUS GENOTYPES IN INJECTING DRUG USERS FROM ROMANIA**. Central European journal of medicine. 2011;6(5):672-8.
Due to the increasing number of infections related to injecting drug use, both the pattern of hepatitis C virus (HCV) transmission, and the circulating genotypes in Europe have changed. As there are little available data in this respect for Romania, the aim of our study was a preliminary analysis of the distribution of HCV genotypes circulating among injecting drug users (IDUs). Of the 45 IDUs evaluated (86.7% men, mean age - 27.6+/-3.7 years, mean age at first drug use - 17.5+/-3.9 years), 88.9% presented anti-HCV antibodies, with higher rates in those with an injecting history of more than 10 years; 57.8% of the subjects had detectable HCV viral load. Only 6.7% had markers of chronic hepatitis B infection, and none had anti-HIV antibodies. While HCV subtype 1b is still prevalent (in 50% of the viraemic subjects), other subtypes begin to emerge, especially in younger patients (1a - in 23.1%, 4 - in 11.5%, 3a - in 7.7% of the cases). These data indicate the possibility of major shifts in the distribution of the dominant subtype, underlining the need for close surveillance of HCV infections in IDUs, who can act as a bridging group toward the general population.
Pharris A, Wiessing L, Sfetcu O, Hedrich D, Botescu A, Fotiou A, . . . van de Laar MJ. **Human immunodeficiency virus in injecting drug users in Europe following a reported increase of cases in Greece and Romania, 2011**. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2011;16(48).
Greece and Romania reported an increased number of HIV cases among injecting drug users (IDUs) during 2011. Most European countries reported no changes in the rate of newly diagnosed cases of HIV or HIV prevalence in IDUs; however, six countries did report increases and several additional countries reported increases in injecting risk indicators or low coverage of prevention services. These indicate a potential risk for increased HIV transmission and future outbreaks unless adequate prevention is implemented.

Co-infection

Juganariu G, Teodor A, Petrovici C, Cristina N, Miftode E. **CHARACTERISTICS OF HEPATITIS B VIRUS COINFECTION AMONG HIV-INFECTED PREGNANT WOMEN**. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2015;119(4):1010-7.
UNLABELLED: The similar routes of transmission for HIV and HBV place patients with either infection at greater risk for HIV/HBV co-infection. AIM: To determine the particularities of hepatitis B virus (HBV) coinfection in pregnant women infected with human immunodeficiency virus (HIV) and its influence on pregnancy. METHODS: Retrospective study of 74 HIV-infected women monitored during pregnancy in the Iasi Regional HIV/AIDS Center (Romania) from 2010 to 2013. The subjects were divided into 2 groups according to the presence or absence of HBV coinfection. RESULTS: Most subjects belonged to age group 20-24 years (90% in the HIV group versus 75.5% in the HIV/HBV-coinfected group). HIV infection was most commonly transmitted by parenteral route (65.5% vs. 48.9%). The majority of patients were married (60% vs. 65%) and primiparous at the time of enrollment (71.1% vs. 96.6%). In the HIV/HBV-coinfected group CD4 level was lower and mean plasma viral load higher (1.92 log10 copies/mL vs. 2.31 log10 copies/ml). The proportion of cases with severe immunosuppression was similar in both groups (18.1% vs. 17.9%). HBV-HIV coinfection induced a risk of prematurity of 1.51 times, but did not increase the risk of newborns with low birth weight. CONCLUSIONS: Advanced stages of HIV disease, age group 21-30 years, low CD4 counts, and low levels of education are significant risk factors for preterm birth and low birth weight.

Lazar C, Uta M, Branza-Nichita N. **Modulation of the unfolded protein response by the human hepatitis B virus**. Frontiers in microbiology. 2014;5:433.
During productive viral infection the host cell is confronted with synthesis of a vast amount of viral proteins which must be folded, quality controlled, assembled and secreted, perturbing the normal

function of the endoplasmic reticulum (ER). To counteract the ER stress, cells activate specific signaling pathways, designated as the unfolded proteins response (UPR), which essentially increase their folding capacity, arrest protein translation, and degrade the excess of misfolded proteins. This cellular defense mechanism may, in turn, affect significantly the virus life-cycle. This review highlights the current understanding of the mechanisms of the ER stress activation by Human Hepatitis B virus (HBV), a deadly pathogen affecting more than 350 million people worldwide. Further discussion addresses the latest discoveries regarding the adaptive strategies developed by HBV to manipulate the UPR for its own benefits, the controversies in the field and future perspectives.

Dumitru IM, Rugina S, Alexandrescu L, Dumitru E. **Increased rate of spontaneous clearance of hepatitis C virus in patients infected with HIV**. Journal of gastrointestinal and liver diseases : JGLD. 2014;23(4):461-2.

Arbune M, Georgescu C. **Characteristics of Hepatitis B Co-infection and Disease Evolution in HIV-Positive Paediatric Patients in Romania**. Balkan medical journal. 2013;30(3):263-7.
BACKGROUND: Infection with hepatitis B virus (HBV) contributes to morbidity and mortality in people living with human immunodeficiency virus (HIV). AIMS: The aim of the present study is to assess the influence of HBV co-infection in clinical characteristics and disease evolution among nosocomial HIV infected youth in Romania. STUDY DESIGN: Retrospective study. METHODS: We assessed HBsAg in 179 young people with nosocomial paediatric HIV infection. Demographic data, ALAT level, CD4-count, HIV-RNA, antiretroviral therapy and clinical behaviour were all statistically compared in patients who were HIV mono-infected and HBV-co-infected. RESULTS: THE CHARACTERISTICS OF PATIENTS ARE AS FOLLOWS: sex ratio M/F: 55.3%, AIDS category 88%, median nadir CD4-count 126/mm(3). The prevalence of persistent HBsAg was 44.6%. The mortality rate was 11.1%, but no correlation with HBsAg was found. An average of three antiretroviral combinations is experienced by 97.7% of patients, including Lamivudine for over 5 years in 76% of cases and Tenofovir/Emtricitabine in 16.75% of patients. Patients under antiretroviral therapy achieved 53.07% sustained undetectable HIV-RNA and 40.78% restored immunity CD4-count >500/mm(3). ALAT enzyme was found to be high in 54.75% of patients. CONCLUSION: During our research, we noticed that HBsAg was elevated in young people with HIV in Romania. Mortality rate was not statistically correlated to HBsAg. High ALAT levels are related with HBV, HDV co-infections, virological failure to antiretroviral treatment and the risk of death.

Others

Schiller A, Timar R, Siriopol D, Timar B, Bob F, Schiller O, . . . Covic A. **Hepatitis B and C virus infection in the hemodialysis population from three romanian regions**. Nephron. 2015;129(3):202-8.
BACKGROUND: After 10 years of systematically nationwide applied measures for reduction of infection risk, in this national prospective observational study, we reassessed the prevalence of hepatitis virus infection prevalence and its influence on the outcome of end-stage kidney disease (ESKD) patients treated with hemodialysis. METHODS: Six-hundred ESKD patients (332 men and 268 women, median age 56 years) treated with chronic HD in seven centers from all the historical regions of Romania have been assigned to this study on 1st of November 2010. The aims of this study were to reevaluate the prevalence of the hepatitis B and C virus infection in a HD population from Romania after 10 years of systematically nationwide applied measures for reduction of infection risk and also to assess the impact of these infections on the prognosis of HD patients. RESULTS: HBsAg was positive in 9.5% (n = 57) of the patients, anti-HCV antibodies were detected in 27.3% (n = 164) and 5% (n = 30) were positive for both HBV and HCV infection. The mortality risk was significantly influenced only by age, the presence of coronary artery disease and the 25 OH vitamin D levels. CONCLUSIONS: This study shows that the systematically nationwide applied measures for reduction of infection risk significantly decreased HV infection prevalence in HD patients in Romania. The presence of HV infection did not significantly influence the mortality risk in this population.

Hatu G, Brumboiu MI, Czernichow P, Bocsan IS. **The risk for hepatitis C infection in blood donors in Cluj County, Romania**. Transfusion clinique et biologique : journal de la Societe francaise de transfusion

sanguine. 2014;21(2):94-7.
Blood products safety is based on different criteria including the selection of blood donors. Blood donors referred to Cluj County (Romania) Blood Transfusion Centre in January-March 2012 completed a self-administered questionnaire and were examined by a physician. Data collected from first-time and repeat donors were compared for possible risk factors for hepatitis C infection. In total, 1100 donors were selected. In first-time donors, most frequent factors were age<26 years, female gender and history of health care procedures. Behavioural risk factors (e.g. drug use, sexual promiscuity) may not be properly filtered out in blood donors, suggesting the necessity of improving the health screening process.

HaTu G, Brumboiu IM, BocSan IS. **HCV Infection Frequency and Trends Among Voluntary Blood Donors in Cluj County (Romania) Between 2006 and 2011**. Clujul medical (1957). 2014;87(3):159-62.
BACKGROUND AND AIMS: In Europe a wide variation in HCV prevalence between countries was described, ranging from 0.1 to 6.0%, higher in Eastern Europe than in Western Europe, which may threaten the biological safety of donated blood. The HCV frequency among blood donors in Romania has has made the object of only very few published studies. The aim of this study was to analyze the frequency of anti-HCV antibodies in blood donors from Cluj County (Romania) and its trend, in the period 2006-2011. PATIENTS AND METHODS: Between 2006-2011 all donors, new and repeat donors were screened for hepatitis C virus infections using enzyme-linked immunosorbent assay (ELISA). Reactive results were confirmed using radioimmunoblotting assay (RIBA). The frequency and trends were analyzed using the T-test and X(2)-test. RESULTS: There were 95,181 donors tested in the blood transfusion centre (BTC) laboratories between 2006-2011. The overall prevalence was 0.254 % (95% CI 0.222-0.286). The prevalence rates of anti-HCV antibodies increased with age between both genders, being higher among women, starting to decrease after the age of 51. CONCLUSIONS: The results of this study demonstrate a high HCV prevalence in donations from 2006 to 2011, as compared to other countries in Europe, especially among first time blood donors, an infection that might be a potential threat to blood safety.

Bacusca AI, Coman AE, Felea D, Petrovanu R, Ioan B. **Epidemiology of B/C virus infection hepatitis in the Northern Moldavian correctional facilities risk factors**. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2014;118(2):463-70.
AIM: To identify the specific risk factors for chronic hepatitis B/C virus infections in the correctional system in Moldova (Romania). MATERIAL AND METHODS: The study included 533 subjects imprisoned in three correctional facilities located in the Northern region of Moldova. The subjects were divided into 2 groups: HBV/HBC group--108; Control group--425. RESULTS: The risk factor for transfusion-contracted HBV/HCV was 3.73; the empirical treatment of the HBV/HBC group resulted in a relative infection risk of 2.62; syringe sharing in the HBV/HBC group accounted for a risk factor of over 4 (OR = 4.33); tattooing induced a relative risk factor of 1.25, and piercing was a risk factor of approximately 2 (OR = 1.97); sharing personal care items represented a risk factor of over 2 (OR = 2.02). Injection drugs induced a relative risk of over 4 (OR = 4.33). In the HBV/HCV group, self-aggression represented a risk factor of 1.65. CONCLUSIONS: Prison environment, by its specific and nonspecific contamination modalities (shared with the rest of the population but more common) causes that inmates to be 2-4 times more exposed to hepatitis B/C infection.

Hatu G, Brumboiu MI, Czernichow P, Bocsan IS. **The risk for hepatitis C infection in blood donors in Cluj County, Romania**. Transfusion clinique et biologique : journal de la Societe francaise de transfusion sanguine. 2014;21(2):94-7.
Blood products safety is based on different criteria including the selection of blood donors. Blood donors referred to Cluj County (Romania) Blood Transfusion Centre in January-March 2012 completed a self-administered questionnaire and were examined by a physician. Data collected from first-time and repeat donors were compared for possible risk factors for hepatitis C infection. In total, 1100 donors were selected. In first-time donors, most frequent factors were age<26 years, female gender and history of health care procedures. Behavioural risk factors (e.g. drug use, sexual promiscuity) may not be properly filtered out in blood donors, suggesting the necessity of improving the health screening process.

Sporea I, Sirli R, Hogea C, Sink AA, Serban V. **Diabetes mellitus and chronic HCV infection**. Romanian

journal of internal medicine = Revue roumaine de medecine interne. 2009;47(2):141-7.
UNLABELLED: The aim of our paper was to assess the prevalence of anti HCV antibodies among diabetics from Romania. MATERIAL AND METHOD: We performed two studies: a prospective randomized one, on 559 diabetics from Timisoara, and a second, retrospective-descriptive one, on 625 diabetics from Petrosani, who were tested for anti HCV antibodies. RESULTS: I. In Timisoara, 559 diabetics were prospectively evaluated, 4.5% (25p.) were anti HCV positive. There were no statistically significant differences between the proportions of type I DM in the anti HCV positive group (4%-1p.) as compared to the entire group (12%-67p.) (p=0.3429), nor in the F: M ratio, 1.3:1 vs. 1.5:1 (p=0.838). II. In Petrosani, 625 diabetics were retrospectively evaluated, 7.7% (48p.) were anti HCV positive. There were no significant differences between the proportions of type I DM in the anti HCV positive group (6%-3p.) vs. the entire group (8%-53p.) (p=0.788), nor in the F: M ratio, 1.7:1 vs. 1.7:1 (p=1). CONCLUSION: The prevalence of anti HCV antibodies among diabetics from Romania is rather high (4.5% in a randomized prospective trial and 7.7% in a retrospective descriptive trial) so that this special population (especially type II DM) should be screened for HCV infection, even if the aminotransferases are normal.

Iliuta C. **UNODC and the National Administration of Penitentiaries launched harm reduction programme in Romanian prisons**. International journal of prisoner health. 2009;5(1):52-3.
In February 2008, the National Administration of Penitentiaries and UNODC Project Office in Romania officially launched the common initiative of introducing harm reduction measures for people who inject drugs in three Romanian penitentiaries.
Botez C, Iliescu ML, Zanoschi G. **[Clinical and epidemiological profile of hepatitis B and C virus infection: a 34 soldier hospitalized in a military hospital retrospective study]**. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2009;113(1):217-20.
UNLABELLED: The hepatitis B and C virus infection is a public health problem due to the evolution of the disease and the quality of life of the patients, and the costs involved of the therapy and health care services. AIM: To asses the clinical and epidemiological profile of the 34 militaries hospitalized in a military hospital, infected with these viruses. MATERIAL AND METHOD: The main method of not being ill is to respect the common measures of prevention. CONCLUSION: It is strongly necessary to change the practices of improper parenteral treatment administration in healthcare workers practices, especially in rural areas.

Ribes J, Cleries R, Esteban L, Moreno V, Bosch FX. **The influence of alcohol consumption and hepatitis B and C infections on the risk of liver cancer in Europe**. Journal of hepatology. 2008;49(2):233-42.
BACKGROUND/AIMS: To assess the variability of liver cancer (LC) risk associated with hepatitis B (HBV) and hepatitis C (HCV) viruses and alcohol intake in 2002 throughout Europe. METHODS: Incidence data were obtained from population-based cancer registries whereas mortality, HBV, HCV and alcohol exposures were obtained from the WHO databases. Relative risk of LC and their posterior probabilities to be >1 were obtained and plotted in maps through a Bayesian random effects model. RESULTS: HBV prevalence >2% increased the risk of developing LC a 15% in men and 21% in women; HCV prevalence >2%, 54% in men and 33% in women and, pure alcohol intake >11l, 26% and 14%, respectively (all of them statistically significant). These risk factors played a similar role in the risk of dying from LC among men, whereas HBV and alcohol were not statistically significant among women. Significant high LC risk, after HBV/HCV and alcohol adjustment were observed for both sexes in: Hungary, Moldova, Romania, Croatia, Greece, Italy, Spain, France and Austria. CONCLUSIONS: South-North and East-West decreasing gradients for LC risk were observed in Europe. HBV, alcohol and, mainly, HCV are independent risk factors that could explain this geographical pattern.

2.2 Session 4 Prevention and control of viral hepatitis

Session 4: Prevention and Control of viral hepatitis
Chairs: Antons Mozalevskis - Anca Trifan
11:15- 11:35 HB Vaccination programs in Romania

Session 4: Prevention and Control of viral hepatitis

11:35 - 11:55 Treatment guidelines – Treatment access

Oliviu Pascu

Prevention

Schuz J, Espina C, Villain P, Herrero R, Leon ME, Minozzi S, . . . Zatonski W. **European Code against Cancer 4th Edition: 12 ways to reduce your cancer risk**. Cancer epidemiology. 2015;39 Suppl 1:S1-10.
This overview describes the principles of the 4th edition of the European Code against Cancer and provides an introduction to the 12 recommendations to reduce cancer risk. Among the 504.6 million inhabitants of the member states of the European Union (EU28), there are annually 2.64 million new cancer cases and 1.28 million deaths from cancer. It is estimated that this cancer burden could be reduced by up to one half if scientific knowledge on causes of cancer could be translated into successful prevention. The Code is a preventive tool aimed to reduce the cancer burden by informing people how to avoid or reduce carcinogenic exposures, adopt behaviours to reduce the cancer risk, or to participate in organised intervention programmes. The Code should also form a base to guide national health policies in cancer prevention. The 12 recommendations are: not smoking or using other tobacco products; avoiding second-hand smoke; being a healthy body weight; encouraging physical activity; having a healthy diet; limiting alcohol consumption, with not drinking alcohol being better for cancer prevention; avoiding too much exposure to ultraviolet radiation; avoiding cancer-causing agents at the workplace; reducing exposure to high levels of radon; encouraging breastfeeding; limiting the use of hormone replacement therapy; participating in organised vaccination programmes against hepatitis B for newborns and human papillomavirus for girls; and participating in organised screening programmes for bowel cancer, breast cancer, and cervical cancer.

Barlean L, Danila I, Balcos C, Saveanu I, Balan A. **Preventive attitudes towards infection transmission in dental offices in North-East Romania**. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2012;116(4):1209-12.
AIM: The aim of this study was to evaluate the level of knowledge and the current attitudes towards infection control in the dental offices in the Northeast Romania. MATERIAL AND METHODS: Questionnaire-based study conducted on 152 dentists aged between 25-65 years practicing in 6 Northeast Romania counties. The questionnaire included questions related to current infection control procedures and attitudes. Data were statistically analyzed using SPSS 14.0 and chi-square test ($p<0.05$). RESULTS: The majority of the dentists (83.6%) consider that universities should provide a substantial education regarding infection control through postgraduate courses, but 7.2% of the respondents are not sure about their usefulness. The clinical decision related to patient's treatment is influenced by his infectious status for 67.8% of the dentists. Of these, 19.1% have over 20 years of practice and 48.0% are females. Almost all dentists (93.4%), regardless of gender (96.4% females and 87.8% males) undergo periodic testing for blood-borne viral infections (hepatitis B, C and HIV). Full protective equipment is used for all the patients by 86.2% of the dentists, while 12.5% use it only for the infectious ones. 65.2% of the dentists use steam sterilization equipment (autoclave), and 80,8% use dry heat. The majority of the dentists (82.6%) believe that the patient must always be informed about the adopted infection control measures, but 21.7% declare to do so only in some particular cases. CONCLUSIONS: Dentists knowledge and attitudes towards infection control must be improved by educational interventions in order to adhere to

Control – Treatment

Hepatitis B

Leblebicioglu H, Arama V, Causse X, Marcellin P, Ozaras R, Postawa-Klozinska B, . . . Zarski JP. **Predictors associated with treatment initiation and switch in a real-world chronic hepatitis B population from five European countries**. Journal of viral hepatitis. 2014;21(9):662-70.
In Europe, healthcare systems differ between countries and different factors may influence Chronic hepatitis B (CHB) treatment choices in different counties. This analysis from a prospective, longitudinal, non-interventional study in five EU countries aimed to explore determinants associated with treatment initiation or switch in patients with CHB. A total of 1267 adult patients with compensated CHB in Germany, France, Poland, Romania and Turkey were prospectively followed for up to 2 years (March 2008-December 2010). Determinants of treatment initiation or switch were analysed using multivariate Cox proportional hazards regression. Median time since CHB diagnosis was 2.6 (0-37.7) years. Among 646 treatment-naive patients, the probability of treatment initiation during follow-up was higher: in Germany (P = 0.0006), Poland (P < 0.0001) and Romania (P = 0.0004) compared with Turkey; in patients with alanine transaminase (ALT) 1-2 x upper limit of normal (ULN) (P = 0.0580) or >2 x ULN (P = 0.0523) compared with ALT </= 1 x ULN; and in patients with hepatitis B virus (HBV) DNA >/= 2000 IU/mL (P < 0.0001) compared with HBV DNA <2000 IU/mL or undetectable. Among 567 treated patients, 87 switched treatment during follow-up. The probability of treatment switch was higher: in France (P = 0.0029), Germany (P = 0.0078) and Poland (P = 0.0329) compared with Turkey; and in patients with HBV DNA <2000 (P < 0.0001) or >/= 2000 IU/mL (P < 0.0001), compared with undetectable. Viral load and ALT level were identified as the major drivers of treatment initiation. HBV DNA level was also a significant determinant of treatment switch. Results were statistically different across EU countries.

Marcellin P, Arama V, Leblebicioglu H, Zarski JP, Zeuzem S, Mauss S, . . . Simon K. **Chronic hepatitis B treatment initiation and modification patterns in five European countries: a 2-year longitudinal, non-interventional study**. Antiviral therapy. 2014;19(3):235-43.
BACKGROUND: Chronic hepatitis B (CHB) is an important health concern, but there are few studies describing its management in different countries. This prospective, longitudinal, non-interventional study aimed to assess differences in CHB management in five European countries (Germany, France, Poland, Romania and Turkey). METHODS: Data were collected from CHB patients' records between 2008 and 2010. Patients were stratified by treatment status at baseline (treated or untreated). The primary objective was to estimate the probability of a CHB management modification (treatment initiation or change) among patients from each country during a 2-year follow-up. RESULTS: A total of 1,267 patients were included (567 treated, 700 untreated). Baseline characteristics between countries and treatment status groups were broadly comparable. Most patients had an alanine aminotransferase measurement in the 12 months prior to baseline; proportions of patients with an HBV DNA assessment varied by country and treatment status. The Kaplan-Meier-estimated probability of any treatment modification ranged from 9.4% (Turkey) to 30.1% (Poland) at 12 months and 10.0% (Turkey) to 40.0% (Poland) at 24 months. Modifications were more common in treated than untreated patients. The most frequently reported reasons for modifying treatment were HBV-DNA-related. The majority of treated patients were treated with monotherapy; however, choice of therapy differed between countries. CONCLUSIONS: This is the first longitudinal study describing CHB management in European countries. Differences were observed in treatment and monitoring between countries, but alanine aminotransferase and HBV DNA levels consistently emerged as key tests in the management of CHB in all five countries.

Preda CM, Baicus C, Negreanu L, Tugui L, Olariu SV, Andrei A, . . . Diculescu MM. **Effectiveness of entecavir treatment and predictive factors for virologic response**. Revista espanola de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patologia Digestiva. 2014;106(5):305-11.
INTRODUCTION: Entecavir (ETV) is a potent inhibitor of hepatitis B virus (HBV) replication. In patients adherent to treatment, virologic remission rates of > 95 % can be maintained with entecavir at 3-5 years. AIM AND METHODS: A cohort study was performed, including all subjects who received ETV for chronic hepatitis B, in the South- Eastern Romania. We assessed viral response, HBeAg loss and seroconversion, HBsAg loss and seroconversion, biochemical response. Comparison of categorical data was performed

by Chi2-test or Fisher s exact where applicable. RESULTS: Data from 533 patients were available: predominantly males (64 %), 82.6 % nucleotide naive, 23.1 % HBe-Ag positive, 78.2 % with elevated ALT, 8 % with cirrhosis. The median follow up was 24 months (range 12-48 months). Rate of undetectable HBV DNA increased constantly from year 1 to 3, reaching 91.2 %. Positive predictive factors for virologic response were low score of fibrosis (p-0.006), low level of HBV DNA (p-0.003), while negative predictive factors were: HBe antigen positive status (p-value < 0.001), prior IFN therapy (p 0.015). Virologic rebound was found in 7.8 % (breakthrough in 0.8 %). Rate of HBe Ag loss increases with the therapy duration, reaching 47.83 % in year 3,with two positive predictive factors: Male sex (p = 0.007), and undetectable HBV DNA at 24 weeks (p = 0.002). The percentage of HBs Ag loss was 1.31 %. CONCLUSIONS: ETV maintained and even increased the high initial response rate (from 78 % to 91.2 %). Low score of fibrosis, low level of HBV DNA, HBe antigen negative status, absence of prior interferon therapy predict a good virologic response. Virologic rebound was found in a higher rate in our population, due probably to a poor drug compliance. Lamivudine-resistant patients usually respond well to ETV, but 15.62 % are non-responders, suspect of Entecavir resistance.

Streinu-Cercel A, Sandulescu O, Stefan M, Streinu-Cercel A. **Treatment with lamivudine and entecavir in severe acute hepatitis B**. Indian journal of medical microbiology. 2016;34(2):166-72. BACKGROUND: Severe acute hepatitis B (SAHB) is an insufficiently described clinical entity, with relatively scarce data on anti-viral therapy available in field literature. METHODS: We performed an open-label study to evaluate specific anti-viral therapy in SAHB in Bucharest, Romania, during 2005-2009. Patients were allocated to two treatment groups and one control group: Group 1 - lamivudine 100 mg/day, Group 2 - entecavir 0.5 mg/day and Group 3 - standard of care, without anti-viral therapy. The primary endpoint was hepatitis B surface antigen (HBsAg) to hepatitis B surface antibody (anti-HBs) seroconversion by 24 weeks. Additional analyses included assessment of HBsAg clearance and hepatitis B e antigen (HBeAg) to hepatitis B e antibody (anti-HBe) seroconversion. RESULTS: In Group 1, 7/69 patients (10.14%, P = 0.032) reached HBsAg/Ab seroconversion by 24 weeks, compared with 9/21 (42.85%, P = 0.053) in Group 2 and 25/110 (22.72%) in Group 3. HBsAg clearance by 24 weeks: 16/69 patients (23.18%, P = 0.027) in Group 1, 11/21 (52.38%, P = 0.256) in Group 2 and 43/110 (39.09%) in Group 3. HBeAg/Ab seroconversion: 46/61 (75.40%, P = 0.399) in Group 1, 9/19 (47.36%, P = 0.001) in Group 2 and 74/100 (74.00%) in Group 3. CONCLUSION: Anti-viral therapy can be considered for managing selected cases of SAHB. Biochemical as well as virological parameters need to orient the choice of the anti-viral agent. Lamivudine displayed a greater decrease in viral load compared to controls, but it was associated with lower levels of HBsAg to anti-HBs seroconversion. Patients treated with entecavir showed a better response in terms of HBs seroconversion by 24 weeks.

Hepatitis C

Trifan A, Stanciu C, Gheorghe L, Iacob S, Curescu M, Cijevschi Prelipcean C, . . . Singeap AM. **Efficacy and safety of paritaprevir/ritonavir, ombitasvir, and dasabuvir with ribavirin for the treatment of HCV genotype 1b compensated cirrhosis in patients aged 70 years or older**. Medicine. 2017;96(50):e9271. Advanced age has been a major limitation of interferon-based treatment for chronic hepatitis C virus (HCV) infection because of its poor response and tolerability. Direct-acting antiviral (DAA) drug regimens are safe and highly effective, allowing administration of treatment also in elderly. This study aims to assess the efficacy and safety of paritaprevir/ritonavir, ombitasvir, and dasabuvir (PrOD) with ribavirin for the treatment of patients aged >/=70 years with HCV genotype 1b compensated cirrhosis.A total of 1008 patients with HCV genotype 1b compensated cirrhosis were prospectively treated with PrOD + ribavirin for 12 weeks, between December 2015 and July 2016. Sustained virologic response 12 weeks after the end of treatment (SVR12), adverse effects (AEs), comorbidities, discontinuation, and death rates were recorded. Efficacy and safety of therapy were assessed in patients aged >/=70 years and compared with data from patients <70 years.There were 117 patients aged >/=70 years, preponderantly females (58.9%), mean age 73.3 +/- 2.8 years (range 70-82), and 37 (31.6%) were treatment-experienced. Comorbidities were reported in 60.6% of patients >/=70 years and in 39.8% of those <70 years (P < .001). SVR12 rates based on intention-to-treat and per-protocol analyses were 97.4% and 100%, respectively, in patients >/=70 years, compared to 97.8% and 99.6%, respectively, in patients <70 years

(P = ns and P = ns). Severe AEs were reported in 4 (3.4%) patients >/=70 years, compared to 23 (2.6%) in those <70 years (P = ns). One death was recorded in a patient aged 79 years (0.9%) and 6 deaths (0.8%) in those <70 years (P = ns).Treatment with PrOD + ribavirin in patients 70 years of age or older with HCV genotype 1b compensated cirrhosis proved as effective, safe, and well tolerated, as it did in younger patients.

Mangia A, Foster GR, Berg CP, Curescu M, Ledinghen V, Habersetzer F, . . . Mauss S. **Efficacy and safety profile of boceprevir- or telaprevir-based triple therapy or dual peginterferon alfa-2a or alfa-2b plus ribavirin therapy in chronic hepatitis C: the real-world PegBase observational study**. Annals of gastroenterology. 2017;30(3):327-43.
BACKGROUND: The aim of the study was to determine the efficacy and safety of triple therapy with a first-generation protease inhibitor (PI; boceprevir, telaprevir) plus peginterferon alfa-2a or -2b plus ribavirin, and dual therapy (peginterferon alfa-2a or -2b plus ribavirin) in patients with chronic hepatitis C (CHC) in routine clinical practice. METHODS: PegBase was an international, prospective, observational study in which 4441 patients with CHC were enrolled in 27 countries. This analysis focuses on results in 4100 treatment-naive and previously treated patients treated with PI-based triple therapy or dual therapy, according to the discretion of the investigator and local standards of practice. The primary efficacy outcome was sustained virological response after 12-week follow up (SVR12). RESULTS: SVR12 rates in treatment-naive genotype (G) 1 patients were 56.6% and 62.9% for recipients of boceprevir plus peginterferon alfa-2a/ribavirin and boceprevir plus peginterferon alfa-2b/ribavirin, respectively, and 65.3% and 58.6% for recipients of telaprevir plus peginterferon alfa-2a/ribavirin and telaprevir plus peginterferon alfa-2b/ribavirin, respectively. In previously treated patients assigned to these four regimens, SVR12 rates were 43.6%, 48.3%, 60.3% and 56.1%, respectively. Among treatment-naive patients assigned to peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin, respectively, SVR12 rates were 49.2% and 41.9% in G1 patients, 75.7% and 83.3% in G2 patients, 65.9% and 65.9% in G3 patients, and 49.7%, and 51.1% in G4 patients. The safety and tolerability of dual and triple therapy were consistent with previous reports. CONCLUSION: The efficacy and safety of first-generation PI-based triple-therapy and dual-therapy regimens in this real-world cohort were broadly comparable to those of previous studies.

Kamal AM, Mitru TP, Kamal KC, Tica OS, Niculescu M, Alexandru DO, Tica AA. **Clinical importance of pharmacogenetics in the treatment of hepatitis C virus infection**. Romanian journal of morphology and embryology = Revue roumaine de morphologie et embryologie. 2016;57(2 Suppl):675-80.
Globally, over 4% of the world population is affected by hepatitis C virus (HCV) infection. The current standard of care for hepatitis C infection is combination therapy with pegylated interferon and ribavirin for 48 weeks, which yield a sustained virological response in only a little over half of the patients with genotype 1 HCV. We investigated the clinical importance of pharmacogenetics in treatment efficacy and prediction of hematotoxicity. A total of 148 patients infected with HCV were enrolled. All patients were treated for a period of 48 weeks or less with pegylated interferon and ribavirin. Four genotypes were investigated: inosine triphosphatase (ITPA) rs1127354, C20orf194 rs6051702, interferon lambda (IFNL)3 rs8099917, IFNL3/4 rs12979860 in the population from southwestern Romania. Genetic variants for rs129798660 and rs6051702 proved once more to represent an indisputable clinical tool for predicting sustained virological response (SVR) (69.23%, chi-square p=0.007846, p<0.05 and 63.29%, chi-square p=0.007846, p<0.05, respectively). ITPA genetic variants protect against ribavirin-induced hemolytic anemia and C20orf194 also proved to be protective against thrombocytopenia. These clinical findings strengthen the belief that pharmacogenetics should play a constant role in treatment decisions for patients infected with hepatitis C virus.

Ferenci P, Caruntu FA, Lengyel G, Messinger D, Bakalos G, Flisiak R. **Boceprevir Plus Peginterferon Alfa-2a/Ribavirin in Treatment-Naive Hepatitis C Virus Genotype 1 Patients: International Phase IIIb/IV TriCo Trial**. Infectious diseases and therapy. 2016;5(2):113-24.
INTRODUCTION: Boceprevir was not previously studied with peginterferon alfa-2a/ribavirin in phase III trials in treatment-naive chronic hepatitis C patients. The international phase IIIb/IV TriCo study was, therefore, designed to evaluate boceprevir in combination with peginterferon alfa-2a/ribavirin in treatment-naive genotype 1 patients. METHODS: A total of 165 treatment-naive genotype 1 patients were assigned to boceprevir plus peginterferon alfa-2a/ribavirin therapy according to the label. All patients received a 4-week lead-in with peginterferon alfa-2a/ribavirin, after which boceprevir (2400

mg/day) was introduced. The total duration of treatment ranged from 28 to 48 weeks depending on the virological response at Weeks 4, 8, and 24, and on fibrosis status. The primary efficacy outcome was sustained virological response (SVR) [undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) 12 weeks after actual end of treatment, SVR12]. RESULTS: The overall SVR12 rate was 81% (133/165, 95% confidence interval 74-86%). After 8 weeks of treatment, 61% of patients had undetectable HCV RNA, and 78 patients (47%) had an early response (undetectable HCV RNA at Weeks 8 and 24) and were eligible to stop all therapy at Week 28. Among early responders the SVR12 rate was 95% (74/78), and among patients with cirrhosis assigned to 48 weeks' treatment, the SVR12 rate was 67% (14/21). The overall relapse rate was 7% (10/143), and was 4% (3/77) among early responders. The most common adverse events were anemia (41%), neutropenia (32%), and dysgeusia (31%). CONCLUSION: High SVR12 rates can be achieved with boceprevir plus peginterferon alfa-2a/ribavirin in treatment-naive HCV genotype 1 patients, including patients with well-compensated cirrhosis. Treatment is well tolerated when label restrictions are taken into account. TRIAL REGISTRATION NUMBER: ClinicalTrials.gov Identifier: NCT01591460. FUNDING: F. Hoffmann-La Roche Ltd.

Stanciu C, Trifan A. **Hepatitis C Virus Treatment Revolution: Eastern European Story**. Hepatitis monthly. 2015;15(7):e28969.
Hepatitis C can be cured and even eradicated by new "revolutionary" treatments. However, at present exorbitant prices, Eastern European countries cannot afford the new treatments, while in western rich and developed countries (e.g. Germany and France) they are already available. Concerted efforts of governments, public health officials, and the community at large, are needed to negotiate agreements with pharmaceuticals companies to make the new treatments accessible and affordable. When science has demonstrated that hepatitis C can be cured, it would be unforgivable if millions of infected patients from eastern parts of the continent were denied access to new treatment on grounds of high prices and financial constraints.

Neukam K, Munteanu DI, Rivero-Juarez A, Lutz T, Fehr J, Mandorfer M, . . . Pineda JA. **Boceprevir or Telaprevir Based Triple Therapy against Chronic Hepatitis C in HIV Coinfection: Real-Life Safety and Efficacy**. PloS one. 2015;10(4):e0125080.
BACKGROUND AND AIMS: Clinical trials of therapy against chronic hepatitis C virus (HCV) infection including boceprevir (BOC) or telaprevir (TVR) plus pegylated interferon and ribavirin (PR) have reported considerably higher response rates than those achieved with PR alone. This study sought to evaluate the efficacy and safety of triple therapy including BOC or TVR in combination with PR in HIV/HCV-coinfected patients under real-life conditions. METHODS: In a multicentre study conducted in 24 sites throughout five European countries, all HIV/HCV-coinfected patients who initiated a combination of BOC or TVR plus PR and who had at least 60 weeks of follow-up, were analyzed. Sustained virologic response 12 weeks after the scheduled end of therapy date (SVR12) and the rate of discontinuations due to adverse events (AE) were evaluated. RESULTS: Of the 159 subjects included, 127 (79.9%) were male, 45 (34.4%) were treatment-naive for PR and 60 (45.4%) showed cirrhosis. SVR12 was observed in 31/46 (67.4%) patients treated with BOC and 69/113 (61.1%) patients treated with TVR. Overall discontinuations due to AE rates were 8.7% for BOC and 8% for TVR. Grade 3 or 4 hematological abnormalities were frequently observed; anemia 7%, thrombocytopenia 17.2% and neutropenia 16.4%. CONCLUSION: The efficacy and safety of triple therapy including BOC or TVR plus PR under real-life conditions of use in the HIV/HCV-coinfected population was similar to what is observed in clinical trials. Hematological side effects are frequent but manageable.

Hezode C, Asselah T, Reddy KR, Hassanein T, Berenguer M, Fleischer-Stepniewska K, . . . Pol S. **Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial**. Lancet (London, England). 2015;385(9986):2502-9.
BACKGROUND: Hepatitis C virus (HCV) genotype 4 accounts for about 13% of global HCV infections. Because interferon-containing treatments for genotype 4 infection have low efficacy and poor tolerability, an unmet need exists for effective all-oral regimens. We examined the efficacy and safety of an all-oral interferon-free regimen of ombitasvir, an NS5A inhibitor, and paritaprevir (ABT-450), an NS3/4A protease inhibitor dosed with ritonavir (ombitasvir plus paritaprevir plus ritonavir), given with or without ribavirin. METHODS: In this multicentre ongoing phase 2b, randomised, open-label combination trial (PEARL-I), patients were recruited from academic, public, and private hospitals and clinics in France,

Hungary, Italy, Poland, Romania, Spain, Turkey, and the USA. Eligible participants were aged 18-70 years with non-cirrhotic, chronic HCV genotype 4 infection (documented >/=6 months before screening) and plasma HCV RNA levels higher than 10,000 IU/mL. Previously untreated (treatment-naive) patients were randomly assigned (1:1) by computer-generated randomisation lists to receive once-daily ombitasvir (25 mg) plus paritaprevir (150 mg) plus ritonavir (100 mg) with or without weight-based ribavirin for 12 weeks. Previously treated (treatment-experienced) patients who had received pegylated interferon plus ribavirin all received the ribavirin-containing regimen. The primary endpoint was a sustained virological response (HCV RNA <25 IU/mL) 12 weeks after the end of treatment (SVR12). Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT01685203. FINDINGS: Between Aug 14, 2012, and Nov 19, 2013, 467 patients with HCV infection were screened, of whom 174 were infected with genotype 4. 135 patients were randomly assigned to treatment and received at least one dose of study medication; 86 patients were treatment-naive, of whom 44 received ombitasvir plus paritaprevir plus ritonavir and 42 received ombitasvir plus paritaprevir plus ritonavir with ribavirin, and 49 treatment-experienced patients received the ribavirin-containing regimen. In previously untreated patients, SVR12 rates were 100% (42/42 [95% CI 91.6-100]) in the ribavirin-containing regimen and 90.9% (40/44 [95% CI 78.3-97.5]) in the ribavirin-free regimen. No statistically significant differences in SVR12 rates were noted between the treatment-naive groups (mean difference -9.16% [95% CI -19.61 to 1.29]; p=0.086). All treatment-experienced patients achieved SVR12 (49/49; 100% [95% CI 92.7-100]). In the ribavirin-free group, two (5%) of 42 treatment-naive patients had virological relapse, and one (2%) of 44 had virological breakthrough; no virological failures were recorded in the ribavirin-containing regimen. The most common adverse event was headache (14 [29%] of 49 treatment-experienced patients and 14 [33%] of 42 treatment-naive patients). No adverse event-related discontinuations or dose interruptions of study medications, including ribavirin, were noted, and only four patients (4%) of 91 receiving ribavirin required dose modification for haemoglobin less than 100 g/L or anaemia. INTERPRETATION: An interferon-free regimen of ombitasvir plus paritaprevir plus ritonavir with or without ribavirin achieved high sustained virological response rates at 12 weeks after the end of treatment and was generally well tolerated, with low rates of anaemia and treatment discontinuation in non-cirrhotic previously untreated and previously treated patients with HCV genotype 4 infection. FUNDING: AbbVie.

Dinu S, Calistru PI, Ceausu E, Tardeil G, Oprisan G. **SCREENING OF PROTEASE INHIBITORS RESISTANCE MUTATIONS IN HEPATITIS C VIRUS ISOLATES INFECTING ROMANIAN PATIENTS UNEXPOSED TO TRIPLE THERAPY**. Roumanian archives of microbiology and immunology. 2015;74(1-2):7-17.

Although the European recommendations include the use of new antiviral drugs for the treatment of hepatitis C, in Romania the current treatment remains interferon plus ribavirin. First generation viral protease inhibitors (i.e. boceprevir, telaprevir), which have raised the chances of obtaining viral clearance in up to 70% of infection cases produced by genotype 1 isolates, have not been introduced yet as standard treatment in our country. The success of these new antivirals is limited by the occurrence and selection of resistance mutations during therapy. We set-up a molecular study aiming to detect any resistance mutations to boceprevir and telaprevir harbored by hepatitis C isolates infecting Romanian patients naive to viral protease inhibitors. Since these new antivirals are efficient and approved for genotype 1 infection, viral samples were genotyped following a protocol previously developed by our research group. We analyzed by both population sequencing and molecular cloning and sequencing the NS3 protease region of hepatitis C virus isolates infecting patients which were not previously exposed to boceprevir and telaprevir. All the analyzed samples were subtype 1b and resembled the samples collected in recent years from Romanian patients. Molecular cloning followed by sequencing showed great intra-host diversity, which is known to represent the source of isolates with different resistance phenotypes. Both population sequencing and molecular cloning followed by clone sequencing revealed two boceprevir resistance mutations (T54S and V55A), respectively, a telaprevir resistance mutation (T54S) in the sequences obtained from a patient with chronic hepatitis C. To our knowledge, this is the first study indicating the existence of pre-treatment resistance mutations to boceprevir and telaprevir in hepatitis C virus isolates infecting Romanian patients.

Gheorghe L, Iacob S, Simionov I, Caruntu F, Motoc A, Arama V, . . . Rednic N. **A real life boceprevir use in treatment-experienced HCV genotype 1 patients with advanced fibrosis**. Journal of gastrointestinal and liver diseases : JGLD. 2014;23(1):45-50.

BACKGROUND: A number of high quality randomized clinical trials examining the efficacy and safety of

triple therapy in genotype-1 HCV-infected patients have been published. However, these trials included a small number of patients with advanced fibrosis, and selected a population different from that in real-world settings. AIM: To determine the efficacy of boceprevir, pegInterferon and ribavirin regimen in genotype-1 treatment-experienced HCV-infected patients with cirrhosis and bridging fibrosis in real-life setting. METHOD: 167 treatment-experienced patients (85.6% relapsers) out of which 33.5% had cirrhosis, with a mean age of 52.6 years, registered in the Romanian Name Patient Program Database were included into the study. RESULTS: 16.7% of patients had a viral load >100 IU/mL. Undetectable HCV RNA was encountered in 77.3% of patients at week 12. Multiple logistic regression analysis revealed the following independent predictors, measured at week 8, for an HCV RNA >/=100 IU/mL at week 12 of triple therapy: alanine aminotransferase values (p=0.01), hemoglobin level (p=0.04) and <2 log drop of viral load (p<0.0001). A stopping score at 8 weeks was created as the sum of these 3 parameters, with a total of 4 possible points. AUROC of this score was 0.84, with a sensitivity of 75% and a specificity of 86.2%. CONCLUSION: Triple therapy in this cohort of real-life genotype-1 HCV-infected patients with advanced fibrosis showed robust early virological response (EVR) rates. A week 8 model predicting lack of EVR was created, with good clinical utility that can be validated in prospective larger cohorts.

Florea D, Neaga E, Nicolae I, Maxim D, Popa M, Otelea D. **Clinical usefulness of HCV core antigen assay for the management of patients with chronic hepatitis C**. Journal of gastrointestinal and liver diseases : JGLD. 2014;23(4):393-6.
AIM: The study aimed to evaluate the clinical utility of the chemiluminescent HCV core Ag test compared to viral load assessment in the management of patients with chronic hepatitis C. METHODS: A retrospective study was performed at a tertiary-care infectious diseases hospital on samples collected from anti-HCV positive patients. Seventy-six samples were tested with the Architect HCV core Antigen kit and Cobas AmpliPrep/Cobas Taqman HCV kit. The HCV Ag test accuracy was estimated using data from all the HCV RNA tested samples received between January 2011 and December 2012. RESULTS: The HCV Ag test showed a good correlation between the logarithmic values of HCV RNA and HCV Ag (R=0.98), with a 100% specificity and PPV, but with reduced sensitivity for viral loads lower than 1,000 UI/mL. In a model using data from 2,478 HCV RNA tested samples and a cut-off of the Ag assay corresponding to 1,000 UI/mL HCV RNA, the Ag test would have a sensitivity of 82.4%, a NPV of 80.9% and a high specificity and PPV (100%) compared to the viral load. The sensitivity would be higher for baseline evaluation compared to on-treatment samples (98.5 vs. 50%). The highest NPV (98%) would be obtained at 48 and 72 weeks after the initiation of treatment, with a sensitivity of 88.2% and 96.1%, respectively. CONCLUSION: The Architect HCV core Ag assay might be an alternative for the diagnosis of active HCV infection if molecular tests are not available, and a useful method for the evaluation of sustained virological response in treated patients.

Ferenci P, Aires R, Beavers KL, Curescu M, Abrao Ferreira PR, Gschwantler M, . . . Horban A. **Predictive value of FIB-4 and APRI versus METAVIR on sustained virologic response in genotype 1 hepatitis C patients**. Hepatology international. 2014;8(1):83-93.
PURPOSE: Advanced liver fibrosis is a negative predictor of virologic response in genotype 1 chronic hepatitis C (CHC) patients. Biopsy, however, is invasive, costly, and carries some risk of complications. METHODS: Using data from the prospective, international cohort study PROPHESYS, we assessed two alternative noninvasive measures of fibrosis, the FIB-4 and AST-to-platelet ratio index (APRI), to predict virologic response in CHC patients. RESULTS: CHC genotype 1, monoinfected, treatment-naive patients prescribed peginterferon alfa-2a (40 KD)/ribavirin in accordance with country-specific legal and regulatory requirements and who had baseline METAVIR, FIB-4, and APRI scores (N = 1,592) were included in this analysis. Patients were stratified according to the baseline METAVIR, FIB-4, or APRI score to assess virologic response [hepatitis C virus (HCV) RNA <50 IU/mL] by week 4 of treatment (rapid virologic response) and 24 weeks after untreated follow-up]sustained virologic response (SVR)]. Baseline predictors of SVR were explored by multiple logistic regression, and the strength of the association between each fibrosis measure and SVR was evaluated. Both FIB-4 and APRI scores increased with increasing levels of biopsy-assessed fibrosis. The association between FIB-4 and SVR (p < 0.1 x 10(-30)) was stronger than that between METAVIR (p = 3.86 x 10(-13)) or APRI (p = 5.48 x 10(-6)) and SVR. Baseline factors significantly associated with SVR included male gender, lower HCV RNA, lower FIB-4 score, no steatosis, and higher alanine aminotransferase ratio. CONCLUSION: The FIB-4 index provides a valuable, noninvasive measure of fibrosis and can be used to predict virologic response in patients treated with peginterferon alfa-2a (40 KD)/ribavirin.

Sporea I, Curescu M, Sirli R. **"Standard of care" treatment for chronic viral C hepatitis in 2013 in Romania**. Journal of gastrointestinal and liver diseases : JGLD. 2013;22(3):360-1.

Vere CC, Streba CT, Streba L, Rogoveanu I. **Statins in the treatment of hepatitis C**. Hepatitis monthly. 2012;12(6):369-71.

Predescu O, Streba LA, Irimia E, Streba L, Mogoanta L. **Adverse effects of peg-Interferon and Ribavirin combined antiviral treatment in a Romanian hepatitis C virus infected cohort**. Romanian journal of morphology and embryology = Revue roumaine de morphologie et embryologie. 2012;53(3):497-502.
INTRODUCTION: Adverse effects appearing during combined peg-Interferon and Ribavirin antiviral treatment against chronic infection with the hepatitis C virus are a major cause for treatment failures and abrupt interruption. In the prospect of the imminent introduction of new direct acting antiviral agents, with demonstrated higher rates of adverse effects, our study aimed to assess the severity and incidence of several types of adverse effects in a cohort of genotype 1 infected Romanian patients. MATERIALS AND METHODS: We prospectively included a total of 150 patients (45 men), aged 25 to 64 years, who received combined peg-Interferon and Ribavirin antiviral treatment for chronic hepatitis C. Out of these, 145 patients also had liver biopsies prior to treatment initiation. We recorded their viral loads, hemoglobin values and thrombocyte counts, as well as any dermatological, psychiatric or constitutional adverse effect after twelve doses, eight and twelve months of treatment, with two follow-up examinations at three and six months after treatment completion. RESULTS: Viral loads significantly decreased after 12 doses of treatment, in the end a total of six patients (two men and four women) being declared non-responders. Hemoglobin values and thrombocyte counts significantly decreased during treatment ($p<0.0001$), with their values being restored to pre-treatment levels during the follow-up period. We did not find significant differences between the 12-doses, 8 and 12 months values during treatment ($p>0.05$). We recorded 43 cases (11 men and 32 women) presenting with rashes, drug eruptions and erythema. We only encountered grade 1 and 2 dermatological adverse effects. Psychiatric effects were present in 34 cases (10 men and 24 women, 22.6% of the group) and manifested as mild depressions, which did not require specific medication or antiviral dose adjustment. Patients also presented headaches (80.6%), fatigue (71.3%), nausea (47.3%), arthralgias (35.3%) and fever (30%). CONCLUSIONS: We did not encounter severe hematological adverse effects that would require Ribavirin dosage adjustments. Cutaneous and psychiatric adverse effects were also present in a significant number of patients; however, their severity did not influence the continuity or outcome of the antiviral treatment. Other constitutional effects were also present with no direct consequence on the course of treatment. Future agents employed in antiviral therapy shall require extensive monitoring of all adverse effects already acknowledged during dual combination therapy.

Botianu AM, Demian S, Macarie I, Georgescu D, Oltean G, Bataga S. **Acquired haemophilia complicated with gastrointestinal bleeding and spontaneous iliopsoas muscle haematoma in a woman with chronic C hepatitis under treatment with pegylated IFN alpha 2a and ribavirin**. Journal of gastrointestinal and liver diseases : JGLD. 2012;21(1):93-5.
Acquired haemophilia A is a very rare (1-2 cases per million people) but often life-threatening haemorrhagic disorder characterized by antibodies directed against coagulation factor VIII. We report the case of a 55-year old woman under treatment with Pegylated alpha 2a interferon (IFN) and Ribavirin for chronic viral C hepatitis, who developed a progressive severe haemorrhagic syndrome diagnosed as acquired haemophilia based on supplementary laboratory data (prolonged activated partial thromboplastin time, extremely low factor VIII level - 1%, high titre of factor VIII inhibitor - 30 Bethesda U/ml).The onset was insidious, about three months before presenting to our unit. Antiviral therapy had been stopped three weeks before current admission. Emergency intensive treatment included: haemostatic agents - rFVII (Novoseven), FEIBA (Factor VIII Inhibitor Bypassing Activity), vitamin K, adrenostazin, cryoprecipitate, fresh frozen plasma, as well as immunosuppressive therapy (high dose corticotherapy and cyclophoshamide), immunoglobulins (Humaglobin), prophylactic PPI and antibiotics. The evolution was slowly favourable with the remission of the haemorrhagic syndrome and regression of the iliopsoas muscle haematoma. Clinicians should be aware that acquired forms of haemophilia do exist, representing a rare diagnosis and a therapeutic challenge. To our knowledge, this is the first reported case of acquired haemophilia in Romania, in a patient with chronic viral C hepatitis under antiviral treatment.

Sporea I, Popescu A, Curescu M, Sirli R, Dan I, Goldis A, . . . Deleanu A. **The Correlation of Il28B Genotype With Sustained Virologic Response In Romanian patients With Chronic Hepatitis C**. Hepatitis monthly. 2011;11(12):975-9.
BACKGROUND: Multiple variables influencing the sustained virologic response (SVR) in chronic hepatitis C have been evaluated. One of them is genetic polymorphism near the IL28B gene. OBJECTIVES: The aim of this study was to evaluate the influence of IL28B genotypes on SVR rates in a group of patients with chronic hepatitis C from the western part of Romania. PATIENTS AND METHODS: A retrospective study was performed in 107 consecutive patients, previously treated with standard-of-care medication for chronic hepatitis C, identified from the databases of 2 centers. Patient demographics, viral load before treatment and at 12, 24, and 72 weeks from the treatment start, and IL28B genotype were evaluated. RESULTS: Among the 107 patents in the study group, 54 patients had SVR (50.5%), and 62 (57.9%) showed a complete early virologic response (cEVR). The SVR rates according to IL28B genotype were as follows: 73.1% in patients with genotype C/C, 40.9% in those with genotype C/T, and 57.1% in those with genotype T/T (i.e., 73.1% among patients with the C/C genotype vs. 43.7% among those with non-C/C genotypes; P = 0.0126). The cEVR rates were 80.8% in patients with the C/C genotype vs. 51.2% in those with non-C/C genotypes (P = 0.011). CONCLUSIONS: In our cohort of 107 Caucasian HCV patients, the SVR rate was 50.5% with standard-of-care treatment. The SVR rate was directly related to the IL28B genotype: 73.1% in the C/C genotype vs. 43.7% in non-C/C genotypes (P = 0.0126).

Pascu O, Voiculescu M, Gheorghe L, Micu L, Seicean A, Iliescu L, . . . Mateescu B. **Early virological response in 1220 patients with HCV (genotype Ib) chronic hepatitis and cirrhosis treated with PegInterferon plus Ribavirin**. Romanian journal of internal medicine = Revue roumaine de medecine interne. 2011;49(2):105-12.
UNLABELLED: There are over 5000 patients with genotype 1b HCV chronic infection in Romania on national waiting lists. This allowed us to evaluate the complete and partial early virological response rates (EVRc and EVRp), as well as the factors influencing the response rates to treatment. METHODS: PATIENTS: We studied 1220 treatment naive patients with HCV chronic hepatitis who started antiviral therapy during 2009. Mean age was 48 years and female gender was predominant (58%). Chronic hepatitis was documented by liver biopsy in 1129 patients (93%) or by non-invasive tests in 91 cases (7%). Most patients presented advanced liver disease (F3 + F4 Metavir = 62.3%). Viral load was over 400000 iu/mL in 61% patients and over 600000 iu/mL in 52% patients. Treatment was performed with peginterferon alpha-2a in 75.2% patients and with peginterferon alpha-2b in 24.8% patients, with comparative histology. The influence of histology, viral load, gender, age and type of peginterferon on the response rates to treatment was evaluated. RESULTS: EVRc was obtained in 76.6% patients, while 16.2% presented EVRp. From those with EVRp, 78.8% had undetectable viral load after 6 months of therapy. The nonresponder rate was 9.6%. EVRc was influenced by viral load and age, but not by fibrosis stage or type of interferon. CONCLUSIONS: We noticed a high rate of EVRc, which was not influenced by histology, gender or type of interferon. The number of nonresponders and of patients who interrupted therapy due to lack of compliance or adverse events was low.

Gheorghe L, Baculea S. **Cost-effectiveness of peginterferon alpha-2a and peginterferon alpha-2b combination regimens in genotype-1 naive patients with chronic hepatitis C**. Hepato-gastroenterology. 2010;57(101):939-44.
BACKGROUND/AIMS: Pegylated interferons (Peg-IFNs) with ribavirin represent the standard treatment in chronic C viral hepatitis in Romania. Primary aim was to evaluate the cost-effectiveness of Peg-IFN alpha-2a plus ribavirin versus IFN alpha-2b plus ribavirin in genotype-1 patients in Romanian setting. The second end point was to make an indirect comparison of the cost-effectiveness of combination therapy of the two Peg-IFNs. METHODOLOGY: Published clinical data on sustained virological response rates (SVR) and early virological response rates (EVR) from more recent published studies were used for both combination therapies. A Markov model with seven health states was built. The reference patient was a 45-year-old male with chronic non-cirrhotic liver disease due to chronic HCV infection. Time horizon is patient lifetime. Published data on the natural history of hepatitis C, local mortality data, published utilities and local expertise were used for assessment of local procedures, resources used and costs. The perspective is that of the National Health Insurance Agency (NHIA). RESULTS: The incremental cost of treatment with Peg-IFN alpha-2a plus ribavirin is 19,056 RoI per LY gained and 27,175 RoI per QALY gained. A one-way sensitivity analysis showed that results are sensitive to the discount rate used, but they still are highly cost-effective. The indirect comparison of cost-effectiveness of Peg-IFNs

combination therapies over IFN alpha-2b showed superiority of Peg-IFN alpha-2a and ribavirin therapy. CONCLUSION: This study demonstrates a higher cost-effectiveness of the current state-of-the art treatment with Peg-IFN alpha-2a with ribavirin over the standard IFN and ribavirin combination. Although a slight superiority of Peg-IFN alpha-2a over Peg-IFN alpha-2b combined regimen was shown in Romanian setting in terms of LYs and QALYs gained, there are no significant differences in cost-effectiveness of the two therapies.

General treatment

Gheorghe L, Sporea I, Iacob S, Sirli R, Trifan A, Dobru D, . . . Dumitrascu D. **Position paper on treatment of hepatitis C in Romania, 2017. Part one**. Journal of gastrointestinal and liver diseases : JGLD. 2017;26(2):171-81.
BACKGROUND AND AIMS: Hepatitis C Virus (HCV) infection is a common condition with endemic prevalence in some areas of the world. In Romania the mean prevalence is about 3%. New treatments became available on the market in recent years and new drugs are in the pipeline. A re-evaluation of HCV therapy was considered mandatory. The Romanian Society of Gastroenterology and Hepatology undertook this task for the practitioners of this country. METHODOLOGY: A group of recognized experts was created who screened the available literature and the major available guidelines. A list of items requiring attention has been created. These items were discussed and rated. Decisions were taken by consensus. RECOMMENDATIONS: We present here the first of the two parts of our Society's recommendations for chronic HCV infection treatment. An agreement was reached regarding the diagnostic tools, the assessment of severity and the up-dated therapy schedules. CONCLUSIONS: This Position Paper represents a guide for the assessment and the therapy of HCV infection. The recommendations are in concordance with other guidelines but are applied to the real-life conditions in this country.

Gheorghe L, Sporea I, Iacob S, Sirli R, Trifan A, Diculescu M, . . . Dumitrascu DL. **Position Paper on Treatment of Hepatitis C in Romania 2017. Part Two**. Journal of gastrointestinal and liver diseases : JGLD. 2017;26(3):309-17.
BACKGROUND AND AIMS: Hepatitis C virus (HCV) infection is a common condition with endemic prevalence in some areas of the world. In Romania, the mean prevalence is about 3%. New treatments have become available on the market in recent years and new drugs are in the pipeline. A re-evaluation of HCV therapy was considered mandatory. The Romanian Society of Gastroenterology and Hepatology undertook this task for the practitioners of this country. METHODOLOGY: A group of recognized experts was created who screened the available literature and the major available guidelines. A list of items requiring attention was created and these were discussed and rated. Decisions were taken by consensus. RECOMMENDATIONS: We present here the second part of the Society's recommendations for chronic HCV infection treatment. An agreement between experts was reached regarding the therapy of the special categories of patients infected with HCV, complications and monitoring of the therapy, follow-up of the patients who reached sustained virologic response and re-treatment of the patients with therapy failure. CONCLUSIONS: This Position Paper represents a guide for the assessment and the therapy of HCV infection. The recommendations are in concordance with other guidelines but are applied to real-life conditions in Romania.

Preda CM, Popescu CP, Baicus C, Constantinescu I, Oproiu A, Voiosu T, . . . Manuc M. **Risk of hepatitis B virus reactivation in hepatitis B virus + hepatitis C virus-co-infected patients with compensated liver cirrhosis treated with ombitasvir, paritaprevir/r + dasabuvir + ribavirin**. Journal of viral hepatitis. 2018.
Hepatitis B virus may reactivate in patients with chronic hepatitis C treated with direct-acting antivirals. The aim of this study was to investigate the risk of hepatitis B virus (HBV) reactivation in HBV + hepatitis C virus (HCV)-co-infected patients with compensated liver cirrhosis treated with paritaprevir/ombitasvir/ritonavir, dasabuvir with ribavirin. We reviewed prospectively gathered data from a national cohort of 2070 hepatitis C virus patients with compensated liver cirrhosis who received reimbursed paritaprevir/ombitasvir/r, dasabuvir with ribavirin for 12 weeks from the Romanian National

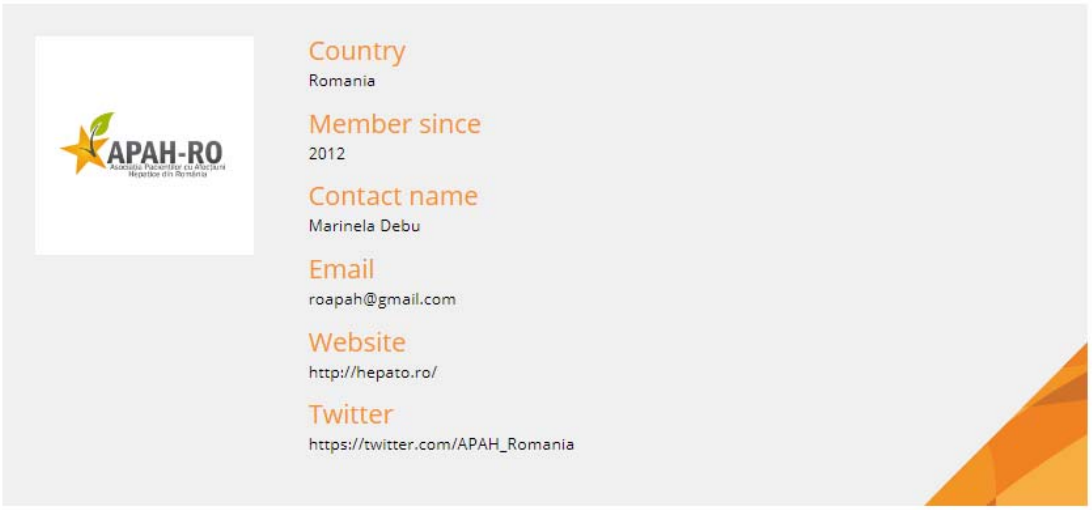
Health Agency during 2015-2016. Twenty-five patients in this cohort were HBs antigen positive (1.2%); 15 untreated with nucleotide analogues agreed to enter the study. These patients were followed up: ALT monthly, serology for HBV and DNA viral load at baseline, EOT and SVR at 12 weeks. Hepatitis B virus (HBV)-co-infected patients were all genotype 1b and 52% females, with a median age of 60 years (51 / 74); 76% were pretreated with peginterferon + ribavirin; 72% were with severe necroinflammatory activity on FibroMax assessment; 40% presented comorbidities; and all were HBe antigen negative. Hepatitis C virus (HCV) SVR response rate was 100%. Hepatitis B virus (HBV)-DNA viral load was undetectable in 7/15 (47%) before therapy, and for the other 8 patients, it varied between below 20 and 867 IU/mL. Five patients (33%) presented virological reactivation (>2 log increase in HBV-DNA levels) during therapy. One patient presented with hepatitis associated with HBV reactivation, and two started anti-HBV therapy with entecavir. Hepatitis B virus (HBV) virological reactivation was present in 33% in our patients. Generally, HBV-DNA elevations were mild (<20 000 IU/mL); however, we report one case of hepatitis associated with HBV reactivation.

Petraru C, Balan G. **[Some aspects of viral hepatitis B and C. Observations on patients treated in Bacau County, between 2007 and 2010]**. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2012;116(2):452-6.
UNLABELLED: The study aim was to assess some features of samples of patients assisted for viral hepatitis B and C, as well as cirrhosis, and included in a national antiviral treatment protocol. MATERIAL AND METHODS: The study considered patients assisted in the medical assurance system in the Bacau County, Romania, during 2007 and 2010. RESULTS: A sample of 1127 patients with chronic viral hepatitides B and C was assisted, from which 154 cases with B virus (13.7%) with a male predominance and 973 with C virus (86.3%) and a female predominance. An increase trend for both hepatitides prevalence was highlighted and a number of non-responders every year (18.1% of total cases). CONCLUSIONS: A correct diagnosis and treatment of\cases with chronic viral hepatitis B and C and to have a smaller number ofnon-responders represent major purposes of specialists in the Bacau County also.

Session 4: Prevention and Control of viral hepatitis	
11:55 - 12:15	Prevention and control activities by Civil society and patient organisation ***Marinela Debu and Marian Ursan***

APAH-RO website: https://hepato.ro/

Assocation of patients with hepatic diseases in Romania



APAH-RO is a Romanian NGO, established in 2009, by a group of patients affected by liver disease. Currently, the association has branches and regional centres across the country, in Alexandria, Arad, Brasov, Bucharest, Iasi and Cluj.

Through its actions, the association secures the liaison between key stakeholders – medical community and representatives of the authorities, voicing the main concerns of the Romanian patients with liver diseases.

APAH-RO acts under the „For Your Rights!" motto and fights for patients rights, aiming to have in Romania:

- A National Program for Hepatitis – prevention, diagnosis, access to treatment and monitoring
- Screening program for the early diagnosis of hepatic affections
- A National Register for Hepatitis
- Access to treatment for a large number of patients
- Psychological support for hepatitis patients
- Broad campaigns aiming to raise awareness in regards to prevention, diagnosis and treatment
- Broad campaigns aiming to raise awareness on patients' rights and the issues related to discrimination (employment, integration in communities)

APAH-RO is a member of:

- European Liver Patients Association (ELPA)
- World Hepatitis Alliance (WHA)
- The Alliance of Patients with Chronic Disease in Romania (APCR)

Carusel website: https://carusel.org

Carusel aim to improve the quality of life for drug and alcohol users, sex workers or individuals who have multiple sex partners, persons who live on the streets, socially and economically challenged people end the ones that are at risk of getting sick or facing social exclusion.

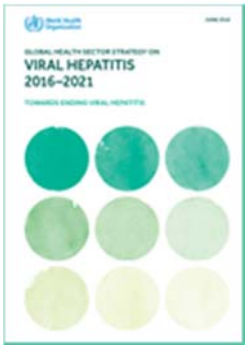
The mission of Carusel is to create an active, proactive and reactive social environment, in order to promote and defend the human rights and civil liberties.

2.3 Session 5 Prevention and control of viral hepatitis

Session 5: groups discussion What are the needs to Eliminate viral hepatitis by 2030	
13:30 - 13:50	National Hepatitis plan - Romania ***Dr Cora Pop***
13:50 - 15:20	Groups discussion: *Assess the needs to achieve the WHO's Regional office for Europe- targets for elimination viral hepatitis in Romania by 2030*

WHO Elimination Goals

Global health sector strategy on viral hepatitis 2016-2021



This is the first global health sector strategy on viral hepatitis, a strategy that contributes to the achievement of the 2030 Agenda for Sustainable Development.

It covers the first six years of the post-2015 health agenda, 2016–2021, building on the Prevention and Control of Viral Hepatitis Infection: Framework for Global Action, and on two resolutions on viral hepatitis adopted by the World Health Assembly in 2010 and in 2014.

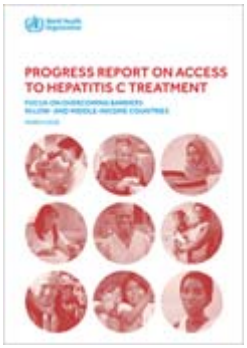
The strategy addresses all five hepatitis viruses (hepatitis A, B, C, D and E), with a particular focus on hepatitis B and C, owing to the relative public health burden they represent.

Global hepatitis Report 2017

In May 2016, the World Health Assembly endorsed the *Global Health Sector Strategy (GHSS) on viral hepatitis 2016–2021*. The GHSS calls for the elimination of viral hepatitis as a public health threat by 2030 (reducing new infections by 90% and mortality by 65%).
This WHO *Global hepatitis report* describes, for the first time, the global and regional estimates on viral hepatitis in 2015, setting the baseline for tracking progress in implementing the new global strategy.
The report focuses on hepatitis B and C, which are responsible for 96% of all hepatitis mortality. It presents data along the five strategic directions (strategic information, interventions, equity, financing and innovation) – key pillars of the GHSS to facilitate monitoring of progress in countries, regions and globally, and to measure the impact of interventions on reducing new infections and saving lives between 2015 and 2030.

Progress report on access to hepatitis C treatment

Focus on overcoming barriers in low- and middle-income countries



Increased access to highly effective direct-acting antivirals (DAAs) for the treatment of infection with the hepatitis C virus (HCV) is revolutionizing the prospect of ending HCV epidemics. Globally, the number of people who initiated DAA-based treatment for HCV rose between 2015 and 2016, from approximately 1 million to 1.5 million.

This report updates the first edition, published in 2016, and reviews the progress countries have made in expanding access to life-saving DAAs. The report reviews the main challenges countries face and describes recent developments in relation to five key factors that determine access to DAA medicines: affordability, quality assurance, regulatory approval, government commitment and financing. It highlights key areas for action by ministries of health and other government decision-makers, pharmaceutical manufacturers and technical partners.

Action plan for the health sector response to viral hepatitis in the WHO European Region (2017)

This first Action plan for viral hepatitis in the WHO European Region adapts the Global Health Sector Strategy on Viral Hepatitis, 2016–2021 to the context of the European Region.

The plan was developed through a participatory process, finalized and endorsed at the 66th session of the WHO Regional Committee for Europe, along with resolution EUR/RC66/R10. While the Action plan addresses all five hepatitis viruses, its major focus is on hepatitis B and C, given the high public health burden they represent in the Region.

The goal of the Action plan is elimination of viral hepatitis as a public health threat in the WHO European Region by 2030 through the reduction of transmission, morbidity and mortality due to viral hepatitis and its complications, and by ensuring equitable access to comprehensive prevention, recommended testing, care and treatment services for all.

Fact sheets on sustainable developments goals: health target, Viral hepatitis

The facts sheets on the SDG health targets present key facts and figures, ongoing commitments, guidance on action, and indicators to monitor progress – in the context of the WHO European Region. They also provide specific highlights on how WHO/Europe supports its Member States in achieving these targets, and cover key SDG aspects such as equity, partnerships and intersectoral collaboration

Public health, elimination of viral hepatitis- Romania

Voiculescu M. **How Far we are towards Eradication of HBV Infection**. Journal of gastrointestinal and liver diseases : JGLD. 2015;24(4):473-9.
Hepatitis B virus (HBV) infection is a major health problem with an important biological and a significant socio-economic impact all over the world. There is a high pressure to come up with a new and more efficient strategy against HBV infection, especially after the recent success of HCV treatment. Preventing HBV infection through vaccine is currently the most efficient way to decrease HBV-related cirrhosis and liver cancer incidence, as well as the best way to suppress the HBV reservoir. The vaccine is safe and efficient in 80-95% of cases. One of its most important roles is to reduce materno-fetal transmission, by giving the first dose of vaccine in the first 24 hours after birth. Transmission of HBV infection early in life is still frequent, especially in countries with high endemicity. Successful HBV clearance by the host is immune-mediated, with a complex combined innate and adaptive cellular and humoral immune response. Different factors, such as the quantity and the sequence of HBV epitope during processing by dendritic cells and presenting by different HLA molecules or the polymorphism of T cell receptors (TOL) are part of a complex network which influences the final response. A new potential therapeutic strategy is to restore T-cell antiviral function and to improve innate and adaptive immune response by immunotherapeutic manipulation. It appears that HBV eradication is far from being completed in the next decades, and a new strategy against HBV infection must be considered.

Access to Treatment

Marshall AD, Cunningham EB, Nielsen S, Aghemo A, Alho H, Backmund M, . . . Grebely J. **Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe**. The lancet Gastroenterology & hepatology. 2018;3(2):125-33.
All-oral direct-acting antiviral drugs (DAAs) for hepatitis C virus, which have response rates of 95% or more, represent a major clinical advance. However, the high list price of DAAs has led many governments to restrict their reimbursement. We reviewed the availability of, and national criteria for, interferon-free DAA reimbursement among countries in the European Union and European Economic Area, and Switzerland. Reimbursement documentation was reviewed between Nov 18, 2016, and Aug 1, 2017. Primary outcomes were fibrosis stage, drug or alcohol use, prescriber type, and HIV co-infection restrictions. Among the 35 European countries and jurisdictions included, the most commonly reimbursed DAA was ombitasvir, paritaprevir, and ritonavir, with dasabuvir, and with or without ribavirin (33 [94%] countries and jurisdictions). 16 (46%) countries and jurisdictions required patients to have fibrosis at stage F2 or higher, 29 (83%) had no listed restrictions based on drug or alcohol use, 33 (94%) required a specialist prescriber, and 34 (97%) had no additional restrictions for people co-infected with HIV and hepatitis C virus. These findings have implications for meeting WHO targets, with evidence of some countries not following the 2016 hepatitis C virus treatment guidelines by the European Association for the Study of Liver.

Leblebicioglu H, Arends JE, Ozaras R, Corti G, Santos L, Boesecke C, . . . Salmon D. **Availability of hepatitis C diagnostics and therapeutics in European and Eurasia countries**. Antiviral research. 2018;150:9-14.
BACKGROUND: Treatment with direct acting antiviral agents (DAAs) has provided sustained virological response rates in >95% of patients with chronic hepatitis C virus (HCV) infection. However treatment is costly and market access, reimbursement and governmental restrictions differ among countries. We aimed to analyze these differences among European and Eurasian countries. METHODS: A survey including 20-item questionnaire was sent to experts in viral hepatitis. Countries were evaluated according to their income categories by the World Bank stratification. RESULTS: Experts from 26 countries responded to the survey. As of May 2016, HCV prevalence was reported as low (</=1%) in Croatia, Czech Republic, Denmark, France, Germany, Hungary, the Netherlands, Portugal, Slovenia, Spain,

Sweden, UK; intermediate (1-4%) in Azerbaijan, Bosnia and Herzegovina, Italy, Kosovo, Greece, Kazakhstan, Romania, Russia, Serbia and high in Georgia (6.7%). All countries had national guidelines except Albania, Kosovo, Serbia, Tunisia, and UK. Transient elastography was available in all countries, but reimbursed in 61%. HCV-RNA was reimbursed in 81%. PegIFN/RBV was reimbursed in 54% of the countries. No DAAs were available in four countries: Kazakhstan, Kosovo, Serbia, and Tunisia. In others, at least one DAA combination with either PegIFN/RBV or another DAA was available. In Germany and the Netherlands all DAAs were reimbursed without restrictions: Sofosbuvir and sofosbuvir/ledipasvir were free of charge in Georgia. CONCLUSION: Prevalence of HCV is relatively higher in lower-middle and upper-middle income countries. DAAs are not available or reimbursed in many Eurasia and European countries. Effective screening and access to care are essential for reducing liver-related morbidity and mortality.

Ozaras R, Corti G, Ruta S, Lacombe K, Mondelli MU, Irwing WL, . . . Arends JE. **Differences in the availability of diagnostics and treatment modalities for chronic hepatitis B across Europe**. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2015;21(11):1027-32.
The prevalence and management of chronic hepatitis B virus (HBV) infection differ among European countries. The availability and reimbursement of diagnostics and drugs may also vary, determining distinct treatment outcomes. Herein, we analyse differences in medical facilities for the care of patients with chronic HBV infection across Europe. A survey was sent to the members of the ESCMID Study Group for Viral Hepatitis, all of whom are experts in chronic HBV infection management. The comprehensive survey asked questions regarding hepatitis B surface antigen (HBsAg) prevalence, the availability of diagnostics and drugs marketed, and distinct clinical practice behaviours in the management of chronic HBV infection. World Bank data were used to assess the economic status of the countries. With 16 expert physicians responding (69%), the HBsAg prevalence rates were <1% in France, Hungary, Italy, The Netherlands, Portugal, Spain, and the UK, intermediate (1-5%) in Turkey, Romania, and Serbia, and high (>5%) in Albania and Iran. Regarding the availability and reimbursement of HBV diagnostics (HBV DNA and liver stiffness measurement), HBV drugs (interferon, lamivudine, tenofovir, and entecavir), HBV prophylaxis, and duration of HBeAg-positive and HBeAg-negative HBV infection, the majority of high-income and middle-income countries had no restrictions; Albania, Iran and Serbia had several restrictions in diagnostics and HBV drugs. The countries in the high-income group were also the ones with no restrictions in medical facilities, whereas the upper-middle-income countries had some restrictions. The prevalence of chronic HBV infection is much higher in southern and eastern than in western European countries. Despite the availability of European guidelines, policies for diagnostics and treatment vary significantly across European countries.

Papatheodoridis GV, Tsochatzis E, Hardtke S, Wedemeyer H. **Barriers to care and treatment for patients with chronic viral hepatitis in Europe: a systematic review**. Liver international : official journal of the International Association for the Study of the Liver. 2014;34(10):1452-63.
BACKGROUND & AIMS: Despite the availability of effective therapies for hepatitis B (HBV) and C virus (HCV), only a minority of these patients receive treatment. We systematically reviewed published data on barriers to management for chronic HBV/HCV patients in Europe. METHODS: Literature search to identify studies including adult patients with chronic HBV/HCV infection from European countries and data on barriers to treatment. RESULTS: Twenty-five studies including 6253 chronic HBV and 19,014 HCV patients were identified, of which only two were from Eastern Europe. The mean rate of no treatment in HBV patients was 42% being higher in North-Western European countries than Italy (56% vs. 39%, P < 0.001). Immigrants represented the most common barrier to HBV treatment. The mean rate of no treatment in HCV RNA-positive patients was 57%, being highest in Romania (89%), intermediate in France (79%) and lower though still high in other European countries (52%, P < 0.001). The predominant barriers to HCV treatment were lack of financial resources in Romania and direct/indirect limitations of interferon-alfa and/or parenteral drug and alcohol abuse in other countries. The mean rate of no treatment was highest in HCV RNA-positive parenteral drug users (72%) and intermediate in those with HCV-HIV co-infection (64%). CONCLUSIONS: A substantial proportion of diagnosed chronic HBV and the majority of diagnosed HCV patients remain untreated. The rates and most importantly the reasons of barriers to treatment in chronic HBV/HCV patients vary widely among European countries supporting the need for country-specific national strategies, resource allocation and implementation of global management policies.

Arama V, Leblebicioglu H, Simon K, Zarski JP, Niederau C, Habersetzer F, . . . Zeuzem S. **Chronic hepatitis B monitoring and treatment patterns in five European countries with different access and reimbursement policies**. Antiviral therapy. 2014;19(3):245-57.
BACKGROUND: In Europe, health-care policies are determined at a national level and differ between countries. This analysis from a prospective, longitudinal, non-interventional study aimed to describe patterns in the clinical monitoring and treatment of chronic hepatitis B (CHB) in five European countries. METHODS: Country-specific cohorts of adult patients with compensated CHB managed in clinics in Germany, France, Poland, Romania and Turkey were followed for up to 2 years between March 2008 and December 2010. RESULTS: A total of 1,267 patients were included. Baseline age and gender distribution were similar across countries for patients who were treated (n=567) and untreated (n=700) at baseline. Most treated patients were receiving monotherapy at baseline, most frequently with entecavir or tenofovir in Germany, France and Turkey, and with lamivudine in Poland and Romania. Use of pegylated interferon was more frequent in Poland and Romania than in other countries. In Romania monotherapy with entecavir increased after it became reimbursed in 2008. Hospitalizations during follow-up were more frequent in Romania (1.45 hospital days/patient-year) and Poland (1.81 days/patient-year) than in Turkey, France and Germany (0.00, 0.05 and 0.10 days/patient-year, respectively); clinic visits were more frequent in Poland (3.20 versus 0.30-1.78 visits/patient-year across other countries). CONCLUSIONS: These results illustrate country-specific patterns in the management of CHB patients across Europe. Observed monitoring patterns, hospitalization rates and other health-care utilization may be related to cost and reimbursement issues; however, further study in individual countries would be required to confirm these (post hoc) observations.

Gheorghe L, Pascu O, Ceausu E, Csiki IE, Iacob S, Caruntu F, . . . Vadan R. **Access to peginterferon plus ribavirin therapy for hepatitis C in Romania between 2002-2009**. Journal of gastrointestinal and liver diseases : JGLD. 2010;19(2):161-7.
BACKGROUND: An overall prevalence rate of HCV infection in Romanian adult population was recently estimated to be 3.23%. The proportion of treated patients with chronic hepatitis C in our country has never been assessed. AIMS: 1) to analyze the quality and quantity of antiviral therapy delivery; 2) to determine the proportion of patients being annually and ever treated with antiviral therapy in Romania and 3) to identify barriers against treatment of HCV infected-population in Romania. RESULTS: The number of annually treated patients remained relatively stable between 2002 and 2007 (1,813 patients treated with pegylated interferon and ribavirin in 2002 and 2,446 in 2007). There was a doubled increase in reimbursed treatment in 2008 and 2009 (4,503 and respectively 4,701 treated patients) due to a special campaign organized to increase awareness and prevention of HCV transmission. The median time to therapy approval varies from county to county; overall it is 10.23 months. A total number of 25,318 patients with chronic C hepatitis were treated between 2002-2009, corresponding to a cumulative proportion of 4.1% of the prevalent cases of HCV infection treated in Romania until 1st January 2010. The main limiting factor of access to antiviral therapy for hepatitis C in Romania remains the lack of funds. CONCLUSIONS: This is the first analysis of the nationwide practice for treatment of hepatitis C in Romania. Increased public health efforts are required to improve access to antiviral therapy for hepatitis C in Romania.

3. Speakers information

List of publications achieved via speaker's form, when this form was not available a Pubmed MEDLINE search was performed on Name of the speaker in [Author]-field. If more than 10 references were available only the most recent articles are shown.
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FLORENTINA FURTUNESCU,

Director of the National Institute of Public Health
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ODETTE POPOVICI

National Institute of Public Health
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ADRIAN STREINU CERCEL

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1. xxx

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ADRIANA PISTOL

Medical epidemiologist, Director of the National Center for Communicable Diseases Surveillance and Control. National Institute of Public Health
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ALEXANDRU RAFILA

President of the Microbiology Commission Ministry of Health
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President of the Gastroenterology Commission Ministry of Health
From Speakers form:

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State Secretary Ministry of Health

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