

NORTH MACEDONIA

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– SKOPJE

SKOPJE, NORTH MACEDONIA

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# VHPB BALKAN MEETING

## *LESSONS LEARNT, BEST PRACTICES AND FUTURE CHALLENGES*



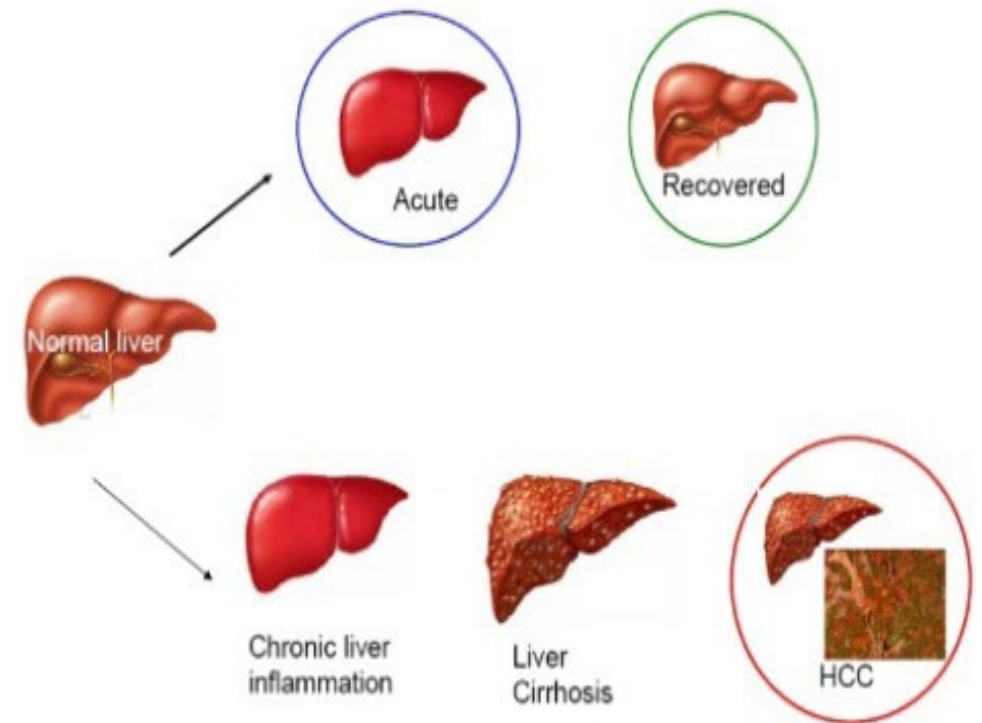
# NORTH MACEDONIA

## NATIONAL PLAN

- 2004 - Consensus for Prevention, Diagnosis, Therapy and Monitoring of Patients with Hepatitis B and Hepatitis C in Republic of Macedonia
- Evidence Based Medicine - last up date 2014
- Local protocol for antiviral treatment in patients with Chronic Hepatitis C from UC for Gastroenterohepatology, Skopje - 2021
- **New written national plan that focuses exclusively or primarily on the prevention and control of viral hepatitis in North Macedonia is necessary**

# HBV INFECTION

- 296 million people were living with chronic hepatitis B infection, with 1.5 million new infections each year, according to the WHO .
- Most adults infected with the hepatitis B virus recover completely, while infants and children, the elderly, and immunocompromised patients are more likely to develop chronic hepatitis B infection.
- N. Macedonia is a country with intermediate prevalence of HBV - between 2 – 4%;



# HEPATITIS B NATIONAL DATA

## BI 6 ACUTE HEPATITIS B

Year	I/100.000	%	cases
2010	7,6	0.007	153
2011	7,6	0.007	154
2012	9,1	0.009	184
2013	8,1	0.008	165
2014	8,4	0.008	171
2015	7,3	0.007	148
2016	5,1	0.005	104
2017	3,5	0.003	72
2018	4,3	0,004	88
2019	4,5	0,004	91
2020	1,8	0,001	37
2021	1,6	0,001	29

# HEPATITIS B NATIONAL DATA

## B18.1 CHRONIC VIRAL HEPATITIS B WITHOUT DELTA-AGENT AND Z22.51 CARRIER OF VIRAL HEPATITIS B

Chronic viral hepatitis B without delta-agent – B18.1

Year	cases
2010	2
2011	10
2012	23
2013	30
2014	32
2015	31
2016	15
2017	39
2018	28
2019	14
2020	5
2021	5

Carrier of viral hepatitis B – Z22.51

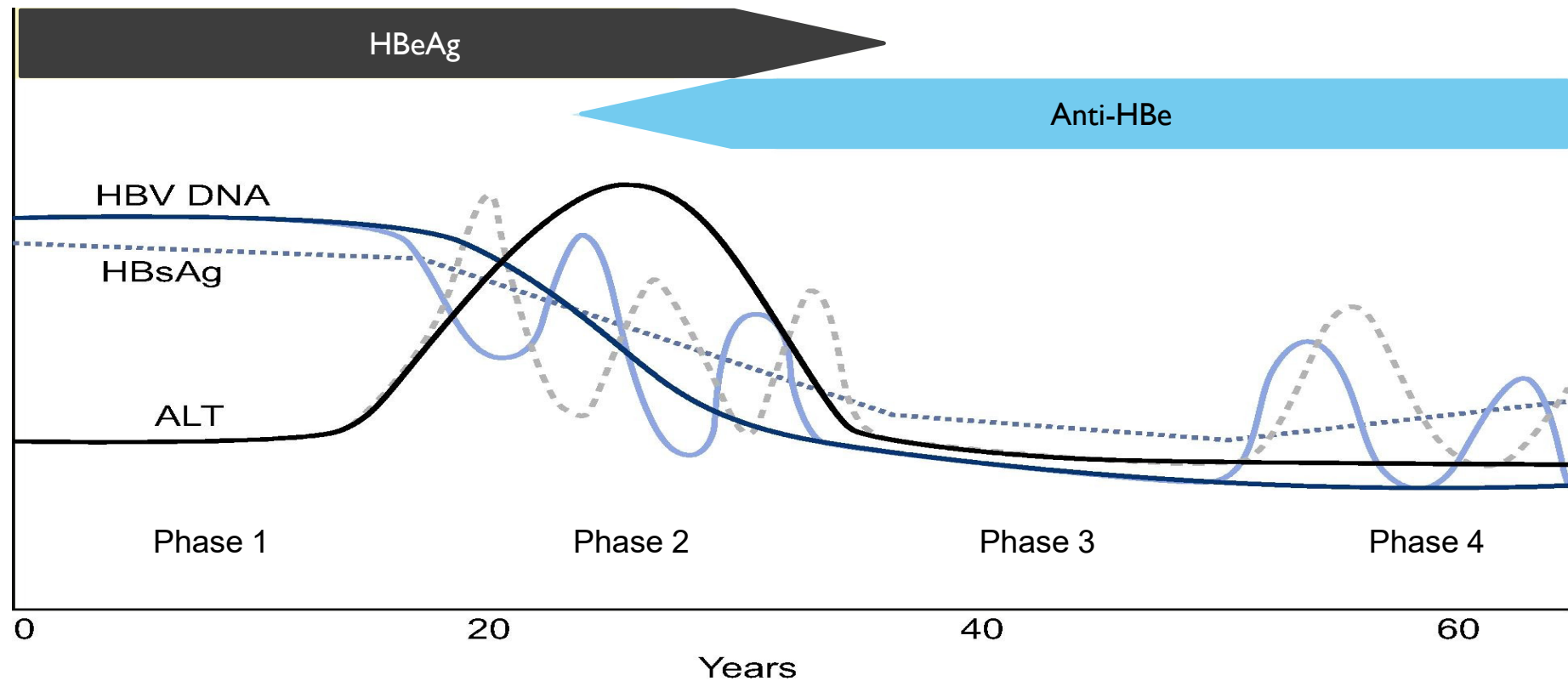
Year	cases
2010	71
2011	50
2012	86
2013	158
2014	91
2015	78
2016	62
2017	49
2018	40
2019	37
2020	18
2021	12

# VACCINATION AGAINST HEPATITIS B

- **Mandatory vaccination against Hepatitis B for all newborns started in November 2004.**
- Recommended vaccination for:
  - Health workers and medical students
  - Patients on hemodialysis
  - Patients with hemophilia
  - PWID
  - Patients with chronic HCV infection
  - People living with HIV (PLHIV)



# PHASES OF CHRONIC HBV INFECTION<sup>1</sup>



**New  
nomenclature<sup>2</sup>**

HBeAg-positive  
chronic HBV infection

HBeAg-positive  
chronic hepatitis B

HBeAg-negative  
chronic HBV infection

HBeAg-negative  
chronic hepatitis B

1. Lok A, et al. J Hepatol 2017;67:847–61;  
2. EASL CPG HBV. J Hepatol 2017;67:370–98

# EASL RECOMMENDATIONS ON TREATMENT OF HEPATITIS B: WHO SHOULD BE TREATED?

- Patients with HBeAg-positive or HBeAg-negative chronic hepatitis B
- Patients with cirrhosis, any detectable HBV DNA, regardless of ALT level
- Patients with HBV DNA  $>20,000$  IU/mL and ALT  $>2\times$  ULN, regardless of severity of histological lesions



# TREATMENT STRATEGIES FOR CHRONIC HEPATITIS B

- Pegylated Interferon - PegIFN
- Entecavir (ETV)
- Tenofovir disoproxil fumarate (TDF)
- Tenofovir alafenamide (TAF)

Subcutaneous injections

Oral route of administration  
Long-term administration of a  
potent NA with a  
high barrier to resistance is the  
treatment of choice

# AVAILABLE THERAPY FOR CHB IN NORTH MACEDONIA

## ■ Available therapy for HBV treatment in North Macedonia:

1. Nucleotide Analogue (NA) with high barrier to resistance: Tenofovir disoproxil fumarate (TDF) and Entecavir (ENT) are registered, but not covered by the health insurance system in NM
2. NA with low barrier to resistance – Lamivudin
3. Pegylated interferon

# TREATMENT OF OUTPATIENTS WITH CHB AT THE UC OF GASTROENTEROHEPATOLOGY FOR A PERIOD JAN. 2021 – SEP. 2022

	LAM	Tenofovir 245
Traitment naive	42	18
Traitment experienced	13	33
<b>Total</b>	<b>55</b>	<b>51</b>
Therapeutical response		
Sustained HBV DNA supression	21 (38.2%)	39 (76.5%)
Non responders or reactivation	34 ( <b>61.8%</b> )	2 ( <b>3.9%</b> )
Unknown or just started		10 (19.6%)

Data from the UC of Gastroenterohepatology Skopje, 2022

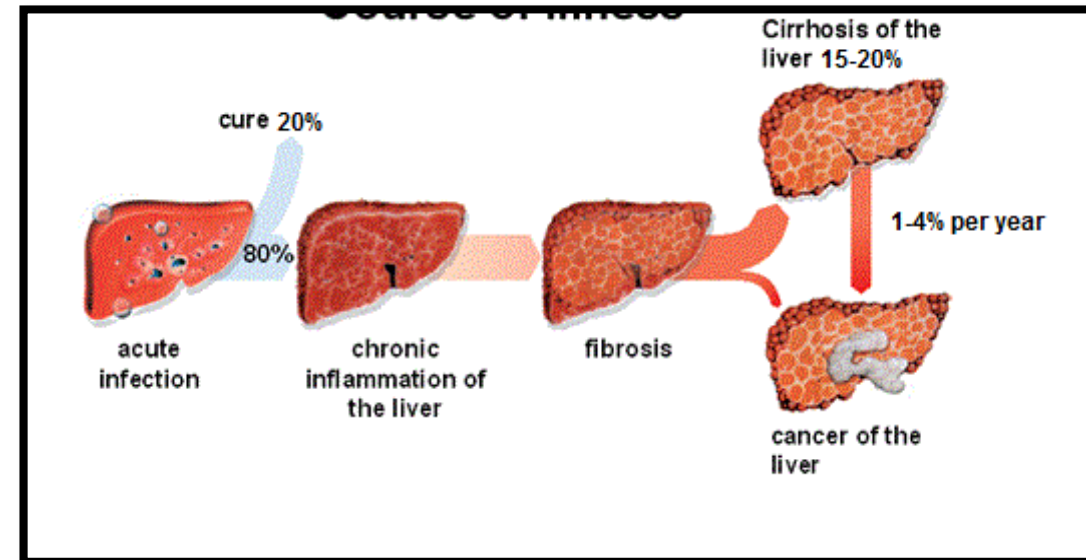
## OLD DATA FROM UC FOR GASTROENTEROHEPATOLOGY ABOUT TREATMENT OF OUTPATIENTS WITH CHB FOR A PERIOD 2009 – 2015

	Peg-IFN 180 mcg/ml	LAM	Tenofovir 245
Treatment naive	95	93	12
Treatment experienced	/	96	35
<b>Total</b>	<b>95</b>	<b>189</b>	<b>47</b>
Therapeutical response			
Sustained HBV DNA suppression	27 (31%)	81 (42.9%)	47 (100%)
Non responders or reactivation	58 ( <b>59.6%</b> )	108 ( <b>57.1%</b> )	0 ( <b>0%</b> )
Unknown	9 (9.4%)		

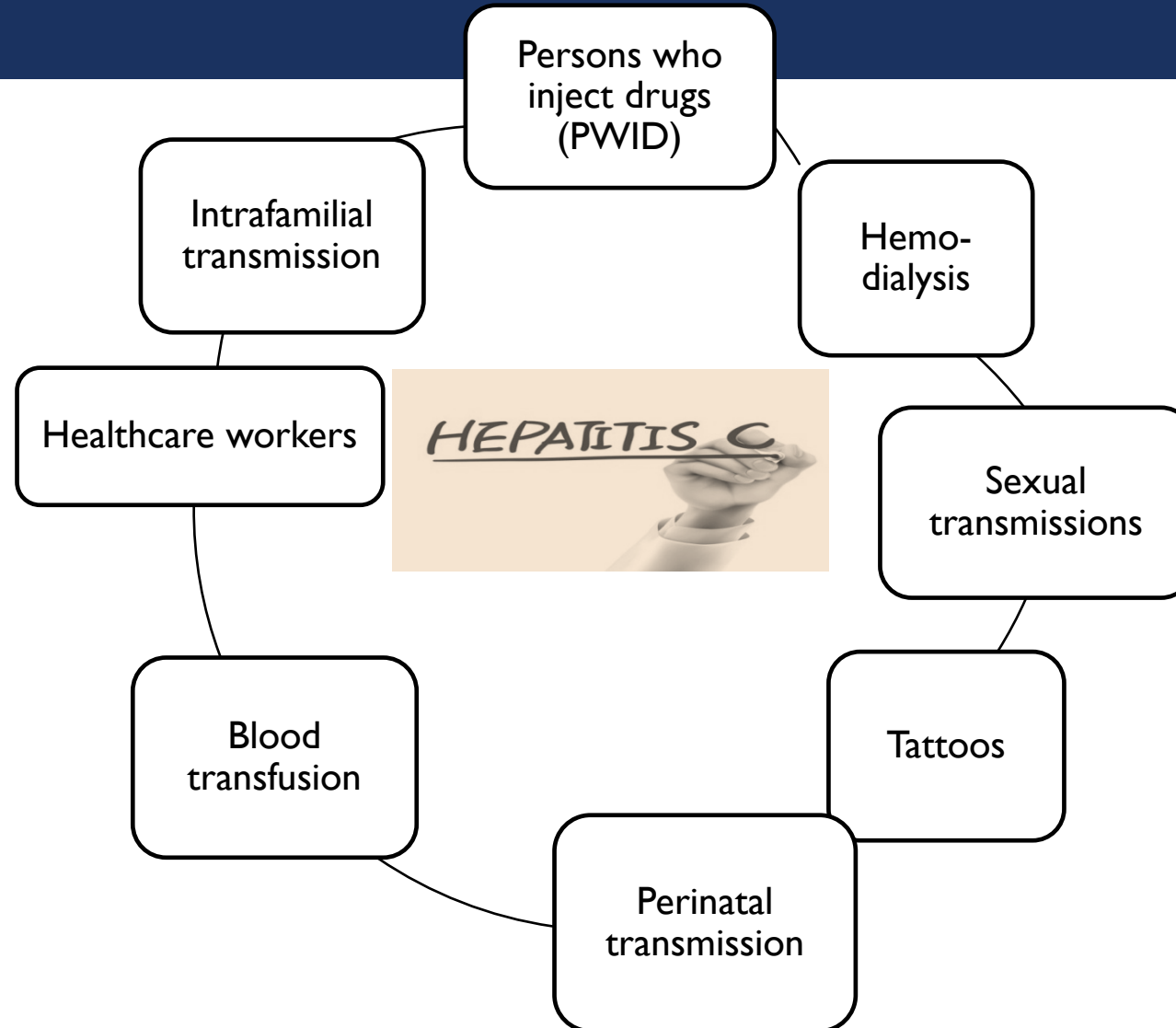
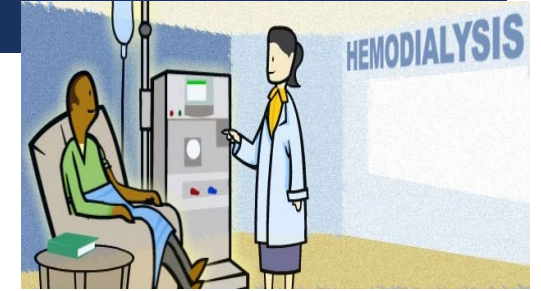
Data from the UC of Gastroenterohepatology Skopje, 2018

# HCV INFECTION

- Global prevalence of HCV infection is 0.5 - 2.3% of the world's population (approximately 58 million people have a chronic infection according to the WHO)
- 50-85% of those people infected with HCV will develop chronic hepatitis which leads to the development of more advanced forms of liver damage and increased risk for HCC
- Prevalence of HCV in N. Macedonia is 1,5 – 1,8% (30.000-40.000 HCV positive individuals);



# MODE OF TRANSMISSION OF HCV, AS WELL AS HBV



# MODE OF TRANSMISSION OF HCV IN N. MACEDONIA

Mode of transmission of HCV(%)

Mode of transmission of HCV	%
PWID	62.3
Hemodialysis	32
Other modes	5.7



Kiprijanovska S, et al. J Med Virol 2013;85(12):2072-8

# HEPATITIS C NATIONAL DATA

## B17.1 ACUTE HEPATITIS C

Year	I/100.000	%	cases
2010	3,5	0.004	72
2011	3,7	0.004	76
2012	8,1	0.008	166
2013	3,4	0.003	70
2014	3.0	0.003	63
2015	2,9	0.003	60
2016	2,2	0.002	45
2017	1,4	0.001	29
2018	1,7	0,001	35
2019	2,4	0,002	50
2020	0,5	0,0004	10
2021	0,2	0,0001	3





# HEPATITIS C NATIONAL DATA

## B18.2 CHRONIC VIRAL HEPATITIS C AND Z22.52 CARRIER OF VIRAL HEPATITIS C

### Chronic viral hepatitis C – B18.2

Year	cases
2010	11
2011	16
2012	9
2013	18
2014	14
2015	27
2016	13
2017	39
2018	42
2019	12
2020	2
2021	4

### Carrier of viral hepatitis C – Z22.52

Year	cases
2010	41
2011	64
2012	66
2013	38
2014	29
2015	27
2016	22
2017	24
2018	6
2019	39
2020	12
2021	7

Data source: Institute for Public Health of N. Macedonia, Skopje, N. Macedonia 2022



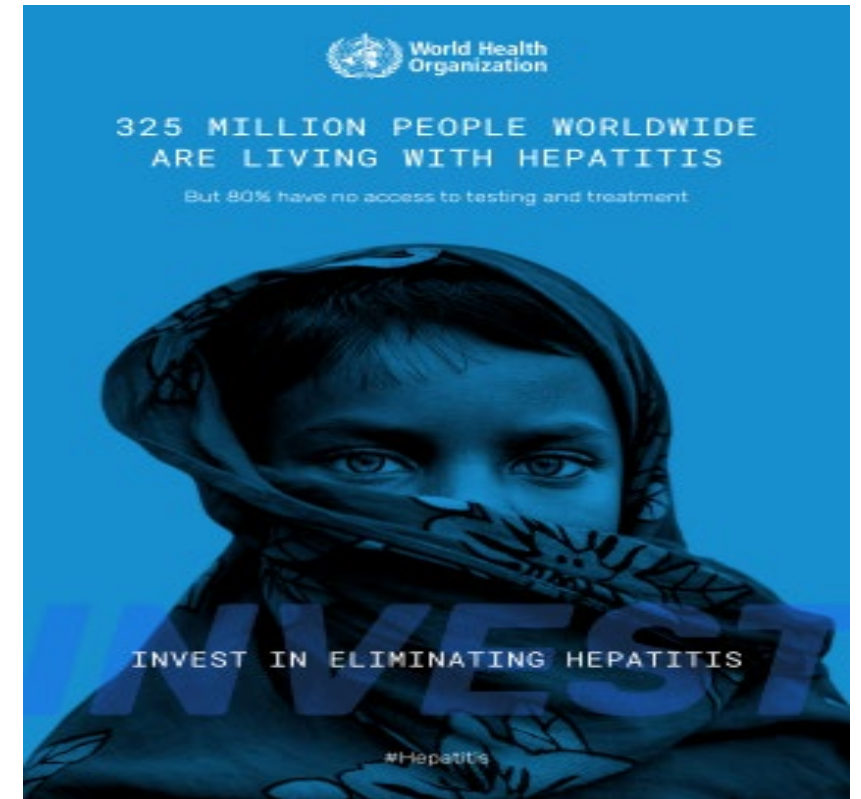
# EASL RECOMMENDATIONS ON TREATMENT OF HEPATITIS C: WHO SHOULD BE TREATED?

- All treatment-naïve and treatment-experienced patients with recently acquired or chronic HCV infection must be offered treatment without delay
- Urgent treatment should be considered:
  1. in patients with significant fibrosis or cirrhosis;
  2. in patients with clinically significant extrahepatic manifestations;
  3. in patients with HCV recurrence after liver transplantation;
  4. in patients at risk of a rapid evolution of liver disease because of concurrent comorbidities;
  5. in individuals at risk of transmitting HCV

# WHO STRATEGY

- The WHO strategy aims to eliminate viral hepatitis as a public health problem by reducing new viral hepatitis infections by 90% and reduce deaths due to viral hepatitis by 65% by 2030

The WHO strategy is our strategy



# EASL RECOMMENDATIONS ON TREATMENT OF HEPATITIS C: PANGENOTYPIC AND NON-PANGENOTYPIC REGIMENS

- Pangenotypic regimens:
  1. The fixed-dose combination of **sofosbuvir (400 mg)** and **velpatasvir (100 mg)** in a single tablet administered once daily;
  2. The fixed-dose combination of **glecaprevir (300 mg)** and **pibrentasvir (120 mg)** in 3 tablets, administered once daily with food;
  3. The fixed-dose combination of **sofosbuvir (400 mg)**, **velpatasvir (100 mg)** and **voxilaprevir (100 mg)** in a single tablet administered once daily with food.
- The non-pangenotypic fixed-dose combination of **grazoprevir (100 mg)** and **elbasvir (50 mg)** in a single tablet administered once daily can also be used in patients infected with HCV genotype 1b

# DAA THERAPY

- Treatment with new DAA therapy for patients with CHC at UC for Gastroenterohepatology started at 2018 as donation of Zepatier (Grazoprevir/ Elbasvir) and Qurevo (Ombitasvir/Paritaprevir/Ritonavir) + Exviera (Dasabuvir) through The Ministry of Health
  
- **Available DAA therapy for HCV treatment at this moment:**
  1. Sofosbuvir 400 mg / Velpatasvir 100 mg- pangenotypic
  2. Grazoprevir 100 mg / Elbasvir 50 mg - non-pangenotypic

# TREATED HCV RNA (+) PATIENTS WITH DAAS – OUR DATA DURING LAST THREE YEARS

	Total No of patients (79)		
	<b>Zepatier</b> (39 pts)	<b>Qurevo+ Exviera</b> (21 pts)	<b>Epclusa</b> (19pts)
SVR 24 (+)	97,4% (38 pts)	85,7% (18 pts)	100% (19 pts)
SVR 24 (-)	2,6% (1 pts)	14,3% (3 pts)	0% (0 pts)

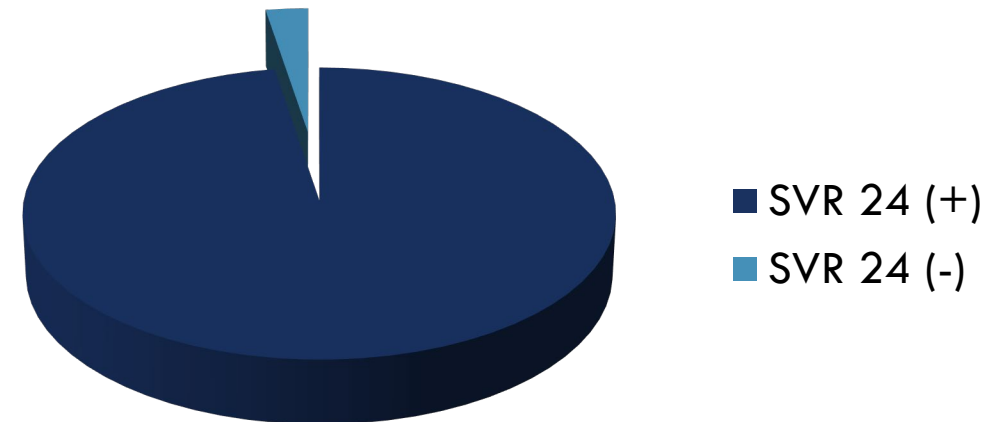
Data from the UC of Gastroenterohepatology Skopje, 2022



# TREATED HCV RNA (+) PATIENTS WITH ZEPATIER (GRAZOPRE VIR/ELBAS VIR)

	Zepatier (39 pts)
SVR 24 (+)	97,40%
SVR 24 (-)	2,60%

Zepatier (39 pts)

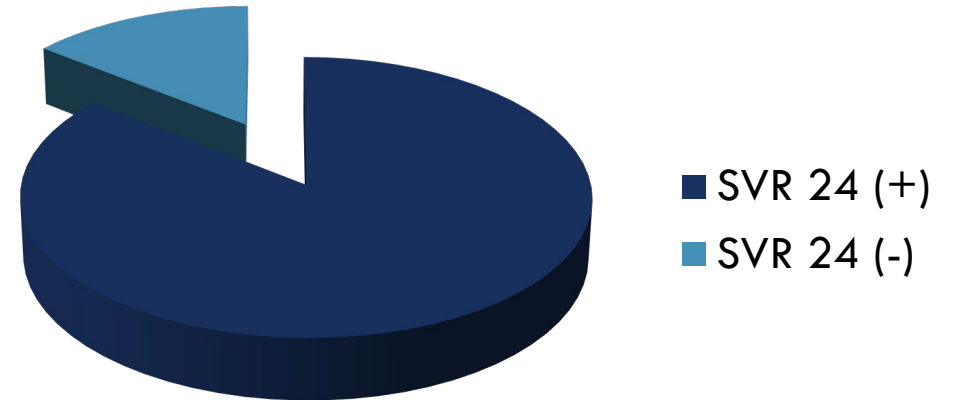


Data from the UC of Gastroenterohepatology Skopje, 2022

# TREATED HCV RNA (+) PATIENTS WITH QUREVO (OMBITASVIR/PARITAPREVIR/RITONAVIR) + EXVIERA (DASABUVIR)

	Qurevo+ Exviera (21 pts)
SVR 24 (+)	85,70%
SVR 24 (-)	14,30%

Qurevo+ Exviera (21 pts)



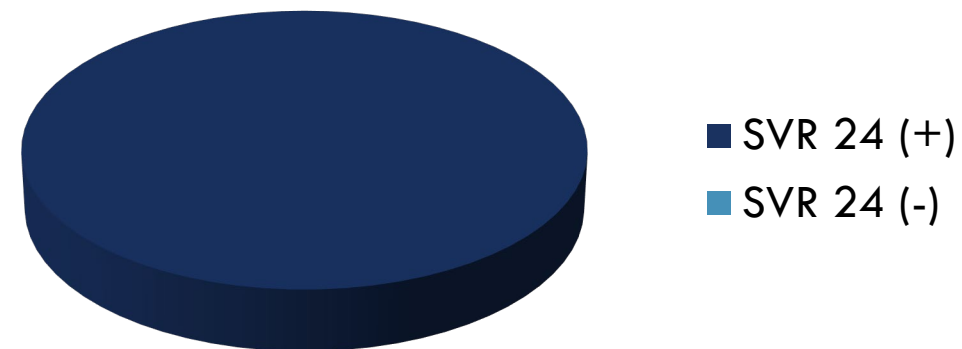
Data from the UC of Gastroenterohepatology Skopje, 2022



# TREATED HCV RNA (+) PATIENTS WITH EPCLUSA (SOFOSBUVIR/VELPATASVIR)

	Epclusa (19 pts)
SVR 24 (+)	100%
SVR 24 (-)	0%

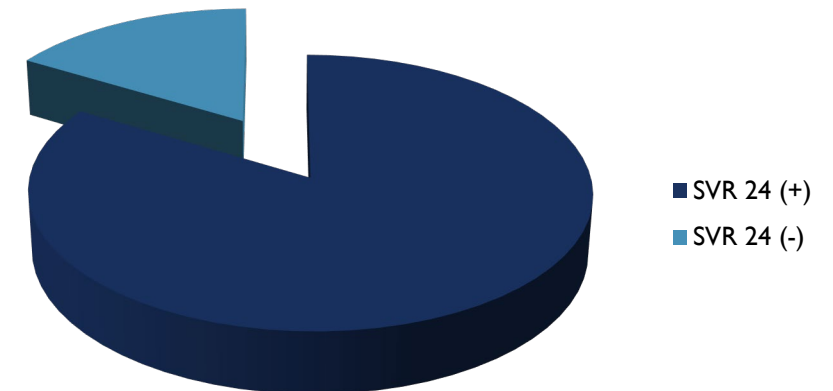
Epclusa (19 pts)



## OLD DATA FROM UC FOR GASTROENTEROHEPATOLOGY ABOUT TREATMENT OF HCV RNA (+) PTS WITH IFN BASED THERAPY FOR A PERIOD 2010–2016

	peg-IFN alpha-2a /2b + ribavirin (226 pts)
SVR 24 (+)	83,60%
SVR 24 (-)	16,40%

peg-IFN alpha-2a /2b + ribavirin  
(226 pts)



# NORTH MACEDONIA

## SPECIFIC VIRAL HEPATITIS ISSUES AND FUTURE CHALLENGES

- Opening a special “**Center for liver diseases**” within the University Clinic for Gastroenterohepatology, Skopje, during next year.
- This Center for patients with chronic liver diseases, such as chronic viral hepatitis B and C, alcoholic liver disease, NAFLD, autoimmune and metabolic disease, will be responsible for:
  1. Active treatment of chronic disease which will prevent the progression of liver disease to a more advanced stage and prevent the occurrence of liver cancer.
  2. Determination of the stage of fibrosis using non-invasive method (shear wave elastography),
  3. Liver cancer screening (ultrasound examinations and tumor markers) every 6 months.
  4. Percutaneous needle biopsy under US guidance

## THE GOALS OF THE CENTER FOR LIVER DISEASES

- Close cooperation with family doctors focused on early detection of factors that lead to liver diseases.
- Close cooperation with Departments of Infective Diseases and Centers for dialysis across the country where the patients with chronic viral hepatitis are diagnosed.
- Cooperation with the Addiction Centers where most of the people infected with Hepatitis B and C viruses are treated
- Close cooperation with patient organization, such as “Hepar Center Bitola”, who are in communication with patients who suffer from chronic viral hepatitis..

## THE GOALS OF THE CENTER FOR LIVER DISEASES

- To improve the detection and surveillance of Chronic Hepatitis B and C throughout the country.
- The number of diagnosed patients with Chronic Hepatitis B and C is very low. **Many infected persons remain undiagnosed.**
- We should work on improvement of diagnostic tools for viral hepatitis.

## THE GOALS OF THE CENTER FOR LIVER DISEASES

- At the moment mandatory screening of HBV and HCV is only for:  
**Blood donors and in vitro fertilization.**
- There is recommendation for: hemodialysis patient, recipients of blood transfusion; recipients and donors of organ transplantation; patients before surgery; patients who need immuno-suppressive therapy; HIV positive persons; injecting drug users; pregnant women; family members of HBV/HCV infected persons; sexual contacts with HBV/HCV infected persons; exposed healthcare medical workers.  
**Recommendations should be extended to: sex workers, men who have sex with men, prisoners, transgender populations.**

## THE GOALS OF THE CENTER FOR LIVER DISEASES

- To provide universal access to HCV and HBV treatment (first line NA therapy: Tenofovir/Entecavir) to all infected patients covered by the health insurance system, thus implementing the WHO strategy for the elimination of viral hepatitis by 2030
- To prepare a national hepatitis action plan together with UC for infectious diseases and febrile conditions and Ministry of Health of the Republic of North Macedonia.

## THE GOALS OF THE CENTER FOR LIVER DISEASES

- To start a registry of patients with viral hepatitis
- To organize the educational programs for prevention of virus transmission between young population and risk groups (people who inject drugs, men who have sex with men, people in prisons, sex workers, transgender populations)



# IMPLEMENTATION OF EUROPE'S "BEATING CANCER PLAN" AND WHO UNITED ACTION AGAINST CANCER

- The Center for liver diseases will be actively involved in the implementation of a single national strategy, by developing a program for prevention and early diagnosis of Hepatocellular Carcinoma, in accordance to the European Plan for Fight against Cancer (adopted by the the EU and WHO-Europe).
- Last year (July 2021), the 1st National Declaration for fight against cancer with accent over liver cancer and personalized approach in its prevention, diagnosis and treatment, was signed.

## IMPLEMENTATION OF EUROPE'S "BEATING CANCER PLAN" AND WHO UNITED ACTION AGAINST CANCER

- This declaration brings together all stakeholders in a multidisciplinary approach to develop a comprehensive national plan for the prevention and control of liver cancer, in line with the European Cancer Plan.
- Involved parties in the implementation of the national plan are: Ministry of Health of the Republic of North Macedonia, PHI University Clinic for Gastroenterohepatology, PHI UC for Radiotherapy and Oncology, PHI UC for Infectious Diseases and Febrile Diseases , GH 8th September - Department of Interventional Radiology and patient organization "Hepar Center Bitola".

# IMPLEMENTATION OF EUROPE'S "BEATING CANCER PLAN" AND WHO UNITED ACTION AGAINST CANCER

- The national plan is structured around four key action areas where the EU and WHO Europe can make the greatest contribution: (1) prevention; (2) early detection; (3) diagnosis and treatment; and (4) the quality of life of cancer patients.
- The Center for liver diseases will be actively involved in prevention and early detection of Hepatocellular Carcinoma.



**The Balkan hepatitis meeting, Skopje, North Macedonia  
27-28 OCTOBER 2022**