Hepatitis Delta Virus in Uzbekistan: A Deep Dive

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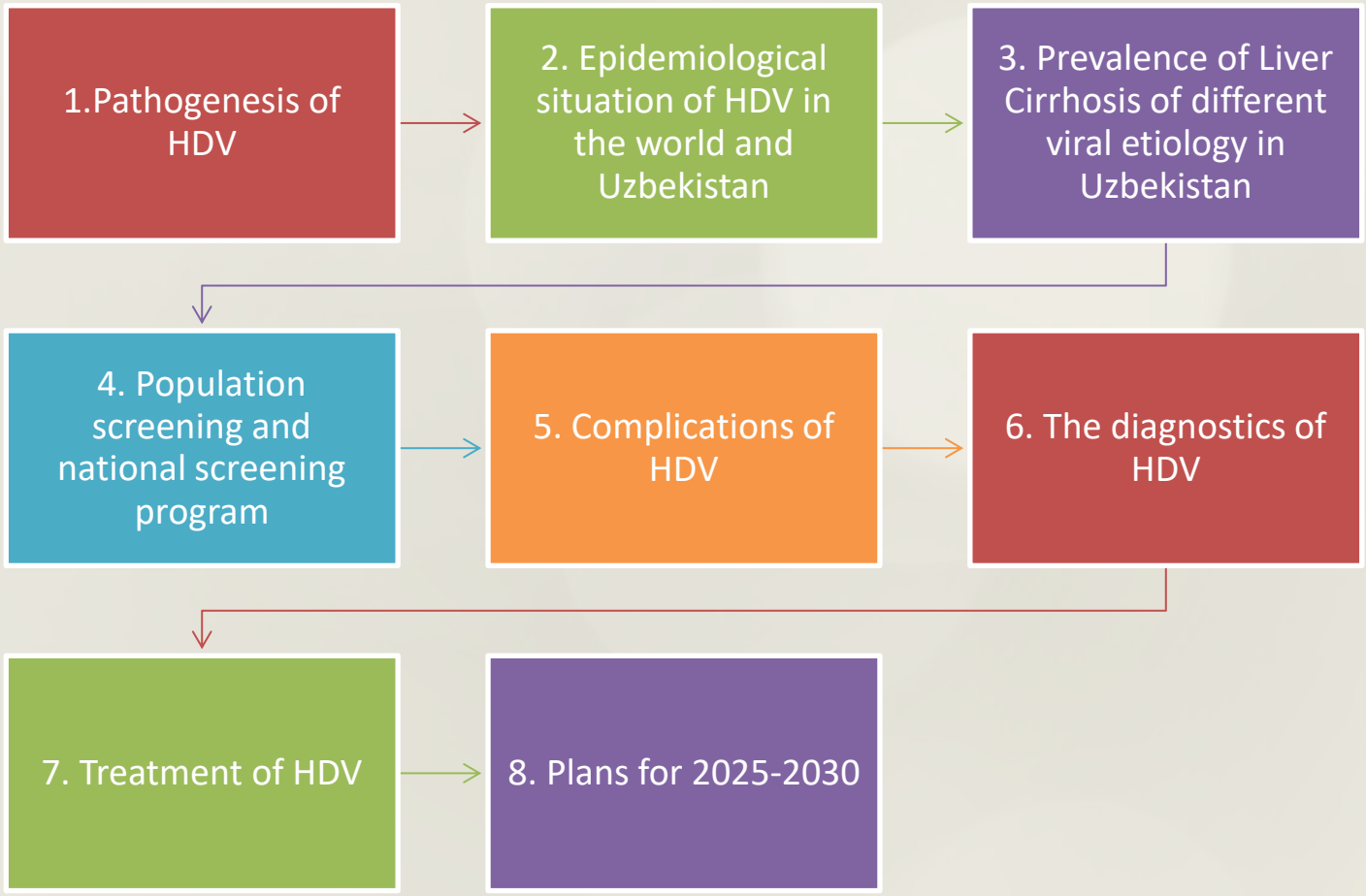
Plan


1.Pathogenesis of HDV
2. Epidemiological situation of HDV in the world and Uzbekistan
3. Prevalence of Liver Cirrhosis of different viral etiology in Uzbekistan
4. Population screening and national screening program
5. Complications of HDV
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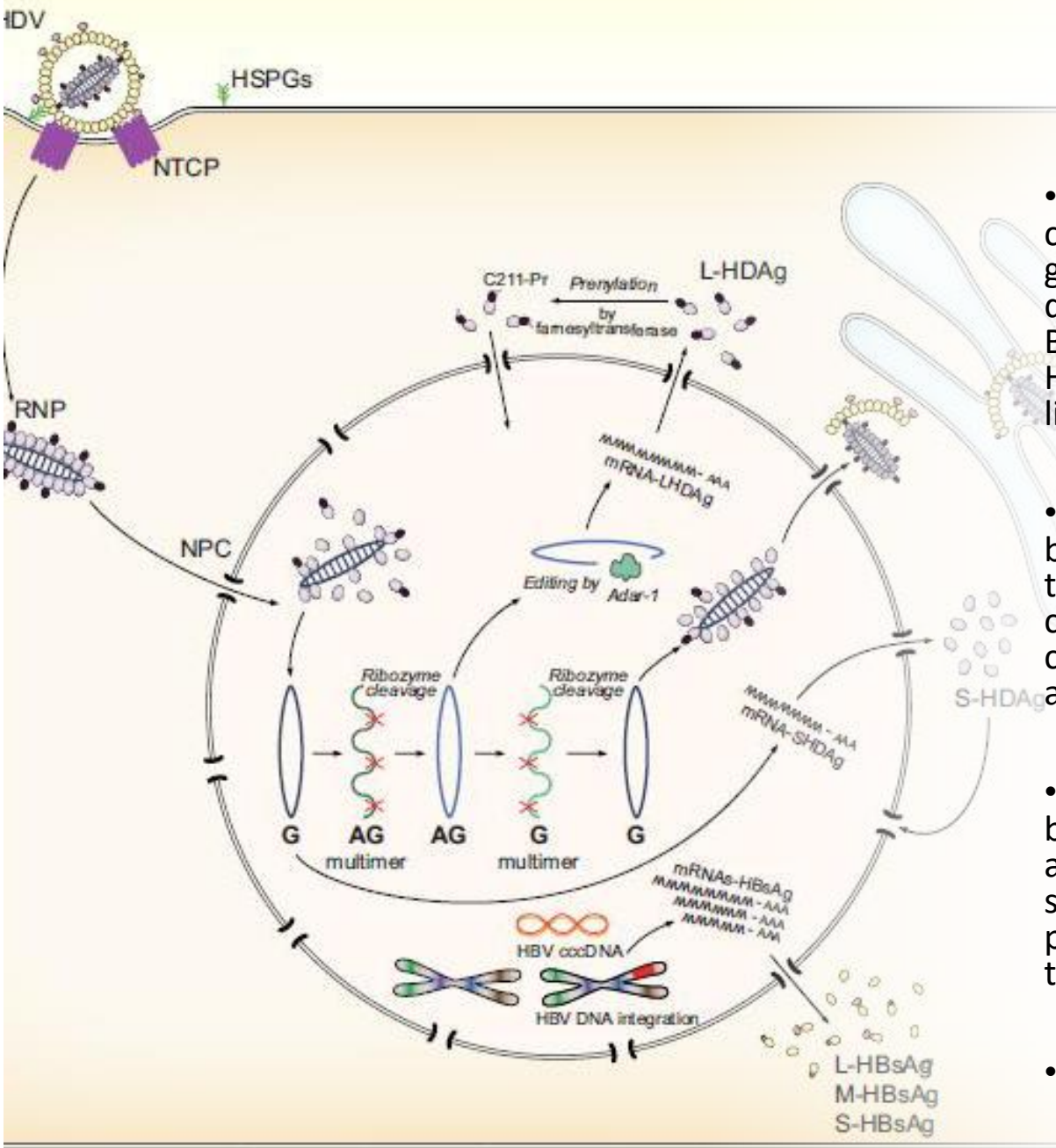
Pathogenesis

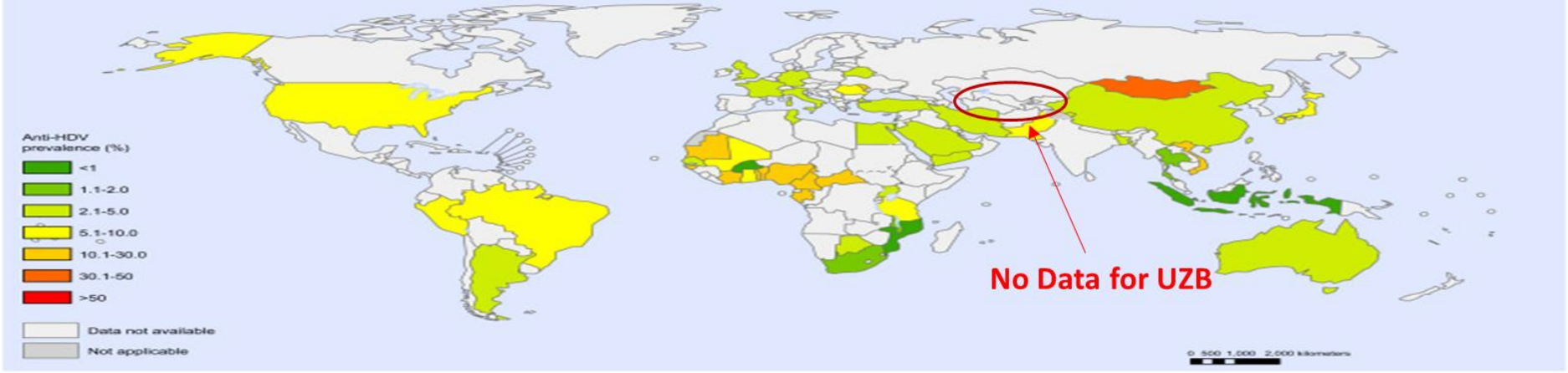


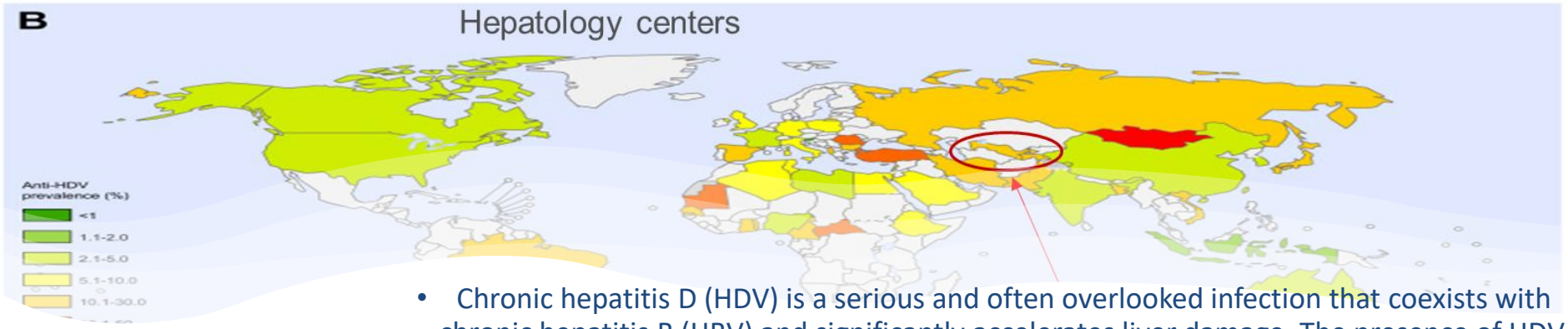
- Hepatitis D virus (HDV) is an RNA-containing virus from the Deltavirus genus. It is highly infectious and is a defective companion of the hepatitis B virus (HBV) since it requires the HBV surface antigen (HBsAg) for its life cycle and envelope formation.

- The HDV genome is represented by a single-stranded circular RNA, the smallest among human RNA-containing viruses. The virus uses cellular polymerases for replication, as it lacks its own polymerases.

- VHD enters hepatocytes by binding via the large HBV surface antigen (L-HBsAg) to the receptor sodium-taurocholate co-transport polypeptide, which is involved in transporting bile acid salts.

- There are 8 genotypes of VHD.





Estimates of anti-HDV prevalence at the country level among HBsAg-positive individuals.

- Chronic hepatitis D (HDV) is a serious and often overlooked infection that coexists with chronic hepatitis B (HBV) and significantly accelerates liver damage. The presence of HDV in individuals already infected with HBV heightens the risk of liver cirrhosis (LC), hepatocellular carcinoma (HCC), and other severe liver-related complications. This dual infection leads to a faster progression of liver disease and has a greater likelihood of resulting in chronic conditions or malignancies.
- According to the World Health Organization (WHO), an estimated **5%** of people with chronic HBV infection are also infected with HDV, equating to approximately **15-20 million** people globally.
- The clinical impact of HDV infection is particularly severe, as it not only increases the severity of liver disease but also contributes to high morbidity among those of working age, leading to social and economic burdens.
- In Uzbekistan, chronic hepatitis D represents a substantial medical and social issue. It poses a heavy burden not only on the affected individuals but also on the healthcare system and the broader society.

Population-based serological study of the prevalence and risk factors of hepatitis B, C, and D in the Republic of Uzbekistan (n=14 000) (unpublished data of 2021-2022).

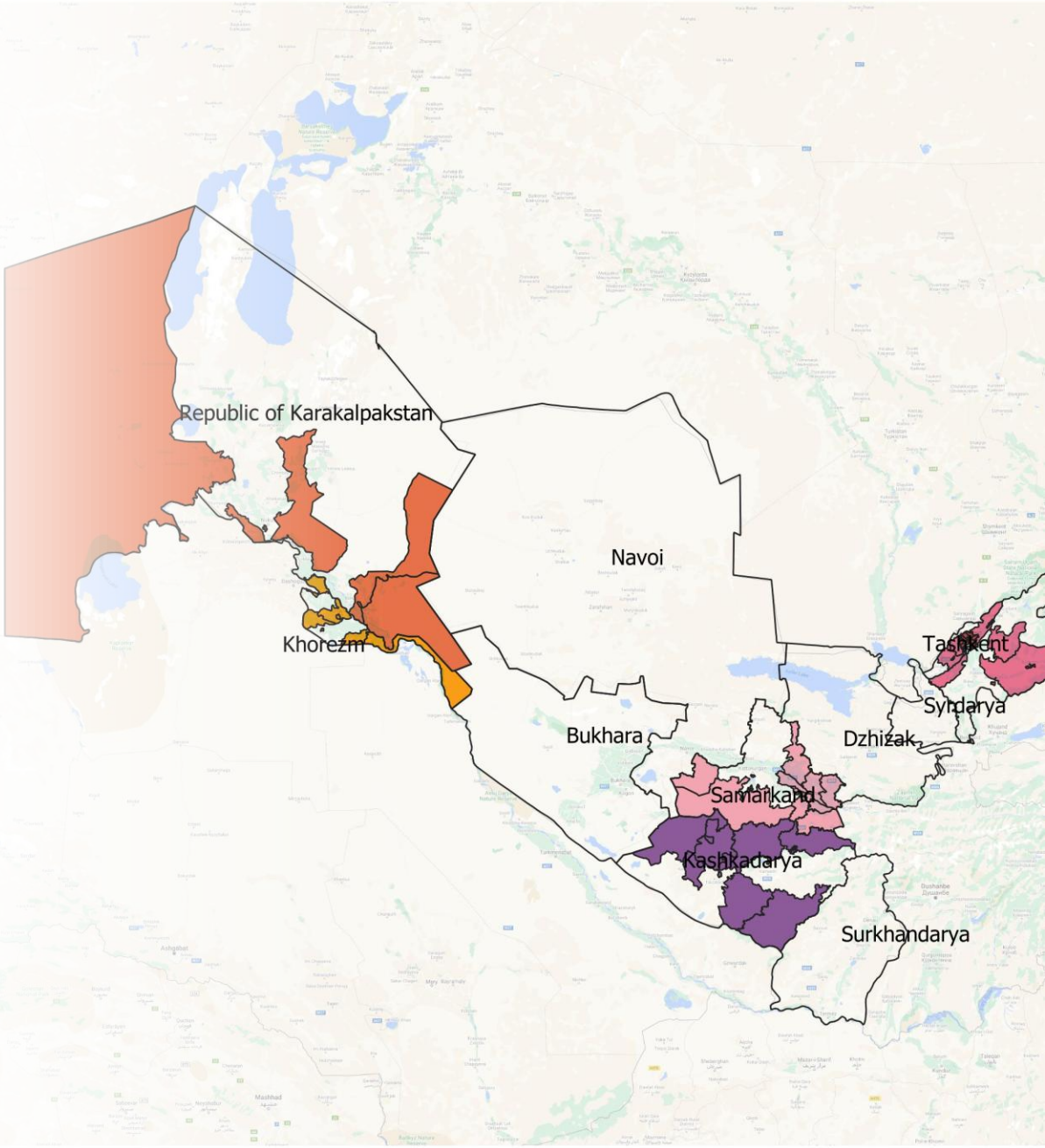
Study objectives for hepatitis B, C and D

To determine the prevalence of HCV, HBV and HDV infection, as well as the prevalence of chronic HCV, HBV, and HDV infection among children **aged 5 to 17 (n=4561)** years and adults **aged 18 years and older (n=9439)** in selected regions of the Republic of Uzbekistan

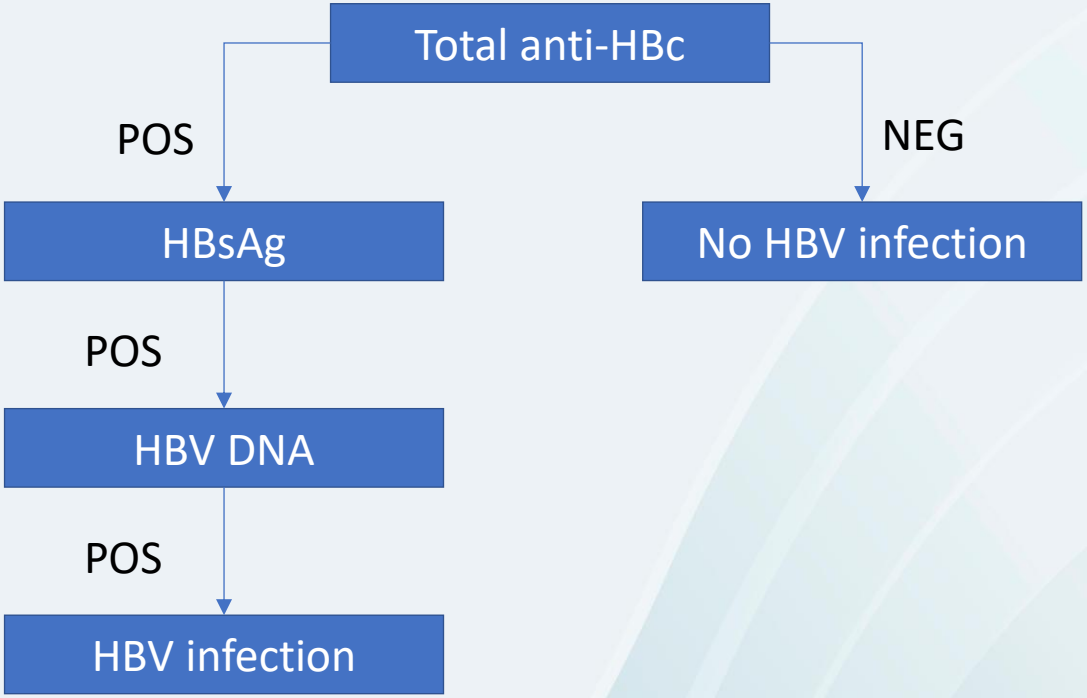
To identify risk factors for HCV, HBV and HDV infection in the Republic of Uzbekistan (behavioral risk factors, parenteral interventions, etc.)

Study design

- A two-stage cross-sectional (single-stage) study of a cluster sample was conducted in 7 out of 14 regions of Uzbekistan.
- Seven out of 14 regions were selected for study based on population data
  - At least half of the population lives in the study regions
  - Different prevalences of hepatitis in these regions (including regions with low, medium, and high prevalence)



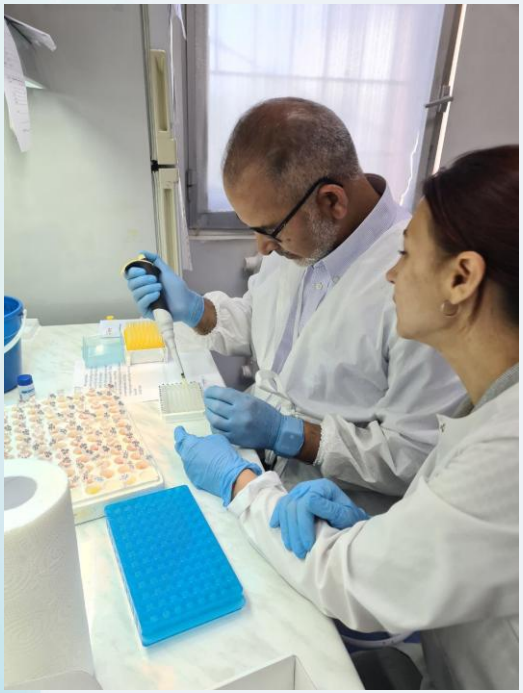
HBV testing strategy

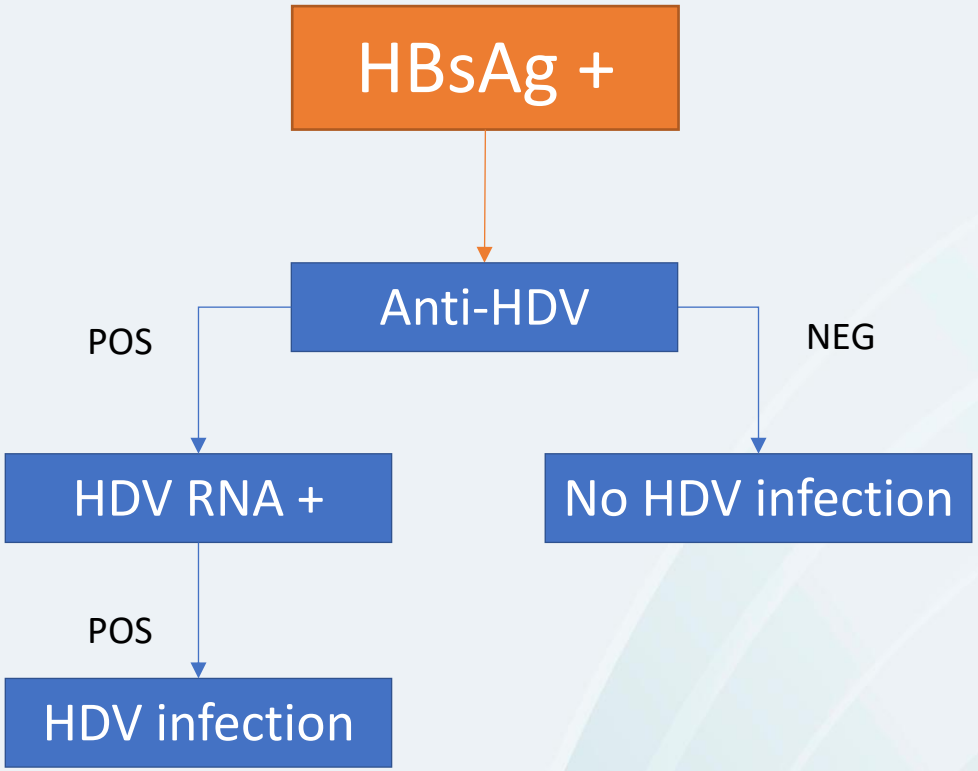


Hepatitis B/Adults (Anti-HBCore/ HBsAg/ HBV DNA)

	Anti-HBCore (n=9439)			HBsAg (n=9439)			HBV DNA (n=9439)		
Region	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Andijan region	767/1592	48.18%	44.78 - 51.58	76/1591	4.78%	3.7 - 5.85	43/1592	2.70%	1.89 - 3.51
Rep. of Karakalpakstan	340/912	37.28%	33.33 - 41.24	40/912	4.39%	3.03 - 5.74	31/912	3.40%	2.2 - 4.6
Kashkadarya region	794/1633	48.62%	45.25 - 52.0	110/1633	6.74%	5.48 - 7.99	73/1633	4.47%	3.45 - 5.5
Khorezm region	382/899	42.49%	38.24 - 46.74	64/899	7.12%	5.38 - 8.86	47/899	5.23%	3.73 - 6.72
Samarkand region	730/1650	44.24%	41.04 - 47.44	106/1650	6.42%	5.2 - 7.65	81/1650	4.91%	3.84 - 5.98
Tashkent region	642/827	43.70%	40.33 - 47.08	54/1415	3.68%	2.7 - 4.66	42/1427	2.86%	1.99 - 3.72
Tashkent city	468/1926	36.45%	33.15 - 39.74	45/1338	3.50%	2.48 - 4.53	19/1326	1.48%	0.81 - 2.15
Total	**4123/9439**	**43.68%**	**42.35 - 45.01**	**495/9439**	**5.24%**	**4.78 - 5.71**	**336/9439**	**3.56%**	**3.18 - 3.94**

HDV testing strategy

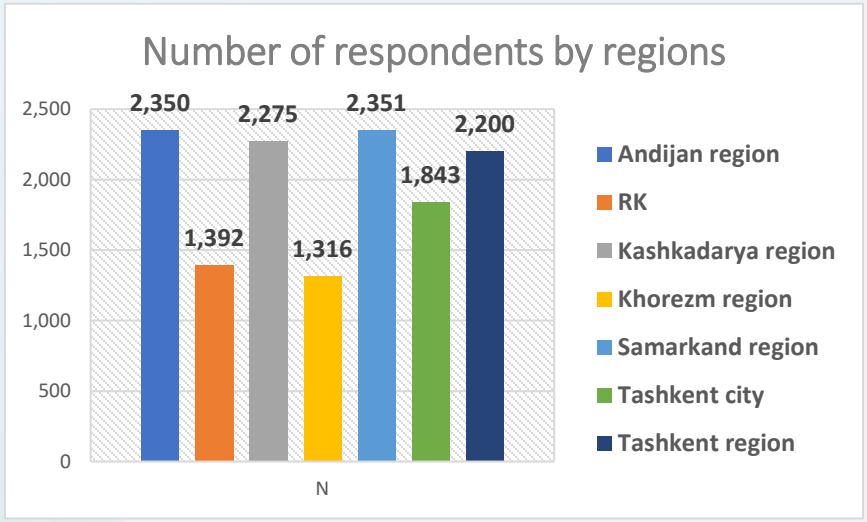


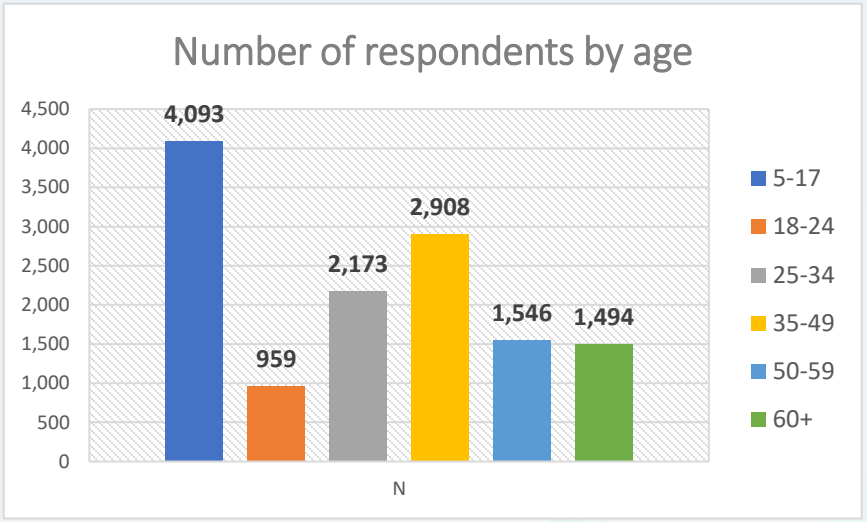


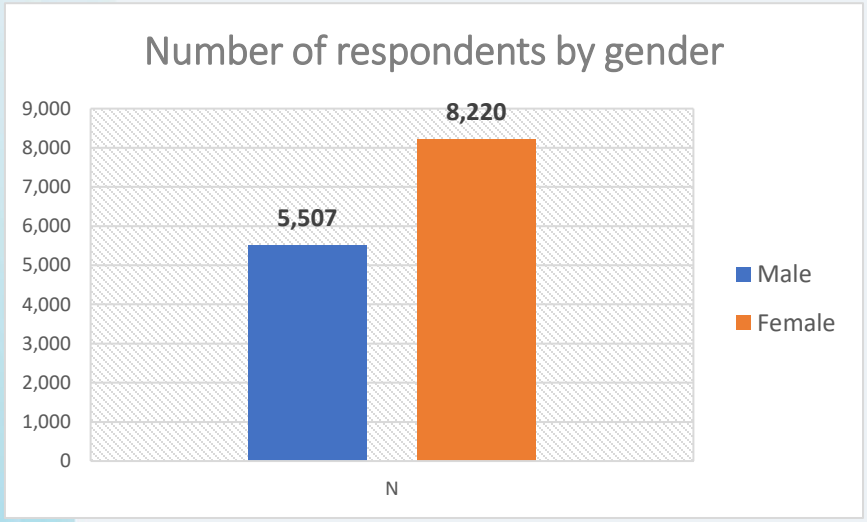
HDV RNA (among HBsAg positive)

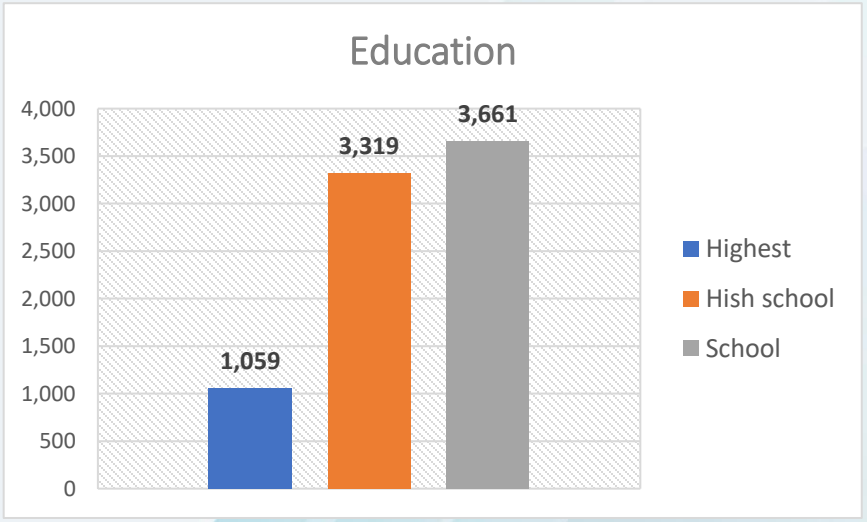
	Adults (n=495)			Children (n=30)			Total (n=525)		
Region	**N**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Andijan region	12/76	15.79%	6.86 - 24.72	2/10	20.00%	0.0 - 47.69	14/86	16.28 %	7.76 - 24.8
Rep. of Karakalpakstan	0/40	0.00%	0.0 - 0.0	0/0	0.00%	0.0 - 0.0	0/40	0.00%	0.0 - 0.0
Kashkadarya region	15/110	13.64%	6.74 - 20.53	3/10	30.00%	0.0 - 63.9	18/120	15.00 %	8.08 - 21.92
Khorezm region	1/64	1.56%	0.0 - 4.62	0/1	0.00%	0.0 - 0.0	1/65	1.54%	0.0 - 4.55
Samarkand region	8/106	7.55%	2.32 - 12.78	0/2	0.00%	0.0 - 0.0	8/108	7.41%	2.28 - 12.54
Tashkent region	5/54	9.26%	1.15 - 17.37	1/5	20.00%	0.0 - 59.16	6/59	10.17 %	2.04 - 18.3
Tashkent city	2/45	4.44%	0.0 - 10.6	0/2	0.00%	0.0 - 0.0	2/47	4.26%	0.0 - 10.15
Total	**43/495**	**8.69%**	**6.09 - 11.28**	**6/30**	**20.00%**	**4.01 - 35.99**	**49/525**	**9.33%**	**6.72 - 11.95**

Preliminary results/Demography

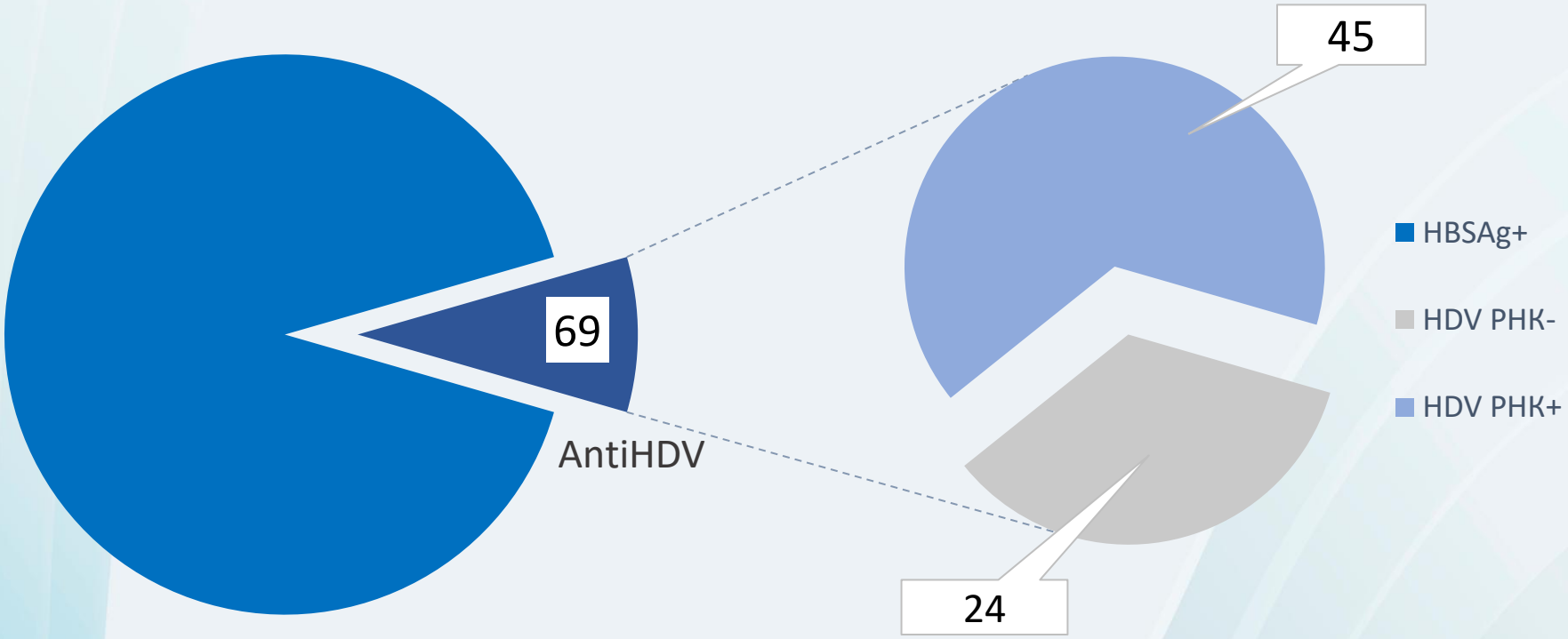




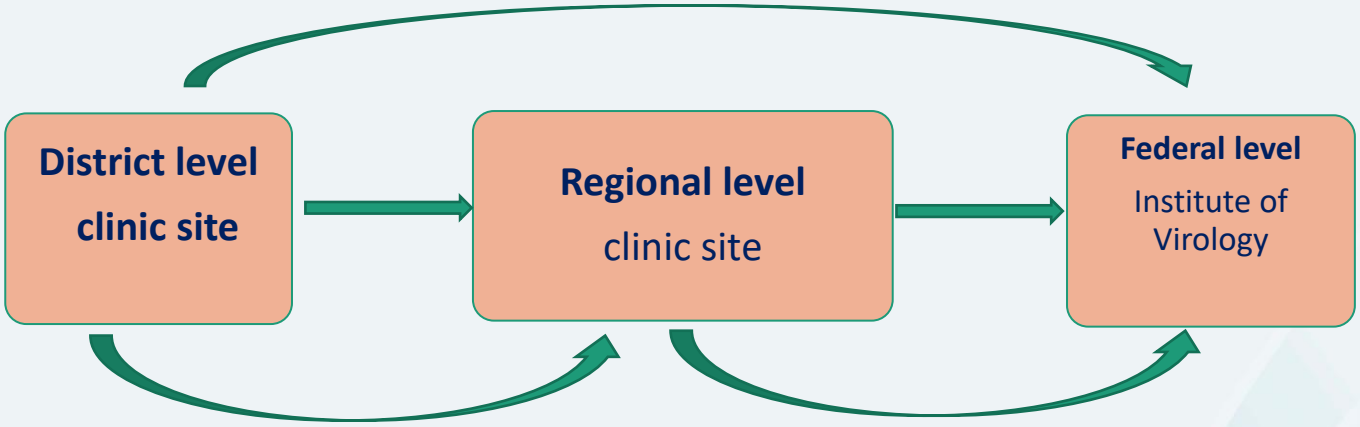




Prevalence of chronic viral hepatitis D among persons with HBsAg detected in blood for the first time (n=703)



Hepatology Center (Research Institute of Virology) is a national observatory for viral hepatitis



The Hepatology Center was established at the Institute of Virology in Tashkent in 2017, which created a database of patients with chronic viral liver disorders recruited as out-patients hospitalised in-patients from all over Uzbekistan.

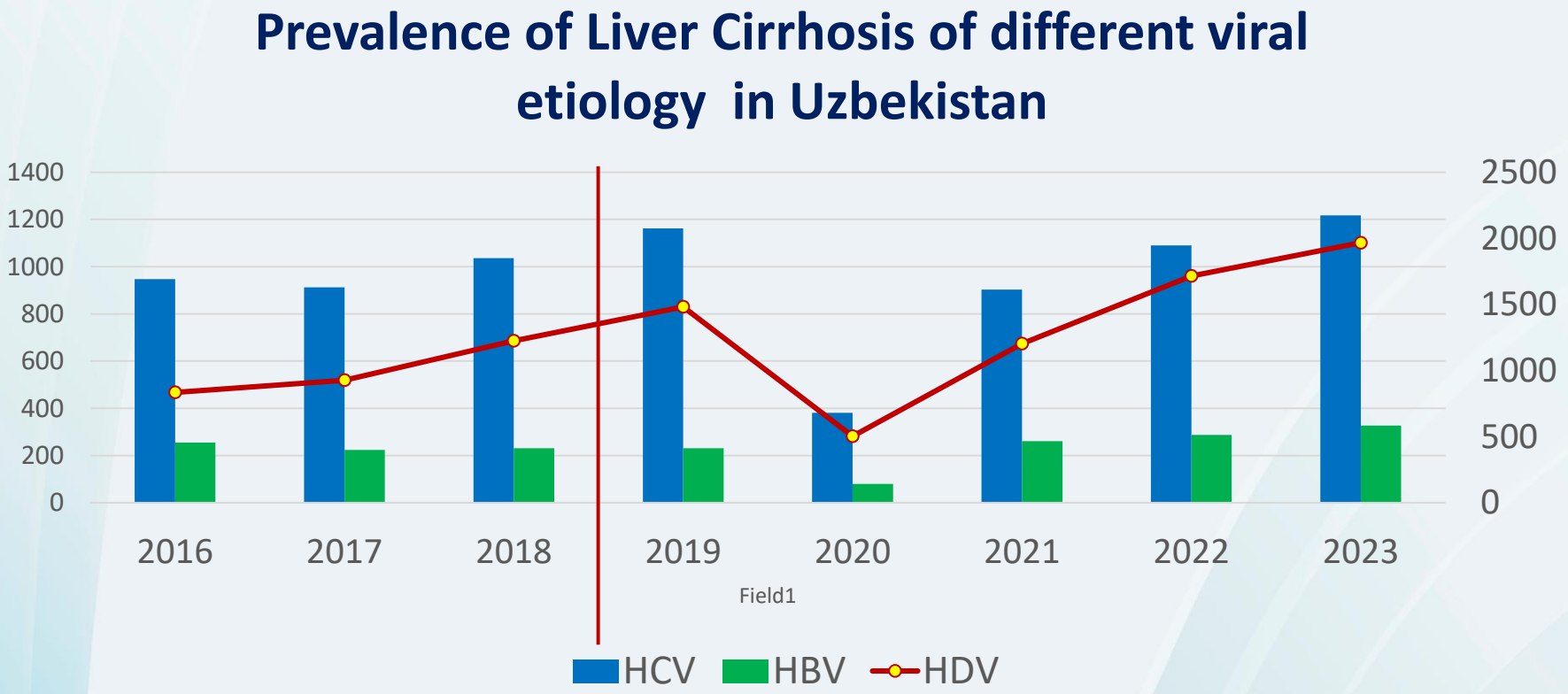
Only the Research Institute of Virology **have a database for all patients with chronic liver disease with HBsAg aetiology and** examined for markers of **Delta hepatitis**.



Mario Rizzetto

- - In 1977, Mario Rizzetto discovered a new antigen/antibody system associated with chronic HBV infection called Delta.
- - This discovery was made possible by the use of the double immunofluorescence technique mastered earlier in London.
- - The Delta antigen turned out to be a marker for a new virus, hepatitis D virus (HDV).
- - The discovery was a significant step in the study of viral hepatitis, especially in southern European countries, where the problem of hepatitis B was most pressing.

Viral etiologies in **19399** liver cirrhosis were recruited from **all over** Uzbekistan. at the Clinical Department of the Tashkent Institute of Virology, **2016-2023**



https://onlinelibrary.wiley.com/doi/10.1111/liv.14243
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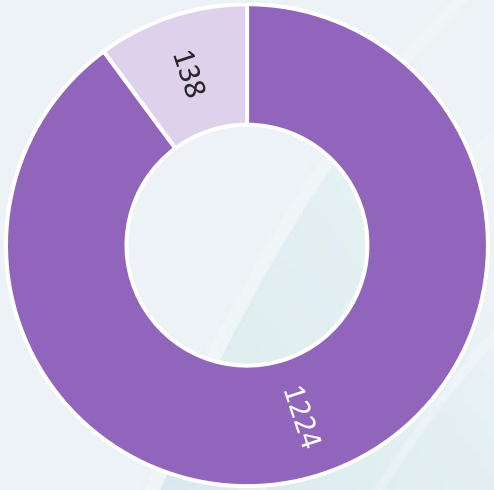
Patients with HDV-cirrhosis hospitalized at the clinical Department of the Institute of Virology in the Republic of Uzbekistan (2016-2018yy)

Demographic features

- Mean Age– 39 (18-53); 19.5% of patients were younger than 30 years
- Male to Female - 100/38 (72%)
- Alcohol- 1%
- Drug addiction - 1%
- Blood transfusion - 21%
- Major Surgery - 7,5%
- Other - 69.5%



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Child-Pugh scoring system for classifying the severity of liver cirrhosis

Parameter	1 point	2 points	3 points
Bilirubin (µmol/L)	< 34	34–50	➢ 50
Albumin (g/l)	> 35	28–35	< 28
INR	< 1,7	1,7–2,3	> 2,3
Ascites	No	Lightweight (controlled)	Moderate/Severe (Uncontrolled)
Hepatic encephalopathy	Absent	Grade 1–2	Grade 3–4

Summary assessment and classification:

Class A (5-6 points): Mild cirrhosis.

Class B (7-9 points): Moderate severity.

Class C (10-15 points): Severe cirrhosis with poor prognosis.

Application:

The Child-Pugh scale is used to predict patient survival and assess indications for liver transplantation:

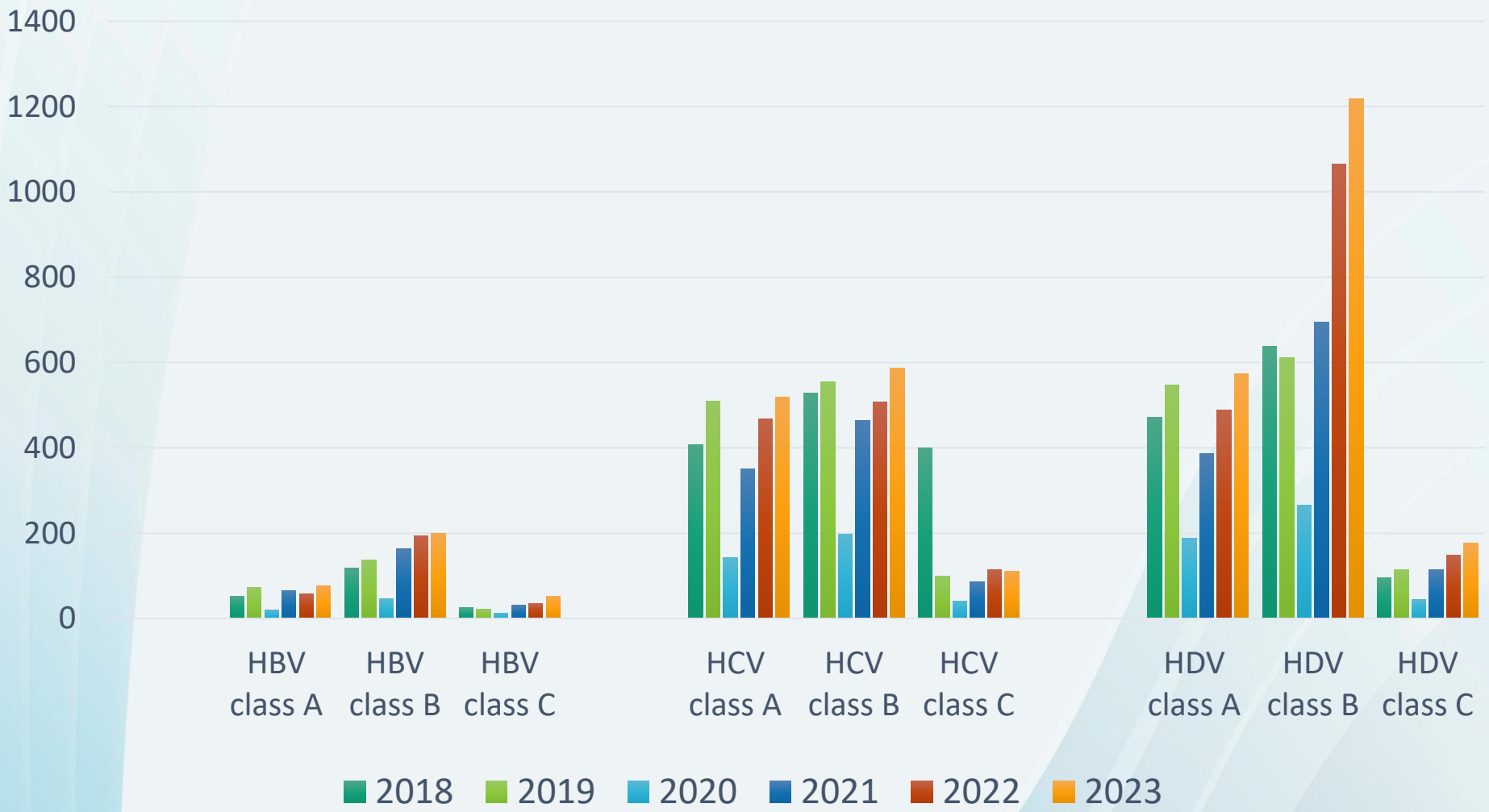
1-2 years of survival:

Class A: >85%.

Class B: 60-80%.

Class C: <45%.

Etiological classification of liver cirrhosis (n=15314)



Stages of implementation of the national program

PRESIDENT DECREE

2017-2021.
Establishment of specialized structures in 13 regions of Uzbekistan and procurement of antiviral drugs.
Annual US$ 1 million

UHEP 1.0.

2018-2020.
Supported by CDAF (USA).
Procurement of rapid hepatitis B and C screening tests 62,000 people

UHEP 2.0

2021-2022.
CDAF supported the procurement of rapid hepatitis B and C tests to screen 500,000 people

Presidential Decree PD No. 243

2022-2025.
Screening for HBV and HCV, treatment of chronic HCV infection

According to Presidential Decree No. 243 dated 16 May 2022, in the direction of elimination of viral hepatitis is planned:

- Implementation of screening tests throughout the country to detect viral hepatitis ‘B’ and ‘C’ diseases
- Hepatitis B infection vaccination among medical personnel who work with blood and its components
- Ensuring the full supply of consumables (reagents and test kits) for the detection of viral infections in the primary care system
- Establishment and management of a single electronic registry of chronic viral liver diseases
- Conducting scientific research on viral infections and implementation of an automated infection control system
- Improving the monitoring of the safety, quality, and efficacy of vaccines, test kits, and antiviral drugs
- Surveillance of HBV and HCV patients for cirrhosis and hepatocellular carcinoma (HCC)

Development and support of an initiative on the elimination of viral hepatitis in Uzbekistan (Research Institute of Virology and CDC project)

Direction 1

- Development of a 5-year National Strategy for the Elimination of Viral Hepatitis for 2026-2030

Direction 2

- Strengthening the capacity of the regional laboratories and primary health care facilities

Direction 3

- HBV micro elimination programme for patients in hemodialysis centres, hematology and oncohaematology departments

Direction 4

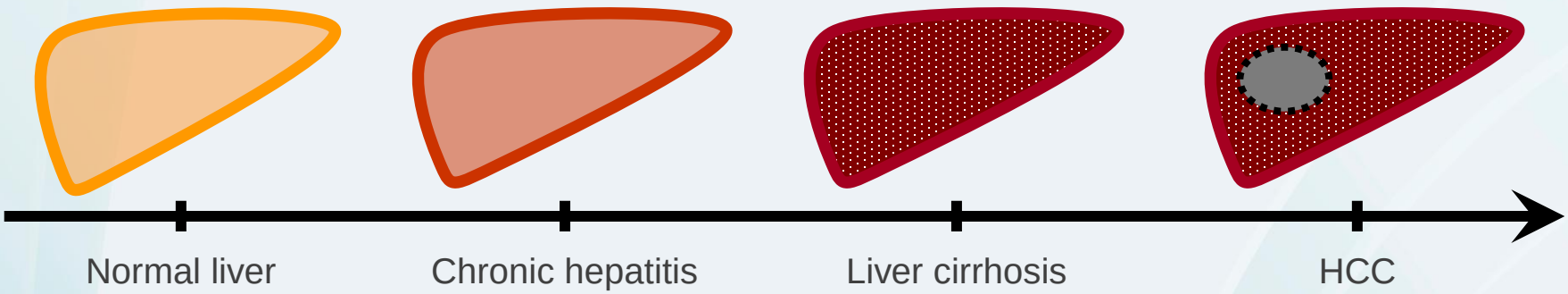
- Developing tools for a public awareness campaign

The Hannover Medical School under the auspices of the GIZ has entered into a clinical partnership with Uzbekistan and is supporting a training program in ultrasound diagnosis of hepatocellular carcinoma (HCC).

- Project PLUTHO (Preventing viral liver cancer in Uzbekistan: Tashkent-Hanover-Liver Network).
- The HCC can be treated very well if we detect them early enough with sonography'. However, this requires not only modern equipment but also qualified staff.

https://biermann-medizin.de/mit-ultraschall-gegen-leberkrebs-partnerschaft-zwischen-der-mhh-und-usbekischer-klinik/

HCC develops gradually, rarely in normal livers, and much more frequently as liver damage progresses through the stages of chronic liver disease.
Patients with chronic hepatitis B, fatty liver dystrophy, alcoholic liver disease, hepatitis C infection, and cirrhosis are at high risk of developing HCC.



Risk Groups for HCC

- Chronic HBV/HCV/HDV infection
- Heavy alcohol use
- Iron overload
- Cirrhosis from any cause
- Metabolic syndromes: Diabetes, Obesity
- Non-Alcoholic SteatoHepatitis (NASH)

Standard tests for the evaluation of patients with HBV with delta agent

In Uzbekistan, all patients with HBV and delta agents are advised to undergo comprehensive abdominal and retroperitoneal ultrasound examinations to identify signs of liver cirrhosis (LC) or hepatocellular carcinoma (HCC).

Recommended Laboratory Tests:

- - Enzyme-linked immunosorbent assay (ELISA) for detecting antibodies to HDV.
- - Quantitative real-time polymerase chain reaction (PCR) for HDV RNA.
- - Liver function tests, including ALT, AST, and bilirubin levels.
- - General blood analysis.
- - Blood creatinine measurement.

Recommended Instrumental Studies:

- Abdominal ultrasound.
- Liver elastography (or serum-based tests like APRI and FIB-4 if elastography is unavailable).

Additionally:

- serum alpha-fetoprotein (AFP) levels should be assessed in all patients with chronic hepatitis D (CHD) and advanced liver fibrosis (F3-F4) to enable early detection of HCC.

Additional tests for the evaluation of patients with HBV infection with delta agent

- Alpha-fetoprotein (AFP) is considered an additional marker for screening hepatocellular carcinoma (HCC) and is most commonly used alongside ultrasound to improve detection rates. The standard recommendation for screening is every 6 months, the same interval used when relying solely on ultrasound.

- AFP testing is advised for patients with HBV and the delta agent who have advanced liver fibrosis (F3-F4) to enable early detection of HCC. High levels of AFP in the blood are associated with an increased risk of HCC, especially in individuals with cirrhosis (LC). Studies have shown a direct link between the degree of liver fibrosis and AFP levels in chronic viral hepatitis.

- When non-invasive tests provide conflicting results, a percutaneous liver biopsy may be necessary to determine the appropriate treatment strategy, particularly for patients with cirrhosis.

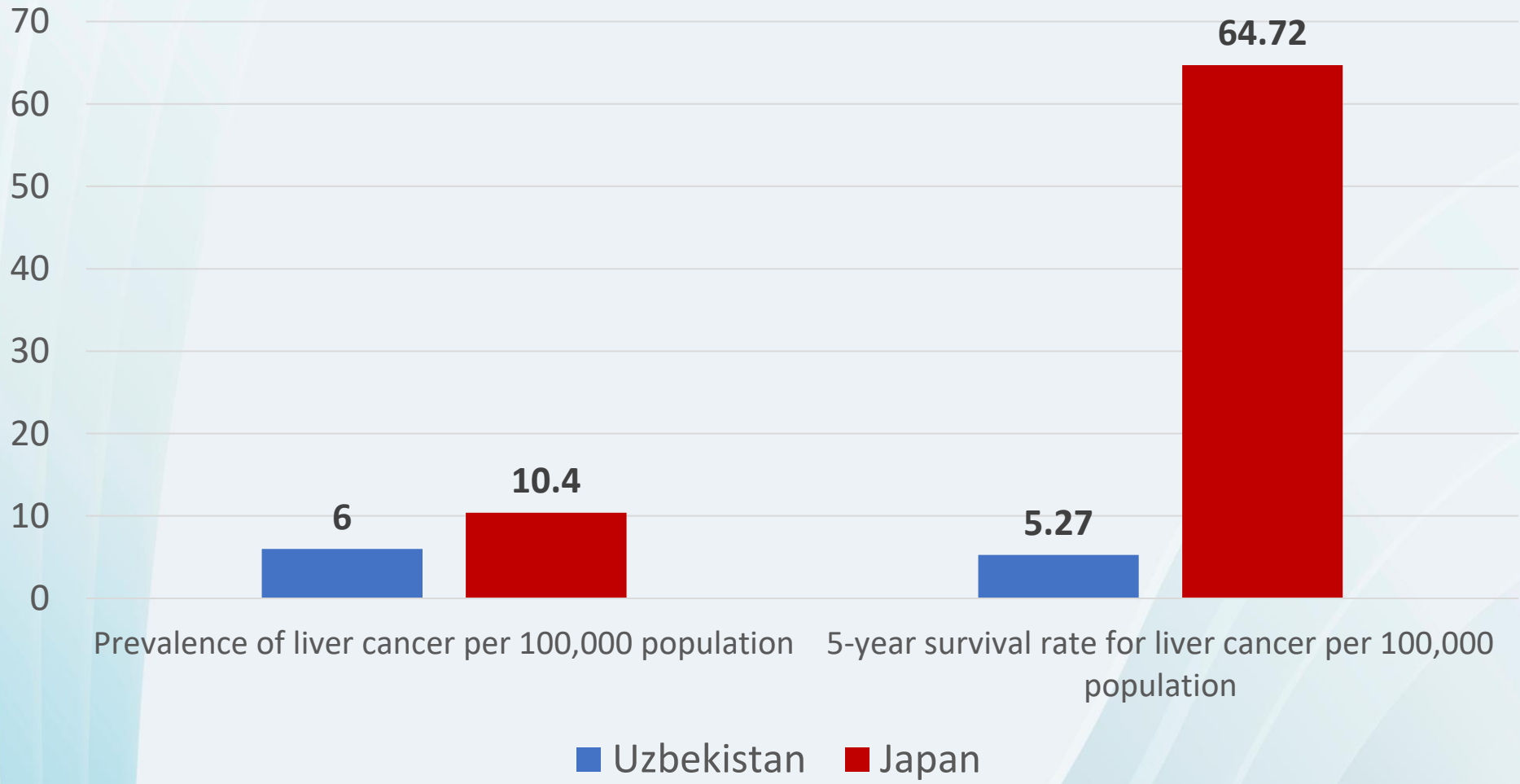
International experience

- Japan is ahead of the world.

- Japan has achieved very favourable results in the treatment of hepatocellular carcinoma (HCC). Several factors have contributed to this achievement. One such factor is the establishment of a nationwide liver cancer screening program, which was developed in the 1980s and involves institutes throughout Japan. Japan was the first country in the world to develop and implement diagnostic ultrasound systems for liver cancer screening. In addition to the already established cancer marker α-fetoprotein (AFP) other markers such as PIVKA-II and AFP-L3 were developed in Japan.
- These two tumor markers were included in screening tests covered by health insurance in 1989 and 1994, respectively. Japan is the only country in the world in which these three tumor markers are included in routine surveillance under national health insurance without restriction.

Kudo, Masatoshi. "Management of hepatocellular carcinoma in Japan as a world-leading model." Liver Cancer 7.2 (2018): 134-147.

Prevalence of liver cancer and 5-year survival rate for liver cancer Japan-Uzbekistan



ACTIVITIES CARRIED OUT WITHIN THE FRAMEWORK OF THE NATIONAL PROGRAM

Indicator	Actions that need to be taken	Years
Early diagnosis of viral hepatitis B and C in the population	1. Examination of 2 million people in the country for viral hepatitis B and C; 2. PCR testing of 60,000 people with a confirmed diagnosis of viral hepatitis C at screening.	2022–2025
Prevention of viral hepatitis through vaccination	1. Organization of full (3x) vaccination against the hepatitis B virus for 119,013,000 medical workers from the group of high risk of hepatitis B virus infection; 2. Formation of a database of vaccinated persons.	2022–2023
Introduction of new technologies for early diagnosis of liver fibrosis and hepatocellular carcinoma after viral hepatitis	1. Purchase of AFP and PIVKA-II kits for early diagnosis of liver fibrosis and hepatocellular carcinoma from 90,000 people for the Research Institute of Virology and 14 regional hepatology centers; 2. Purchase of a total of 46,000 test kits for the quantification of HBsAg (viral antigen) in patients with hepatitis B.	2022–2025
Improving the quality of services of virological laboratories operating in the country, regardless of the form of ownership	Creation and production of national reference panels of sera on the basis of the Research Institute of Virology to assess the quality of detection of viral diseases.	2022–2023

HCC DIAGNOSIS

Ultrasound + tumor markers

CT/MRI

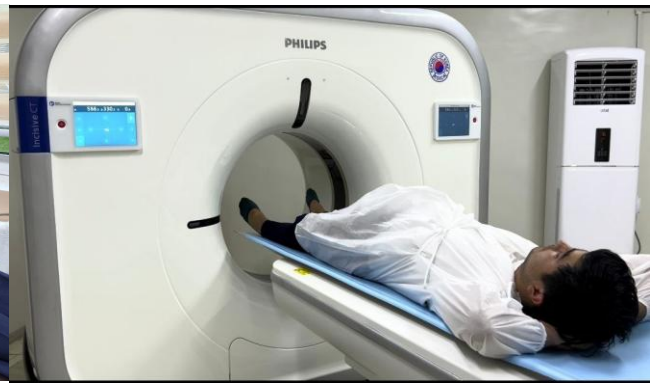
Histology

Number of people examined for AFP at the Research Institute of Virology

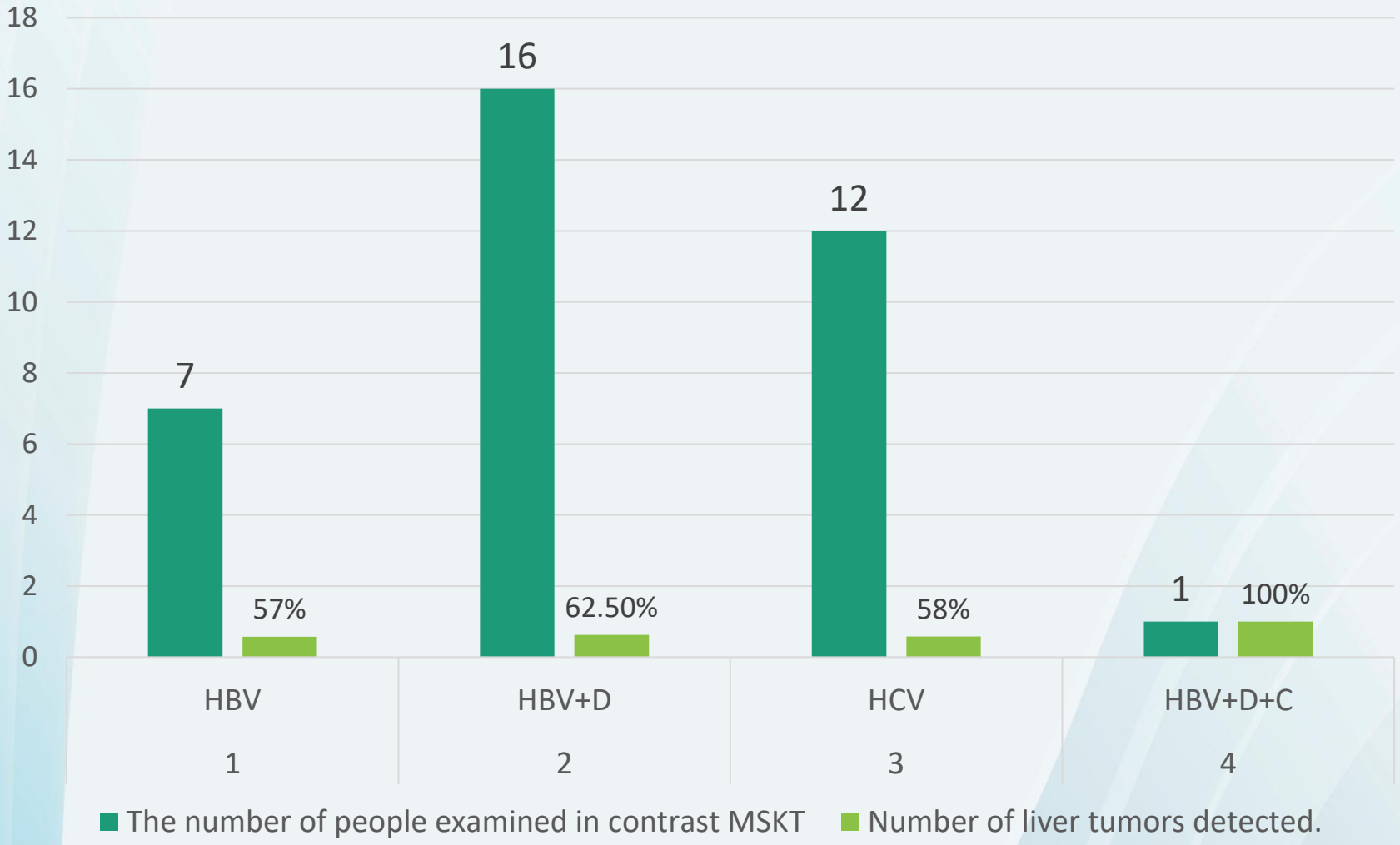
Total number of people examined for AFP		3742 (100%)
Of these,	AFP 0-14 ME/ml	3381 (90,5%)
	AFP 15-100 ME/ml	223 (5,9%)
	AFP 100-200 ME/ml	51 (1,3%)
	AFP above 200 IU/ml	87 (2,3%)

Results of ultrasound and contrast MSCT examination among patients diagnosed with viral hepatitis B and C and an elevated AFP level above 100 ng/ml

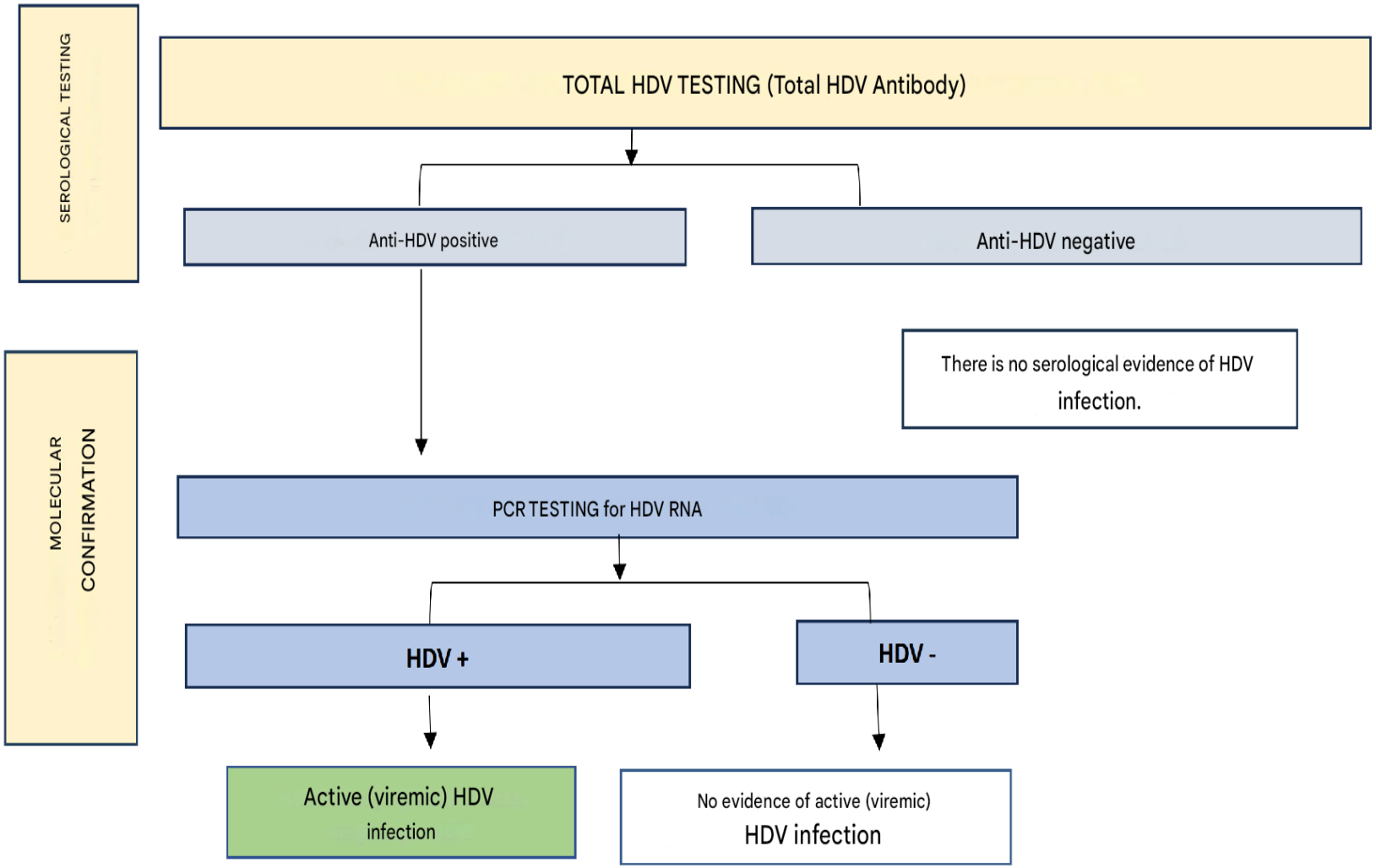
Patients with AFP are higher 100 ng/mL	138 (100%)
Imaging Surveys	138 (100%)
Number of formations detected on ultrasound	40 (29%)
Number of detected formations on MSCT	84 (61%)



CT scanning with contrast-enhanced type of viral hepatitis among patients with an increased AFP blood level



Testing algorithm for the detection of HDV infection among HBsAg-positive individuals



Treatment of HBV with delta agent

- **Non-drug treatment:**
  - Avoidance of negative habits (smoking, alcohol).
  - Rational nutrition, hypocaloric diet in obesity.
  - Physical activity, avoiding a sedentary lifestyle.
  - Adequate fluid intake (2–3 liters per day).
  - Exclusion of risk factors (alcohol, hepatotoxic drugs).

- **Indications for etiotropic treatment (Class IA):**
- 1. HDV replication (HDV RNA in the blood).
- 2. Consent of the patient.
- 3. No contraindications.
- 4. Negative pregnancy test.

Notes:

- PegIFNα: The underlying mechanism involves a synergism of antiviral and immunomodulatory activity aimed at controlling HDV and HBV.
- BLV: Blocks the attachment of HBsAg to NTCP, which prevents the virus from entering cells.
- NA: Use only when indicated for HBV treatment or in cirrhosis.

Purpose of therapy:

- Reducing viral load and slowing disease progression.

Treatment

Treatment method	Indications	Recommendations	Grade/scale of evidence
PegIFNα (pegylated interferon α)	Patients with HBV with delta agent and compensated liver disease, including with or without cirrhosis	Treatment for 48 weeks. Individual correction for HDV RNA, HBsAg and treatment tolerance	IA
Bulevirtide (BLV) **(however, access to the drug is very limited)**	Patients with HBV with delta agent	Long-term treatment of 2 mg once daily is recommended. Can be used in combination with PegIFNα	IC
Combination of PegIFNα and BLV	Patients without intolerance or contraindications to PegIFNα	Consider combination treatment	-
Nucleoside reverse transcriptase (NA) inhibitors: tenofovir, tenofovir, alafenamide, entecavir	- HBV DNA > 2000 IU/mL- Cirrhosis- HBV Reactivation on Withdrawal of Antiviral Treatment for HBV with Delta Agent	They are used only if there are indications for the treatment of HBV. Not recommended in combination with interferons	IC
NA with decompensated LC	Regardless of the presence of detectable HBV DNA	Purpose of NA	IC
NA in compensated LC	Detectable HBV DNA	Purpose of NA	IC

Next steps (national program 2025-2030):

Achieve a 65% reduction in population deaths due to viral liver diseases by 2030.

Coverage of all newly diagnosed HBsAg-positive patients with anti-HDV reflex testing

2025≈60,000 person

2026≈80,000 person

Thank you for your attention!
Katta Rahmat