Chronic hepatitis B and C in Bulgaria
why we need of screening?

L. Mateva, K. Antonov

World Hepatitis Day - 5th July 2012, Sofia,
HBV and HCV infection in Bulgaria

- HBV and HCV infection are a serious public health problem in Bulgaria
  - as many other countries in Europe / World
  - High prevalence and risk of transmission
  - Severe liver complications (particularly HCC) and death
  - Diminished health-related quality of life

- Unfortunately, systematic data for the burden of HBV/HCV infection are not available yet
  - prevalence and incidence
  - negative impact on HBV/HCV-related disease on life-expectancy, morbidity, and mortality
  - Impact on QoL
  - cost
  - There are no effective monitoring / national data base and screening program
Characteristics of HBV infection in Bulgaria
Effective vaccination program in Bulgaria!

Rate of anti-HBc total
  - significantly higher mean age of anti-HBc total (+) subjects than non-reactive: $41.6 \pm 2.2$ vs. $35.1 \pm 1.2$ y.
- **30,4%** - healthy volunteers (all > 40 y.), (2009)

HBsAg carrier rate
- **5.1%** - blood donors (1987)
- **3.9 %** - total population (1999)
- **2.2 %** - blood donors in Sofia (2008) and healthy volunteers (all >40 y.), (2009)

The prevalence of HBsAg carrier rate is still higher among risk groups

- 11.2% - dialyzed patients
- 11.6% - hemophilia and afibrinogenemia
- < 6% - injection drug users (2006)

Vassilev ZP et al, 2006
Prevalence of HBsAg(+) and anti-HCV(+) in 4 different groups from 4 different country regions

**Sofia** blood donors
- 2.2% HBsAg (+)
- 1.1% HCV (+)

**Razgrad** subjects referred from regional physicians
- 2.3% HBsAg (+)
- 2.3% HCV (+)

**Ablanica** adults and adolescence from specific isolated ethical community
- 7.5% HBsAg (+) 0% HCV (+)

**Smolyan** health care workers
- 4.0% HBsAg (+)
- 1.1% HCV (+)

**Average**
- 2.7% HBsAg (+)
- 1.5% anti-HCV (+)

D Jelev et al., 2009, 2011
Characteristics of HBV infection in village of Ablanitza

- 676 subjects were tested
  - 412 adults
  - HBsAg (+) adolescents 2/264
    - Born after 1992 from HBsAg (+) mothers

![Bar chart showing the rate of HBsAg (+) in adults and adolescents. The rate for adults is 7.5% and for adolescents is 0.7%.]
Characteristics of HBV infection in Bulgaria

• HBeAg –negative CHB (n= 260)

• HBV-genotype D or mixed genotypes (D+F, D+E, D+A)

• is predominant in CHB (n=58) and acute hepatitis B (21/23)

HDV infection

- 8.6% among HBsAg (+) subjects (1986)
- 16% - in active liver disease (1999)

Saliva and transmission of HBV infection?

- HBV DNA - 14 parallel serum and saliva samples tested by RT PCR

Ivanova A et all, 2008
Characteristics of HCV infection in Bulgaria
The rate of HCV-Ab (+) carriers

- Bulgarian blood donors
  - 1.4% (1999)
  - 1.1% Blood donors in Sofia (2007)

- Medical personnel in hemodialysis
  - 1.2% (n=114, 1994)

Prevalence of HBsAg(+) and anti-HCV(+) in 4 different groups from 4 different country regions

**Sofia** blood donors
- 2.2% HBsAg (+)
- 1.1% HCV (+)

**Razgrad** subjects referred from regional physicians
- 2.3% HBsAg (+)
- 2.3% HCV (+)

**Ablanica** adults and adolescence from specific isolated ethnic community
- 7.5% HBsAg (+)
- 0% HCV (+)

**Smolyan** health care workers
- 4.0% HBsAg (+)
- 1.1% HCV (+)

**Average**
- 2.7% HBsAg (+)
- 1.5% anti-HCV (+)
High prevalence of HCV in specific groups in Bulgaria

- Patients with haemophilia
  - 75% (1991)

- Patients on haemodialysis
  - 42% (1994)

- Patients with porphyria cutanea tarda
  - 52% (1996) - Family – 20%, sporadic - 63%

Genotype 1b HCV - the most common infection among Bulgarian patients – 90%

- HCV genotype 1
  - 82% -88%
  - Predominantly - subgroup “b”

- Mixed infection (genotype 1 + 2 or 3)
  - Near 4%

- HCV genotype 3
  - 10-12%

IL28B polymorphism (rs12979860) in Bulgarian patients with chronic genotype 1 HCV infection

Ivanova A et al. 2010
IL28B polymorphism (rs12979860) in Bulgarian patients with chronic genotype 1 HCV infection and SVR

Ivanova A et al. 2010
HCV Impacts Quality of Life

No systematic data
Health-related quality of life (QoL) Reductions (-13%) in women with CHC

- HCV-infected Bulgarian women had a worse QoL scores than healthy controls, and women with successfully treated breast cancer, tested by nonspecific disease WHOQoL questionnaires.
  - = DM
  - A reduction was found in all domains

J. Mihaylova, L. Mateva et al., 2002
Disease mortality from HBV/HCV

No systematic data
HCV-related death rates in countries of the WHO European region in 2002


Death rate (deaths per 100,000):

- ≤6
- 6–9
- 9–12
- >12
Causes of death

- Causes of death - 98% cirrhosis-related complications
- liver failure, UGI bleeding, HCC
- Only 2% of patients died from other reasons

L. Mateva at al, 2008
How we starts?

Test and treat
1980 – HBV infection
1990 – HCV infection

Peg-IFN α -based therapy

- HBV – Peg-IFN α

- HCV - Peg-IFN α 2a/2b + Ribavirin 2001
  - has been evaluated as cost-effective (NICE HTA, 2007)
Where we are now?

Bulgarian Society of Gastroenterology

National Association for Fighting Hepatitis
“Hepasist”

NHIF

+ support of Industry

Work together and go forward

* To reduce the impact of HBV/HCV infection in Bulgaria
NHIF: National Program for Diagnosis and Antiviral Treatment of Patients with Chronic Viral Hepatitis (since 2002)


According EASL’s Practice Guidelines
NHIF: National Programme for Antiviral Treatment of Patients with CVH

- 11 Centers – Clinics of Gastroenterology
  - (7- Sofia + Varna, Plovdiv, Pleven, Stara Zagora)

  **Local commissions**
  - Individual assessment of benefit/risks ratio of antiviral therapy -protocol

- **Central committee of experts at NHIF**
  - According acceptable standard criteria and selecting the right patient for treatment
  - Waiting list (up to 2009)
  - Therapy and follow up

100% REIMBURSEMENT
Antiviral therapy

<table>
<thead>
<tr>
<th>CH C</th>
<th>CH B</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Peg-IFNa + RBV</td>
<td>- Peg-IFN</td>
</tr>
<tr>
<td></td>
<td>- NUCs (Lamivudine, Telbivudin, Entecavir, Tenofovir)</td>
</tr>
</tbody>
</table>

**HCV RNA / HBV DNA**

+ **Active viral infection / fibrosis**
Assessment prior to treatment and monitoring during and after therapy

*Schedule for follow-up*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Therapy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>2w</td>
</tr>
<tr>
<td>Haematology</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Standard Clin. chemistry Test+ TSH</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Anti-HCV /Gynotype</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HCV RNA (Quantitative)</td>
<td>G - 2,3</td>
<td></td>
</tr>
<tr>
<td>Anti-HCV /Gynotype</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**HCV RNA negative at 6th mo after stop of therapy ➔ + 24th mo (2nd y)**
Responders, Non-responders, Relapsers

Virological responses during and after therapy

EVR – early: complete or partial, ETR, SVR – sustained
Relapse, partial / null VR – nonresponder
Clinical Endpoint

*significant reduction of HCV/HBV-associated complications and mortality*

**CH C**
- SVR = successful HCV treatment
  - undetectable serum HCV RNA levels 24 wks (6 mo) after end of treatment
- 2 y (24\textsuperscript{th} mo)

**CH B**
- HBV DNA < 10 000 copies/ml (2 000 IU/ml)
  - 24 wks (6 mo) after end of treatment by „real time” PCR
- Seroconversion - HBeAg and HBsAg
NHIF: National Programme for Antiviral Treatment of Patients with CVH

Regional distribution

- NHIF provides treatment of the patients from the whole country who cover the inclusion criteria

Treated patients

G. Kondeva, N. Tarinska, 2005
NHIF: National Programme for Antiviral Treatment of Patients with CVH

Age and sex distribution

More than half are young - aged 18-40 years

[Chart showing age and sex distribution]

- 40% male
- 60% female

- 58.5% aged 18-40 y
- 38.7% aged 41-60 y
- 2.8% > 61 y
Treatment of Patients with CHC

JAN 2003-NOV 2011
- 2188 patients

New cases

<table>
<thead>
<tr>
<th>Year</th>
<th>IFNa+RBV</th>
<th>PegIFNa+RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>158</td>
<td>0</td>
</tr>
<tr>
<td>2005</td>
<td>128</td>
<td>0</td>
</tr>
<tr>
<td>2007</td>
<td>133</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
<td>172</td>
<td>0</td>
</tr>
<tr>
<td>2011</td>
<td>203</td>
<td>0</td>
</tr>
<tr>
<td>November</td>
<td>346</td>
<td>354</td>
</tr>
</tbody>
</table>

98%

2%

IFNa+RBV PegIFNa+RBV
From JAN 2003 to MAY 2005: 564 patients with CHB/CHD (57%) were treated

G. Kondeva, N. Tarinska, 2005
• Peg-IFN - 282 new cases

• NUCs (Lamivudine, Telbivudin, Entecavir, Tenofovir) - 620 new patients

– Total: 902 new patients
Efficacy and Safety of antiviral therapy

No systematic data
CHC: Peg-IFNα + RBV

SVR = 65%- 81%
-Effective therapy
-With usual predictable adverse events

Strong selection and monitoring
Good patient’s collaboration
• Peg-IFNα – effective only in selected patients with low viraemia

• NUC’s therapy – continues
NHIF: National Programme for Antiviral Treatment of Patients with CVH

- Based on firm criteria
- Leading in centers with highly qualified specialists with experience in the treatment of CVH
- Therapy with proved efficacy
- Total reimbursement

Effective

- It may be expanded and optimized according to the new development in the world practice
- The Burden of Hepatitis C in CEE and CIS: An Epidemiological and Economic Assessment

Centre for European Policy Studies, CEPS
BULGARIA, Draft, September 2009

Z. G Ökem, PhD, Seval Akgün, MD, PhD, Prof. of Public Health and Medicine, Baskent University
Epidemiology 2000 – 2015 г.

<table>
<thead>
<tr>
<th>Year</th>
<th>HCV – Number of cases</th>
<th>Incidence per 100,000</th>
<th>Number of HCV infected cases – Prevalence (1.5%)</th>
<th>Acute HCV cases – Proportion (13%)</th>
<th>Chronic HCV cases – Proportion (87%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>218</td>
<td>2.7</td>
<td>120,135</td>
<td>16,018</td>
<td>104,117</td>
</tr>
<tr>
<td>2001</td>
<td>256</td>
<td>3.2</td>
<td>119,316</td>
<td>15,909</td>
<td>103,407</td>
</tr>
<tr>
<td>2002</td>
<td>333</td>
<td>4.2</td>
<td>118,497</td>
<td>15,800</td>
<td>102,697</td>
</tr>
<tr>
<td>2003</td>
<td>350</td>
<td>4.5</td>
<td>117,678</td>
<td>15,690</td>
<td>101,988</td>
</tr>
<tr>
<td>2004</td>
<td>367</td>
<td>4.7</td>
<td>116,859</td>
<td>15,581</td>
<td>101,278</td>
</tr>
<tr>
<td>2005</td>
<td>268</td>
<td>3.5</td>
<td>116,040</td>
<td>15,472</td>
<td>100,568</td>
</tr>
<tr>
<td>2006</td>
<td>326</td>
<td>4.2</td>
<td>115,317</td>
<td>15,376</td>
<td>99,941</td>
</tr>
<tr>
<td>2007</td>
<td>226</td>
<td>3.0</td>
<td>114,594</td>
<td>15,279</td>
<td>99,315</td>
</tr>
<tr>
<td>2008</td>
<td>227</td>
<td>3.0</td>
<td>113,871</td>
<td>15,183</td>
<td>98,688</td>
</tr>
<tr>
<td>2009</td>
<td>228</td>
<td>3.0</td>
<td>113,148</td>
<td>15,086</td>
<td>98,062</td>
</tr>
<tr>
<td>2010</td>
<td>229</td>
<td>3.1</td>
<td>112,425</td>
<td>14,990</td>
<td>97,435</td>
</tr>
<tr>
<td>2011</td>
<td>231</td>
<td>3.1</td>
<td>111,738</td>
<td>14,898</td>
<td>96,840</td>
</tr>
<tr>
<td>2012</td>
<td>232</td>
<td>3.1</td>
<td>111,051</td>
<td>14,807</td>
<td>96,244</td>
</tr>
<tr>
<td>2013</td>
<td>233</td>
<td>3.2</td>
<td>110,364</td>
<td>14,715</td>
<td>95,649</td>
</tr>
<tr>
<td>2014</td>
<td>234</td>
<td>3.2</td>
<td>109,677</td>
<td>14,624</td>
<td>95,053</td>
</tr>
<tr>
<td>2015</td>
<td>236</td>
<td>3.2</td>
<td>108,990</td>
<td>14,532</td>
<td>94,458</td>
</tr>
</tbody>
</table>

- **New cases:** about 230
  
  `0.0030%` or `3.0-3.2 /100000`

- **Prevalence 1.5%**
  
  About 110 000 cases

- **87% - Chronic HCV infection**
Characteristics of HCV infection

- 93% - between 15-59 г.
- 53% - male
- 55% - mild disease
HCV-related mortality

- All-cause mortality rate was 8.05 / 100,000
- 1,494 – liver cirrhosis (34 / 100,000)
- 802 – HCC 1.50 / 100,000)
Treatment rates in Bulgaria

HCV treatment

- Treatment eligible: 91.67%
- Treatment rate: 67.00%
- Response rate: 71.60%
- Compliance: 76.00%
- Recurrence rate: 26.25%
Costs of HCV treatment

- NHIF (2008)
- Without costs of diagnosis

### Costs of HCV treatment per patient in Bulgaria in 2008

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cost (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per outpatient visit</td>
<td>15</td>
</tr>
<tr>
<td>Average drug cost per patient treated with HCV</td>
<td>12,132</td>
</tr>
<tr>
<td>Treating cirrhosis</td>
<td>7,968</td>
</tr>
<tr>
<td>Treating hepatocellular carcinoma</td>
<td>1,036</td>
</tr>
<tr>
<td>Treating ascites</td>
<td>7,968</td>
</tr>
<tr>
<td>Treating esophageal varices</td>
<td>7,968</td>
</tr>
<tr>
<td>Treating hepatocellular encephalopathy</td>
<td>6,129</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>25,000</td>
</tr>
<tr>
<td>Treating post-liver transplant</td>
<td>4,000</td>
</tr>
</tbody>
</table>
Long-term costs and savings from HCV treatment in Bulgaria, 2008-2015 (€ million)

- **Total Cost of HCV treatment (A+B)**: €2.270
- **Cost of untreated HCV (B)**: €1.706
- **Cost of Drug Treatment of Chronic HCV (A)**: €564
- **Savings from averted complications of HCV (B-A)**: €1.143
What we need?

- National Screening program and National register (data base)
  - To decrease rate of infections
  - Early diagnosis - to identifying patients for treatment
  - Early treatment associated with better response rates
  - To follow-up the infected subjects and monitoring therapy
  - To decrease the cost
Why we need of screening program?

• Many of infected persons do not know the risk factors
Risk factors among patients diagnosed with chronic hepatitis C

- **Intravenous drug use**
- **Blood transfusion**
- **Nosocomial**
- **Unknown**
- **Other**

**France, N=1769 2000–2001**
- Intravenous drug use: 25%
- Blood transfusion: 38%
- Nosocomial: 10%
- Unknown: 27%

**Germany, N=747 2000–2001**
- Intravenous drug use: 9%
- Blood transfusion: 23%
- Nosocomial: 54%
- Unknown: 12%

**Belgium, N=1726 1992–2002**
- Intravenous drug use: 5%
- Blood transfusion: 39%
- Nosocomial: 21%
- Unknown: 26%

**Greece, N=1229 1987–2002**
- Intravenous drug use: 3%
- Blood transfusion: 37%
- Nosocomial: 5%
- Unknown: 30%
- Other: 25%

Why we need of screening program?

A large proportion of patients with chronic HBV/HCV infection remain undiagnosed:

- Asymptomatic disease
- Nonspecific symptoms
- First diagnosis – advanced liver cirrhosis

Early diagnosis = screening

ALT

HBsAg, anti-HCV
Thank you!