Treatment policies and access of treatment for chronic hepatitis B and C in Lithuania

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Prevalence of HBsAg and anti-HCV among children and adults in Lithuania, 2001 (n=321)

Arvydas, Ambrozaitis, Kęstutis Žagminas, Ligita Jančorienė, Aušra Stiklerytė, unpublished data
Incidence of acute viral hepatitis B

Since 1990 incidence of acute VHB decreased:
- 10.9 cases / 100 000 population in 2001 (Lithuania)
- 0.9 cases / 100 000 population in 2014 (Lithuania)
- 0.8 cases / 100 000 population in 2012 (EU incidence average)

• Since 50-70% of acute VHB cases are asymptomatic actual incidence may be up to 6 times higher

• Route of acquisition - not detected in 82.1% of acute cases in 2014
• The highest incidence rates - in 25-34 age group

• Infant vaccination started on 1998, coverage rate in 2014 - 97.4%

Centre for Communicable Diseases and AIDS of Lithuania

Prevalence of chronic HBV infection in Lithuania

The estimated HBsAg (+) prevalence in Lithuania is ~ 2%

Evaluation of the prevalence of HBsAg and risk factors for HBV infection among Lithuanian Army soldiers was carried out in Lithuanian military subunits in 2003:

Serum samples from 1,830 soldiers were tested for HBsAg

• 1.97% of soldiers were seropositive for HBsAg
  – prevalence of HBsAg among soldiers who were offered to use drugs was 4.3%
  – In the remaining group the prevalence was 1.9%

Prevalence of chronic HBV infection in Lithuania

The estimated HBsAg (+) prevalence in Lithuania is ~ 2%

Evaluation of the prevalence of HBsAg among first-time blood donors in Lithuanian was carried in Vilnius blood centre in 2005:

Serum samples from 24,880 first-time blood donors were tested for HBsAg
• 1.7% of first-time blood donors were seropositive for HBsAg


HBV genotype distribution in Central and Eastern Europe (n=1148)

Chronic HBV infection in Lithuania

• Estimated prevalence of HBV infection 2%
  ~ 10% had a chronic viral hepatitis B
  ~ 90% are chronic inactive HBsAg carriers

• Patients with chronic HBV infection on follow-up:
  ≈ 3,000 - 5,000

• ≈ 150 - 200 patients with CHB are on long term treatment with antivirals (mostly with Lamivudin)

Lithuanian Guidelines on Chronic Hepatitis B Diagnostics and Treatment (2005)
Access to CHB treatment options in Lithuania 2015

Journal of Hepatology 2012 vol. 57 j 167–185
Treatment of hepatitis B infection:
preferred regimens

Peginterferon alfa-2a (available in Lithuania, 80% reimbursement)
Entecavir (only on personal named based application to Lithuanian Sick Fund)
Tenfovir (only on personal named based application to Lithuanian Sick Fund)

Treatment of hepatitis B infection:
alternative regimens

Lamivudin (available in Lithuania, 80% reimbursement)
Adefovir (only on personal named based application to Lithuanian Sick Fund)
Telbivudin
Emtricitabin

EASL. Journal of Hepatology 2012 vol. 57 j 167–185

Cumulative incidence of HBV resistance to lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (LdT) and tenofovir (TDF)

HBV is not in the list of socially important diseases, not other key health policy documents

Current situation regarding access to hepatitis B treatment in Lithuania

- No real access to preferred treatment regimens with nucleos(t)ide analogues Entecavir and Tenofovir:
  - ~ 20 – 30 patients are on the life long treatment with Entecavir
  - ~ 5 – 10 patients – Tenofovir, most of them covering treatment expenses by themselves

- It is real need of preferred nucleos(t)ide analogues (Entecavir, Tenofovir) treatment availability for about 100 – 150 patients per year with CHB
Current situation regarding access to hepatitis B treatment in Lithuania

- Treatment with Pegylated interferon for CHB reimbursed only 80%; for most of patients treatment with PegIFN is unaffordable due to high cost (20%) of drug surcharge

- HBV-DNA test – most important test for measuring antiviral efficacy – not reimbursed (cost ~ 40 EUR)

- Viral resistance tests are not available yet

Current situation regarding access to hepatitis B treatment in Lithuania

- It is access to alternative treatment regimen with nucleoside analogue Lamivudin (reimbursed only 80%):
  ~ 100 patients are on the life long treatment

- Mostly CHB patients are on long lasting treatment with Lamivudin with the very high percentage of viral resistance after few years of treatment with no way to change treatment to more potent antiviral medication (NAs) with less resistant patterns
Resistant virus – very angry beast!

**Anti-HCV prevalence in the general population of Lithuania (2012)**

- The study enrolled 1528 adults from the 5 biggest cities of Lithuania and its rural regions.

- Anti-HCV prevalence in Lithuania was **2.78%**.

- If adjusted according to the standard European population, anti-HCV rate was **2.85%**.

- Anti-HCV more prevalent among males:
  - crude rates: **4.02%** males vs. **1.49%** females, \( p=0.003 \)

- Vilnius and Kaunas regions have higher infection rates than smaller rural regions (2.92% and 3.01% vs. 2.24%, 0.74% and 1.35%)

Prevalence of HCV genotypes in Lithuania

HCV isolates from 1097 patients, collected in 1998-2006 were tested using INNO-LiPA HCV II assay:

• Prevalence of genotypes:
  – subtypes 1b and 1a – 61.8%:
    • 71% - high VL; 29% - low VL
  – subtype 3a – 29.1%
  – subtypes 2a and 2c – 9.1%

Aušra Stiklerytė, unpublished data

Prevalence of HCV genotypes in Lithuania

• Genotype 1 - 65% (~ 90% of all - G1b)
• Genotype 2 - 8,7% (~ 80% of all - G2a/c)
• Genotype 3 - 26,3% (~ 80% of all - G3a)

Chronic HCV infection in Lithuania

- Estimated prevalence of HCV infection 2-3% (2.85%): \( \approx 50,000 \)
  - Only \( \approx 20\% \) of infected are identified
- Patients with chronic HCV infection on follow-up:
  \( \approx 10,000 - 12,000 \)
- \( 1,000 - 2,000 \) newly diagnosed chronic HCV infection cases per year
- \( 30 - 40 \) newly diagnosed acute HCV infection cases per year


Chronic HCV infection in Lithuania

- **60-70\%** of all CHC patients on follow-up are infected with **G1** HCV
  - 20-25\% of all CHC patients with G1 HCV infection have F3-F4 stage of fibrosis
  - 60\% of all CHC patients with G1 HCV infection have F2 stage of fibrosis
- The is an estimation, that if not treated \( \approx 12\% \) of all CHC patients with F2 stage of fibrosis progress annually to F3 stage

Hepatology 2008;48:418-431
Chronic HCV infection in Lithuania

No data on difficult to treat populations

- HCV/HIV co-infected?
- HCV/HBV co-infected?
- CHC patients with F3&4 stage of fibrosis?
- HCV and decompensated liver cirrhosis?
- HCV and chronic kidney disease and HD?
- HCV in post kidney transplant patients

Treatment of chronic HCV infection in Lithuania

- In 2014 total of 890 patients with CHC treated with antivirals (PegIFN, RBV with or without TVR, BOC)
- Total of 60% of all treated had G1 HCV infection (534 pts)
- From 2014 Lithuanian State Sick Fund (VLK) allocated annually ~ 4 million EUR for the treatment of patients with G1 HCV infection and advanced fibrosis - stage F3-F4

Sveikatos Informacijos centras prie LR SAM. Informaciniai leidiniai.
Access to HCV virology test and other examination for patients with CHC

- From 2008 HCV-RNA testing before, during and after treatment and on follow up reimbursed 100%
- From 2008 HCV genotyping reimbursed 100%
- Liver biopsy prior treatment start is mandatory, should be performed in one of the main centers for infectious diseases or gastroenterology in 5 biggest cities of Lithuania
- Fibroscan equipment is available in two hospitals in Lithuania (Vilnius and Kaunas); transient elastography is not mandatory before treatment. There is a big need of Fibroscan in all 5 main centers of CHC treatment in Lithuania

Hepatitis C treatment milestones in Lithuania

- **1996** – Standard Interferon alfa-2b (*Realdiron®*)
- **2000** – Standard Interferon alfa-2b + Ribavirin
- **2006** – Pegylated Interferon alfa 2a/b + Ribavirin
- **2014** – Pegylated Interferon alfa 2a/b + Ribavirin and Telaprevir for G1 CHC with fibrosis stage F3/F4
- **2015** – Pegylated Interferon alfa 2a/b + Ribavirin and Boceprevir for G1 CHC with fibrosis stage F3/F4
Hepatitis C treatment milestones in Lithuania

- **Since 29 Oct 2015** – Interferon-free therapy with Ombitasvir/Paritaprevir/ritonavir and Dasabuvir +/- Ribavirin (3D) for G1 CHC T-naïve and T-experienced patients with fibrosis stage F3/F4 (100% reimbursement)

- Still not resolved question about the treatment of G1 CHC patients with fibrosis stage F2:
  - Pegylated Interferon alfa 2a/b + Ribavirin and Simeprevir or
  - Ombitasvir/Paritaprevir/ritonavir and Dasabuvir (3D) +/- Ribavirin

An updated Lithuanian Guidelines on Chronic HC Diagnostics and Treatment (2015)
Current Lithuanian treatment guidelines 2015 (Draft) I

<table>
<thead>
<tr>
<th>Treatment of Naïve G1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ F2</td>
<td>PegIFN + RBV</td>
</tr>
<tr>
<td>F3 – 4</td>
<td>OBV/PTV/r + DSV (3D) + RBV or BOC/TVR + PegIFN + RBV if 3D contraindicated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Retreatment of G1 relapsers, partial responders, non-responders</th>
<th></th>
</tr>
</thead>
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<tr>
<td>≤ F2</td>
<td>PegIFN + RBV</td>
</tr>
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<td>OBV/PTV/r + DSV (3D) + RBV or BOC/TVR + PegIFN + RBV if 3D contraindicated</td>
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</table>

G2, G3, G4 ≥ F2 PegIFN + RBV

Lėtinio virusinio C hepatito diagnostikos ir ambulatorinio gydymo kompensuojamaisiais vaistais tvarkos aprašas. 2015 10 21 (projektas, atiduotas tvirtinti LR SAM)

Recommendations of treatment with OBV/PTV/r + DSV (3D)

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Drugs</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b HCV genotype, without cirrhosis</td>
<td>OBV/PTV/r + DSV</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1b HCV genotype, compensated cirrhosis</td>
<td>OBV/PTV/r + DSV + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1a HCV genotype, without cirrhosis</td>
<td>OBV/PTV/r + DSV + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1a HCV genotype, compensated cirrhosis</td>
<td>OBV/PTV/r + DSV + RBV</td>
<td>24 weeks</td>
</tr>
<tr>
<td>4 HCV genotype, without cirrhosis</td>
<td>OBV/PTV/r + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td>4 HCV genotype, compensated cirrhosis</td>
<td>OBV/PTV/r + RBV</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

Exviera SPC, 2015; Viekirax SPC, 2015
**Current Lithuanian treatment guidelines 2015 (Draft) II**

<table>
<thead>
<tr>
<th>Patients awaiting liver transplantation G1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child-Pugh A</strong></td>
<td></td>
</tr>
<tr>
<td>OBV/PTV/r + DSV (3D) + RBV 12 w for G1b; 24 w for G1a</td>
<td></td>
</tr>
<tr>
<td><strong>Child-Pugh B</strong></td>
<td></td>
</tr>
<tr>
<td>OBV/PTV/r + DSV (3D) + RBV <em>Individualized approach</em> or BOC/TVR + PegIFN + RBV if tolerated</td>
<td></td>
</tr>
</tbody>
</table>

**Post-transplant recurrence of HCV infection G1**

OBV/PTV/r + DSV (3D) ± RBV (F0-4) for 24 w

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**Current Lithuanian treatment guidelines 2015 (Draft) III**

**Chronic Kidney Disease (insufficiency) in G1 patients**

<table>
<thead>
<tr>
<th>≤ F2 (CC &gt; 50 ml/min)</th>
<th>PegIFN + RBV 24-48 w</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ F2 (CC 15 - 50 ml/min)</td>
<td>PegIFN + RBV 24-48 w</td>
</tr>
<tr>
<td>F3 – F4 G1 (CC &gt; 15 ml/min)</td>
<td>OBV/PTV/r + DSV (3D) ± RBV</td>
</tr>
</tbody>
</table>

**Hemodialysis patients (no data for 3D)**

| F0 – F4 | PegIFN + RBV (200 mg/day, or TIW) |

**Before kidney transplantation G1**

| F0 – 4 | OBV/PTV/r + DSV (3D) ± RBV (200 mg/day, or TIW if CC ≤ 50 ml/min) |

**After kidney transplantation? (not enough data, no recommendations)**

**HCV & HIV co-infection (Drug-Drug Interactions!!!)**

| ≤ F2 | PegIFN + RBV |
| F3 – 4 G1 | OBV/PTV/r + DSV (3D) ± RBV for 12-24 w |

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Lėtšino virusinio C hepatito diagnostikos ir ambulatorinio gydymo kompensuojamaisiais vaistais tvarkos aprašas, 2015 10 21 (projektas, atižudotas tvirtinti LR SAM)

Lėtšino virusinio C hepatito diagnostikos ir ambulatorinio gydymo kompensuojamaisiais vaistais tvarkos aprašas. 2015 10 21 (projektas, atižudotas tvirtinti LR SAM)
Unresolved problems in HCV infection in Lithuania

Hepatitis C is often referred to as a “hidden” epidemic because it receives far less attention and resources than other potentially deadly viral illnesses, such as HIV infection.

- There remains many HCV undetected patients
- New HCV infection still occurs (mostly by IDU)
- Only a minor fraction of the HCV patients are treated
- Drug resistant associated variants (RAV) should be taken care of
- HCV infection may be cured, but the problem of HCC remains for some time

Challengers in Hepatitis C strategies

Epidemics of viral hepatitis C represent a growing public health concern in most countries of Eastern Europe as well as in Lithuania, and it is urgent need of National Hepatitis Program

- Patient identification by risk assessment or by age (surveillance system) is not in place in Lithuania and should be implemented
- Strategy should emphasize efforts to increase awareness and testing for HCV
- Strategy should prevent stigmatization
- Active prevention measures are necessary especially in health care settings
Challengers in access to treatment for hepatitis C

The term “standard of care” refers to evidence-based, internationally recognized treatment regimens that are most successful in clearing the hepatitis C virus from patients.

- Introduction of newer treatments “usually slow”
  - convince government to pay for treatment
  - long negotiate affordable prices
- The cost of IFN-free medications for CHC are unaffordable for all other patients, who are not included in the group for reimbursement – the access to treatment should be improved, as every CHC patient should be treated
- Well organized treatment programs supported by government with affordable DAAs with SVR rate > 90% should be implemented

Is there another example in medicine where we have the tools but cannot treat a progressive yet curable diseases?

Gary L. Davis, AASLD 2015

Although Lithuania is burdened by HCV infection, I believe, that implementation of new treatments for HCV infection will solve the majority of problems of CHC in next few decades