Availability of diagnostics and treatment modalities for hepatitis B in Albania. Experiences of Infectious Disease Service

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Outline

• Review of some epidemiological aspects and HBV treatment cascade needs in Albania
• Diagnostic and treatment modalities assessment (according to EASL standards)
• Data on TDF treatment at the cohort of HBV patients followed at ID Service, UHC Tirana (CHB, severe HBV, reactivated CHB)
Cascade of care for HBV (no data)
### Sero-prevalence studies of HbsAg among Albanians, 1990-2009

<table>
<thead>
<tr>
<th>Nr</th>
<th>Author</th>
<th>Year</th>
<th>Study area</th>
<th>Target/age</th>
<th>Sample size</th>
<th>% prevalence HbsAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Roussos A et al</td>
<td>90'</td>
<td>Greece, Athens</td>
<td>Albanian refugees, adults, Greece</td>
<td>76</td>
<td>22.4%</td>
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<td>2</td>
<td>Santantonio T. et al</td>
<td>93</td>
<td>Italy</td>
<td>Albanian refugees, all ages, Italy</td>
<td>393</td>
<td>19%</td>
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<td>90'</td>
<td>Greece</td>
<td>Albanian refugees, all ages, Greece</td>
<td>1025</td>
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<td>4</td>
<td>Milionis C</td>
<td>90'</td>
<td>Greece</td>
<td>Albanian refugees, adults</td>
<td>504</td>
<td>11.7%</td>
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<td>5</td>
<td>Chirona M. et al</td>
<td>97</td>
<td>Italy</td>
<td>Albanian refugees, all ages, Italy</td>
<td>670</td>
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<td>6</td>
<td>Malamitsi-Puchner et al</td>
<td>1996</td>
<td>Greece</td>
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<td>500</td>
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<td>7</td>
<td>Papaevangelou V. et al</td>
<td>2003</td>
<td>Greece</td>
<td>Albanian refugees, pregnant women, Greece</td>
<td>409</td>
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<td>8</td>
<td>Duro V, Qyra Sh</td>
<td>1999-2009</td>
<td>Albania</td>
<td>Blood donors</td>
<td>79274</td>
<td>7.9%</td>
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<td>9</td>
<td>Elefsiniotis IS, et al</td>
<td>2003-04</td>
<td>Greece</td>
<td>Albanian refugees, women reproductive age</td>
<td>2040</td>
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<td>10</td>
<td>Resuli B, et al</td>
<td>2004-06</td>
<td>Albania</td>
<td>Adults, different groups (total) Pregnant women</td>
<td>3880, 640</td>
<td>9.5% (total)</td>
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<td></td>
<td></td>
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<td>7.3% (preg wom)</td>
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<td>Katsanos KH, et al</td>
<td>2006</td>
<td>Greece</td>
<td>Albanian refugees, all ages, Greece</td>
<td>410</td>
<td>11.8%</td>
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<td>12</td>
<td>Duro V et al</td>
<td>2004-08</td>
<td>Albania</td>
<td>Blood donors</td>
<td>52727</td>
<td>6.7%</td>
</tr>
</tbody>
</table>
HbsAg sero-prevalence (cross sectional sentinel study): pregnant women

- 6000 pregnant women at O-G hospital Tirana, Jan- Sept 2010.
- 15-43 yrs
- 410 HbsAg +.
- Sero-positivity rate of HBsAg among pregnant women is 6.8%
Reported cases of Hepatitis in Albania (source IPH)

- Hepatitis reported cases
- Unspecified hepatitis
- Hepatitis B

Graph showing the number of hepatitis cases from 1998 to 2013.
### Death rate of HBV at UHCT

#### Hepatitis B in UHCT

<table>
<thead>
<tr>
<th>years</th>
<th>cases</th>
<th>deaths</th>
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<tbody>
<tr>
<td>2006</td>
<td>240</td>
<td>3</td>
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<tr>
<td>2007</td>
<td>196</td>
<td>2</td>
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<tr>
<td>2008</td>
<td>241</td>
<td>10</td>
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<td>2009</td>
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<td>2010</td>
<td>169</td>
<td>2</td>
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<tr>
<td>2011</td>
<td>174</td>
<td>3</td>
</tr>
<tr>
<td>2012</td>
<td>176</td>
<td>3</td>
</tr>
<tr>
<td>2013</td>
<td>246</td>
<td>4</td>
</tr>
</tbody>
</table>

- **Cases**
- **Deaths**
HBV (n=235), HCV (n=196) TB (n=249), sifiliz (n=194) among HIV patients
Specialties treating CHB: GI and ID

• Infectious Disease and Gastro-hepatologist specialist at secondary (regional hospitals) and tertiary level (UHCT: ID Service and Gastro-hepatology Service)
Infectious disease vs. Hepatologist

**Infectious disease:**
(Historically: acute hepatitis)

- Definite acute vs. chronic is not a clear and easy task
- Different world experience: both specialties
- Antivirals (NA) were discovered and used first in HIV
- PCR technique revolutionized the ID specialty
- WHO joint program for HIV/Hepatitis and STI (hepatitis is mainly an STI)
- Common National protocols and guidelines for management of hepatitis

**Hepatologist**
(historically chronic hepatitis)

- Historically: chronic hepatitis
- Chronic vs. end stage liver disease
Treatment and care cascade

- Estimations of infected persons and those in need for treatment needed.
- Screening & Case detection: testing capacities especially at PHC level are weak
- ALT/AST surveillance through “population check-up” – referring for serology diagnosis
- Not all those diagnosed can enter care through so called “referral system”
- Especially vulnerable groups such as IVDU or those without health insurance do have same barriers for access to care
EASL standards: 2012 guidelines

• Assessment of the severity of liver disease:
• Biochemical markers: ALT, AST, yGT, ALP, Bil, serum albumin, globulins, CBC, PPT
• Hepatic ultrasound
• HBV DNA (real time PCR quantification assay)
• Liver necro-inflammation and fibrosis
• Monitoring of Rx: HBVDNA every 3-6 months, Hbe Ag, anti Hbe, HBs every 12 months
Diagnostic availabilities: serology

- Serology screening & diagnosis: not full panel of sero-markers provided at public hospitals
- Quantitative HBs Ag: available only at private labs
Diagnostic availabilities: HBV DNA
(EACL: real time PCR quantification assay; baseline, after 3 m of Rx, every 6 m)

• UHCT situation: PCR equipment available but kits are scarce and quality assurance is an issue

• HBV DNA tests provided at IPH: problems with availability of kits not covering all cases and not all the time, transporting of samples might influence the quality

• Available in private labs: cost; standardization!
Fibroscan

• Liver stiffness measurements (Fibroscan): Available at UHCT since 2014

• Problems:
  – Standardization
  – Training of staff
  – Only medium size probe available
Treatment

• HIF has included in the list of drugs these treatments

• Drugs:
  – Peg-IFN
  – NAs: LAM, TDF
TDF: protocol of HIF

• CHB (all, including those treated with LAM resistant to treatment and cases of reactivation of infection after treatment discontinuation).
• Liver cirrhosis (compensated and decompensated).
• HCC with HBV infection.
• Cronic carriers of HBV under kimiotherapy/immunosupressive therapy (regrdless level of HBV DNA).
• Fulminant/severe HBV hepatitis.
• Infection form HBV during pregnancy.
• Co-infection HIV and HBV (togather with antiretroviral therapy).
HIF protocol: criteria

- HBV DNA > 2.000 UI/ml
- ALT> UNL
- Moderate to severe liver necro-inflammation and/or fibrosis
- (other aspects: age, health status, family history for HCC or cirrhosis, extrahepatic manifestations)
- Compensated cirrhosis: HBVDNA < 2.000 or normal ALT
- Decompensated cirrhosis: imediate treatment
TDF use at ID Service

• 104 cases with HBV infection treated with TDF disoproxil at ID Service between 2014-2016
• CHB: 72 cases
• Reactivated CHB: 20 cases
• Severe acute hepatitis 12 cases
Cases per age

age-group

age 15-25  26-35  36-45  46-55  56-65  > 66
Co-morbidities/predisposing factors

- Chemotherapy: 18 cases
- CLL: 10 cases
- HTA: 8 cases
- Malignancies: 6 cases
- Diabetes: 6 cases
- Thrombocytopenia: 2 cases
- CRI: 2 cases
Risk factors

dental procedures  hemodialysis  needle stick  tatuing  cesarian section  sexual

cases
Diagnosis/testing

cases

ID service | chemotherapy | check up | blood screening | abroad
---|---|---|---|---
25 | 18 | 15 | 10 | 2
Diagnostic criteria: ALT

- ALT: abnormal in 94 cases (out of 104)
- Median value 496 UI/L
- Range 14-2900 UI/L
- Quantitative HBs Ag measurement: 61 cases (59%) (only at baseline not follow-up)
Fibroscan

- 72 cases (70%) measurement of liver stiffness with fibroscan was performed at baseline
HBV DNA

• Measured at baseline in 74 cases (72%)
TDF in severe acute hepatitis B

- 8 cases with severe AHB at ID Service at UHCT, followed during 2013
Characteristics

• Age: 25 yrs (21-33)
• Sex: 7/1 (F/M)
• Risk factors: dental procedures (44%), sexual (11%)
• Onset-hospitalization: 11 days (4-30 days)
• Onset-treatment: 12 days (4-33 d)
Characteristics

- ALT: 1706 UI (1060-3300)
- Bil: 15 mg/dl (8.4-27.2)
- INR: 1.94 (1.6-2.5)
- Encephalopathy: 12% (1/8)
- Hepato-splenomegaly: 75% (6/8)
- HBsAg: 100% (8/8)
- Anti HBc IgM: 100% (8/8)
- HBeAg: 1 positive (out of 2 cases performed)
- HBV DNA: (n=2) $3.2 \times 10^5$
Follow up

• All the patient were followed at least for 6 months (2 cases lost: 1 and 2 months)
• Time on treatment: 5.9 months (1-12)
• Normalization of INR: 11 days (4 days for 7 cases)
• ALT: 60 days (n=7)
• Bil: 50 days (n=7, 26-98 d)
• All the 6 cases who were followed up became HbsAg neg, while only 2 did not seroconvert to anti Hbs Ab.
• No adverse effects to therapy
<table>
<thead>
<tr>
<th>Time to seroconversion and biological normalization</th>
</tr>
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<tbody>
<tr>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td>1 2 3 4 5 6 7 8 Mean days</td>
</tr>
<tr>
<td><strong>HBV DNA</strong></td>
</tr>
<tr>
<td>NA baseline NA NA NA baseline NA</td>
</tr>
<tr>
<td><strong>HBsAg -</strong></td>
</tr>
<tr>
<td>180 180 180 NA 240 180 150 NA</td>
</tr>
<tr>
<td><strong>AntiHBs</strong></td>
</tr>
<tr>
<td>180 180 180 NA 240 180 - NA</td>
</tr>
<tr>
<td><strong>Bilir</strong></td>
</tr>
<tr>
<td>30 65 60 - 98 30 30 40 50</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
</tr>
<tr>
<td>30 100 60 - 98 56 60 60 60</td>
</tr>
<tr>
<td><strong>INR</strong></td>
</tr>
<tr>
<td>5 8 2 2 60 3 2 5 11</td>
</tr>
<tr>
<td><strong>TDF Rx</strong></td>
</tr>
<tr>
<td>180 180 180 30 240 180 360 60 180</td>
</tr>
<tr>
<td>P2</td>
</tr>
<tr>
<td>-----</td>
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<tr>
<td>0.5</td>
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The chart above shows the relationship between INR values and time (days). Each line represents a different condition or parameter (P2 to P8), with INR values plotted against days from 1 to 60.
20 case with reactivated CHB at ID Service, UHCT

• 13 men (65%) average age 54 years.
• associated diseases:
  – Chronic lymphoid leucosis (CLL) 7 cases (35%),
  – Non Hodgkin lymphoma 5 cases (25%),
  – Hodgkin lymphoma 4 cases (20%),
  – myeloma 2 caes (10 %),
  – Breast Ca 1 case (5%)
  – Idiopathic ttombocytopenic Purpura 1 case (5%).
• Reasons of reactivation: only 3 cases serollogically tested (only HBsAg) before initiation of therapy
  – 19 cases (95%) different regimens of chimiotherapy
  – 1 cases cortitherapy with high doses
Clinical forms

- hepato (90%) and splenomegaly (65%),
- Icter (90%)
- bilirubinemia (medium) 7 mg/dl, range 0.3-20 mg/dl, where 8 cases (40%) had bil > 10 mg/dl,
- AST increase in 17 cases. Medium value 176 IU (7-1032),
- ALT increase in 20 cases (100%) values medium 698 UI (7-2325)
- PPT 60% (26-81%) with 1 case < 40%.
- Increase gama globulinemia in 10 cases (76%).
- 8 cases (40%) presenting severe forms.
- 18 cases (90%) treated with tenofovir disoproksil 245 mg/d PO and supportive therapy.
Recommendations (action plan)

- Accurate estimations of sero-prevalence of HBV in Albania, especially among risk groups, estimations of those in need for treatment and care etc.
- Improve screening and diagnostics capacities at all levels of care
- Improve referral system
- Improve access and linkage to care to every one in need regardless health insurance status
- Improve treatment and care and follow up through implementation of updated national guidelines, protocols and SOP in line with WHO and other international guidelines
- Set up Hepatitis Outpatient Clinic, improve database and reporting
• Thank you!