# Therapeutic Strategies for Chronic Hepatitis B in Countries with Limited Resources

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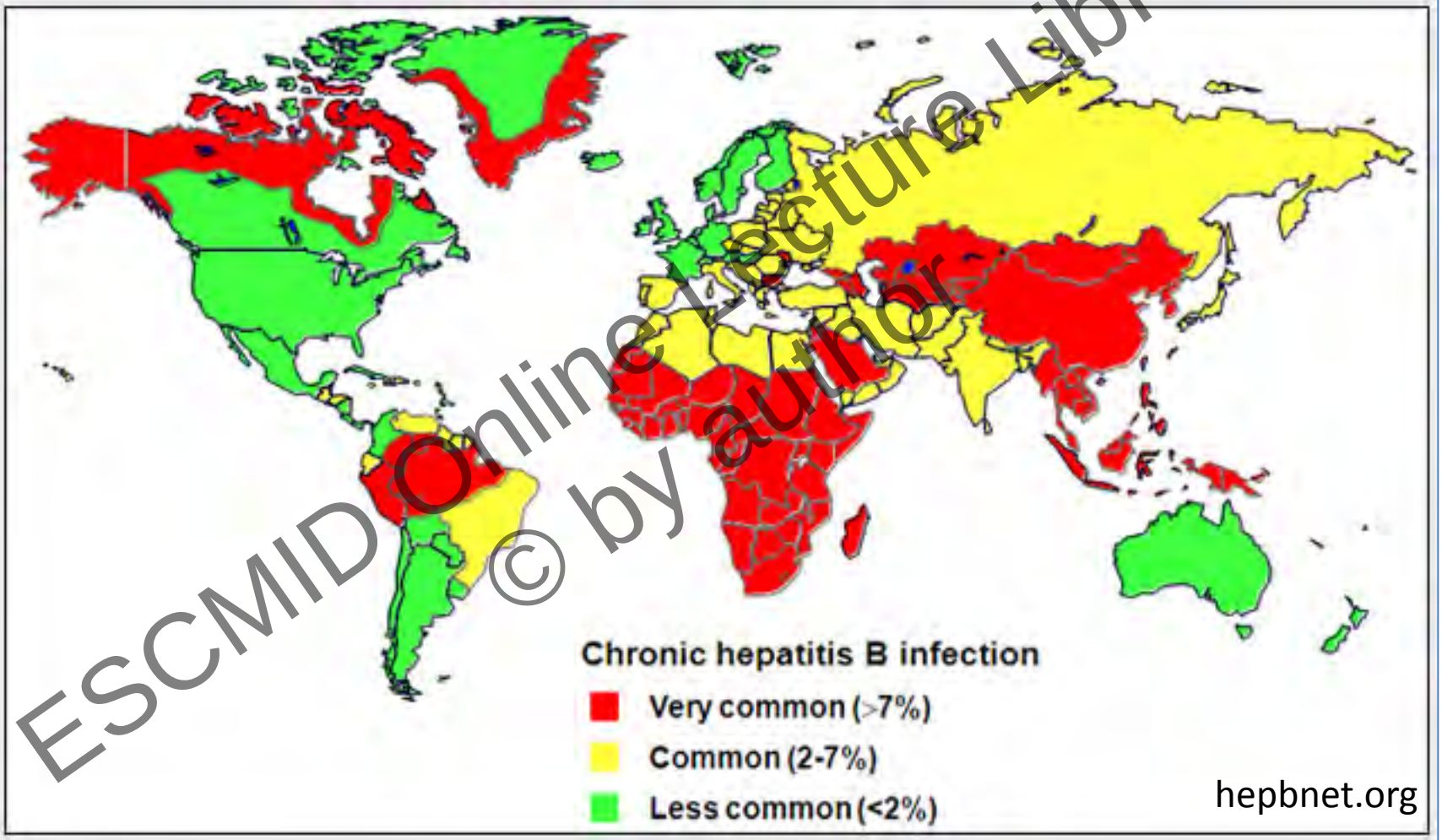
# Q1

- From which region do you participate?
  - A. Europe
  - B. Asia
  - C. Africa
  - D. Americas
  - E. Others

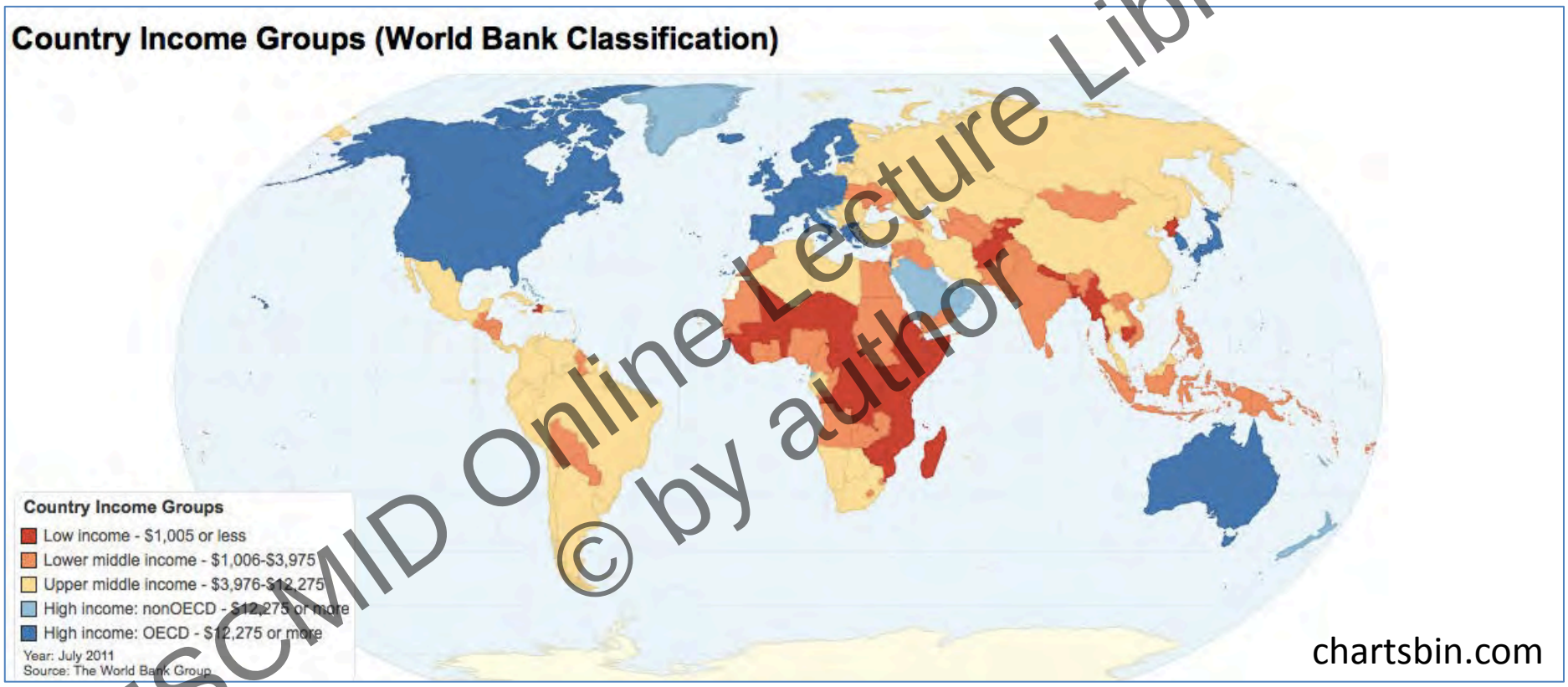
- Hepatitis B virus (HBV) infection is global health problem
- Some parts of the word are more severely affected.

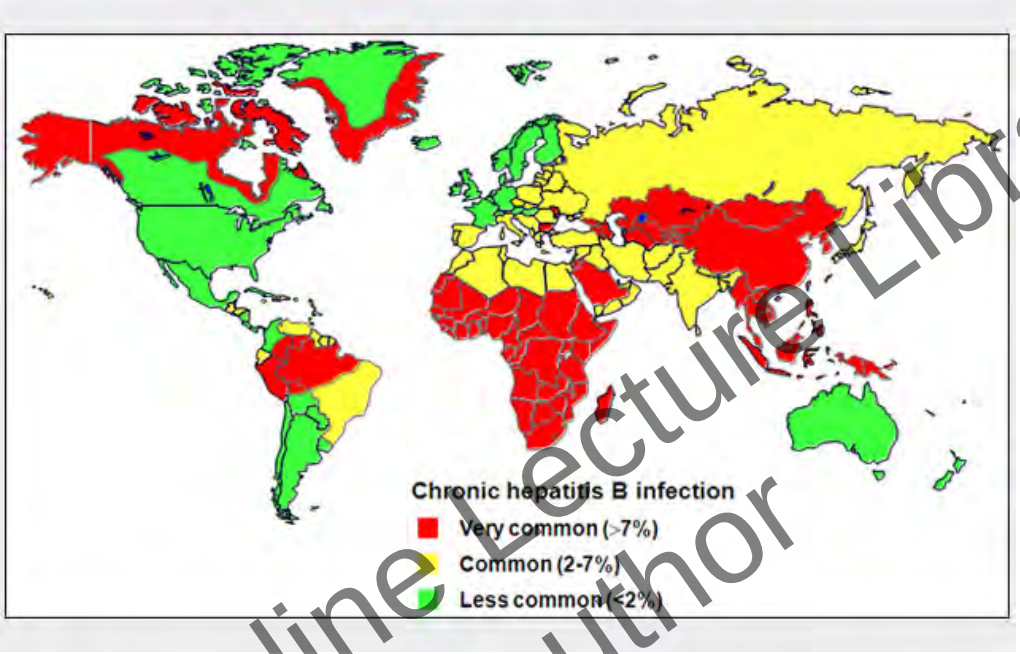


# Q2

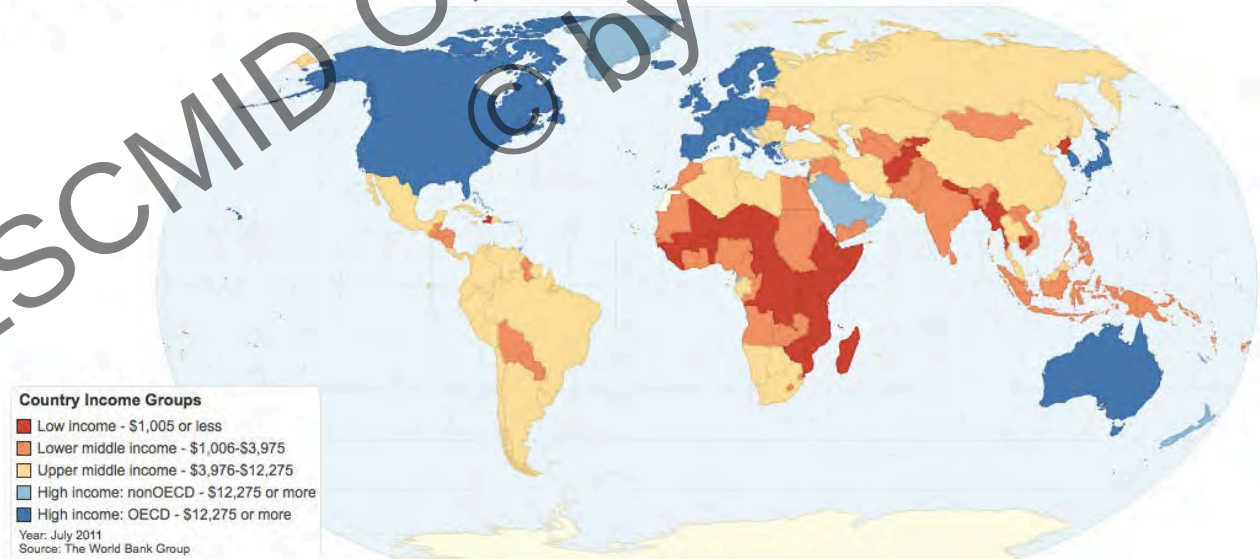
- How do you estimate the prevalence of HBsAg positivity in your country?
  - A. <1%
  - B. 1-5%
  - C. 5-10%
  - D. >10%
  - E. I don’t know

The areas with moderate to high endemicity are, in a great extent, low-income parts as well



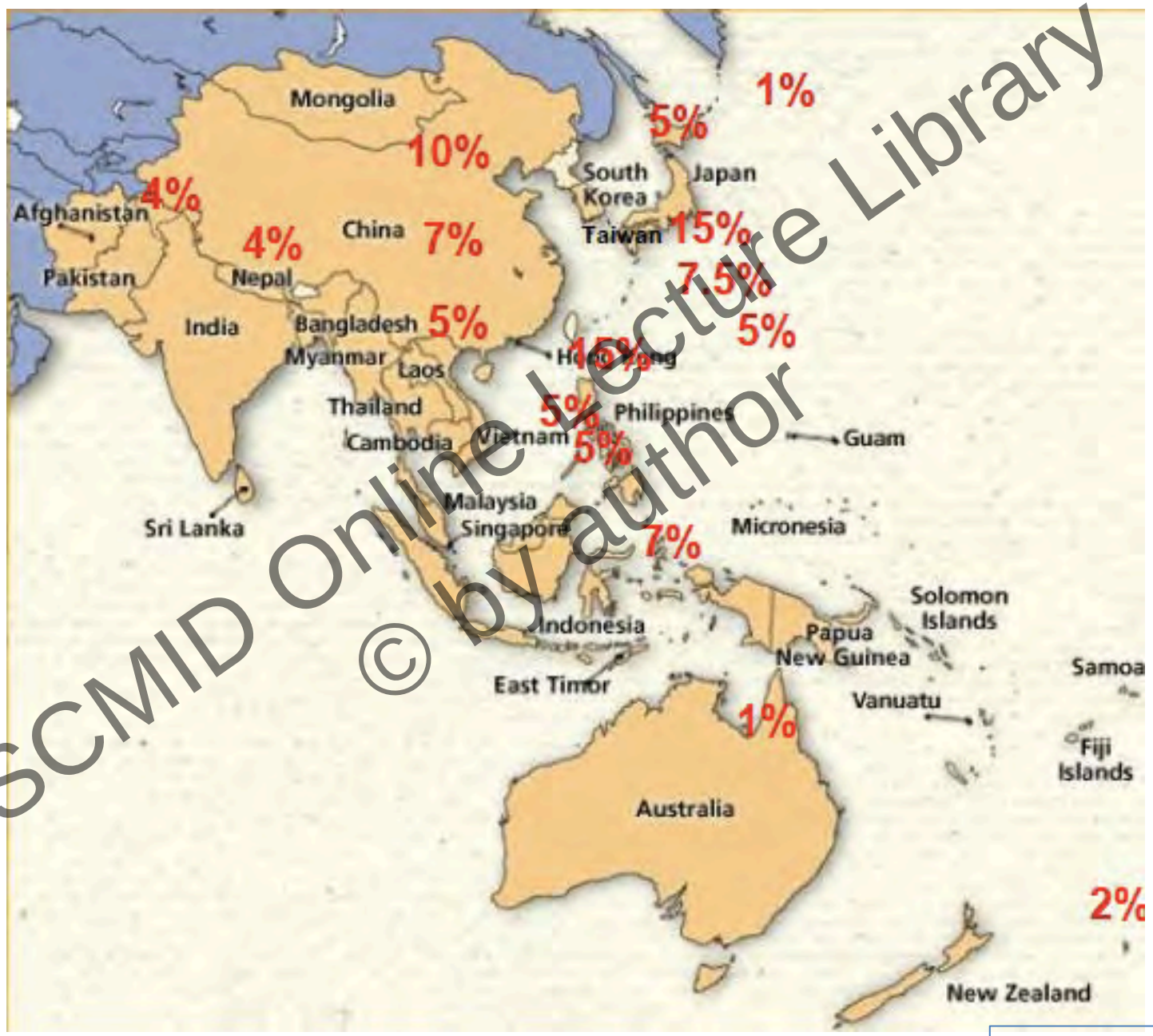



**Country Income Groups (World Bank Classification)**



- The diagnosis, treatment, and management of complications such as liver failure and hepatocellular carcinoma are costly

- Asia is a high endemicity area of chronic HBV infection, which is usually acquired
  - perinatally or
  - during early childhood






Courtesy of Lok ASF

# In China,

- More than half a million people die annually from end-stage HBV complications
- An HBV vaccination program has been implemented
- A one-third decrease in HBV-infected people since 1992: 10% to 7%
- Still, more than 1 million people in China infected with HBV in 2011



Zhang CY, et al. Biosci Trends 2013
Wang Y, et al. Expert Rev Anti Infect Ther 2011

# In India,

- 250,000 people die annually of viral hepatitis or its complications[1]
- HBV carrier rate is 5-7%[2,3]
- Harbors the second largest pool of HBV carriers in the world[2]
- Genotypes A and D are most common.
- The vaccine has been introduced as part of the childhood immunization in some states



1.Acharya SK, et al. Natl Med J India 2006, 2.Abraham P. Clin Lab Med 2012, 3.Tandon BN, et al. Gut 1996

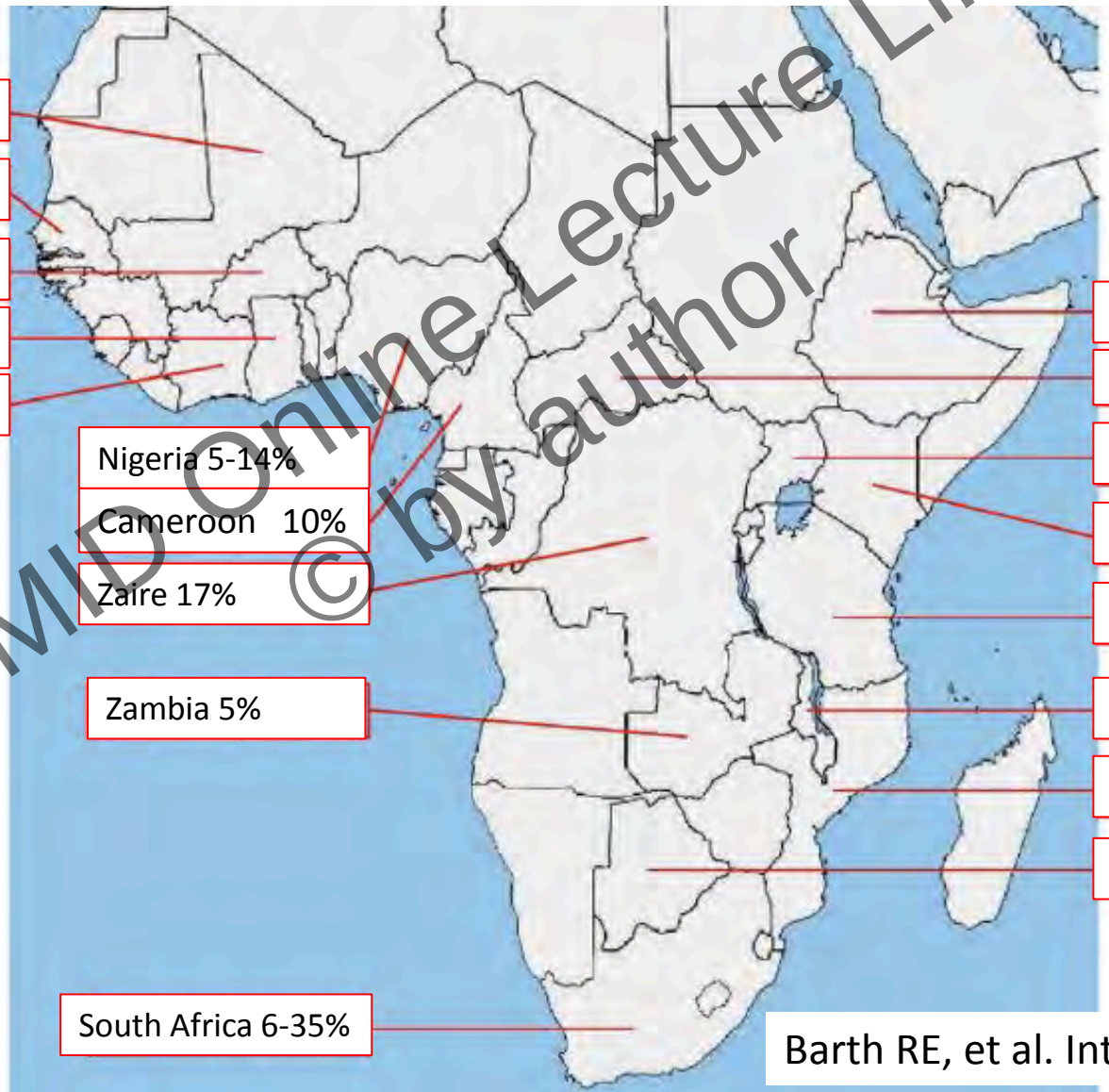
# In Africa

- HBV is highly endemic; at least 65 million chronic HBsAg carriers
- 25% of whom are expected to die from liver disease
- Before the vaccine, in black South Africans, it was 9.6%
- In 1995 the South African Department of Health (SADoH) incorporated the HB vaccine at 6, 10, and 14 weeks of age



Burnett RJ, et al., Vaccine 2012

# HBsAg Prevalence Rates in Sub-Saharan Africa




Barth RE, et al. Int J Infect Dis 2010

- Due to the lack of adequate reimbursement for treatment and diagnostics, adherence to treatment guidelines is unlikely.
- Lamivudine is still widely used in Asia.

# Q3

- How is HBV drug reimbursement policy in your country?
  - A. All drugs (interferons and oral antivirals) are reimbursed
  - B. There are some restrictions (ALT and/or HBV-DNA level and biopsy) for interferon
  - C. There are some restrictions (ALT and/or HBV-DNA level and biopsy) for oral antivirals
  - D. There are some restrictions (ALT and/or HBV-DNA level and biopsy) for all the drugs
  - E. The drugs are not reimbursed at all.

# Reimbursement of HBV Drugs in Asia-Pacific Region

- A survey sent to the experts in 16 countries
  - With prevalences of 1-15%
- 15/16 have policies



Lim SG, AASLD 2009

# First Line Drugs

- LAM
  - LAM only:3
- ADV: 7
- LdT:6
- ETV:9
- TDF:0
- Peg-IFN: 7
- Standard IFN: 3



Lim SG, AASLD 2009

# Reimbursement for Monitoring HBV Therapy

- YES: 10
  - Liver panel: 10
  - HBV-DNA: 8
  - Resistance mutation testing: 1
- NO:5



Lim SG, AASLD 2009

# Q4

- How is HBV diagnostics policy in your country?
  - A. HBV-DNA is commonly available and reimbursed without restrictions
  - B. It is available, reimbursed with some restrictions (baseline, 2-3 times in a year, etc.)
  - C. It is available but not reimbursed
  - D. It is not commonly available

- HIV co-infection is a big concern since 10% of the 40 million people with HIV are estimated to be co-infected with HBV.
- The majority of these co-infected patients live in resource-limited regions of the world; Asia and Africa.

- The consequences of co-infection include
  - Increased liver-related morbidity
  - Mortality
  - Increased hepatitis B viral replication
  - Immune reconstitution to HBV in the setting of antiretroviral therapy
  - Hepatotoxicity from antiretroviral drugs



Hoffmann&Thio Lancet Infect Dis 2007

# HBsAg prevalence rates in sub-Saharan African HIV-infected individuals per country.

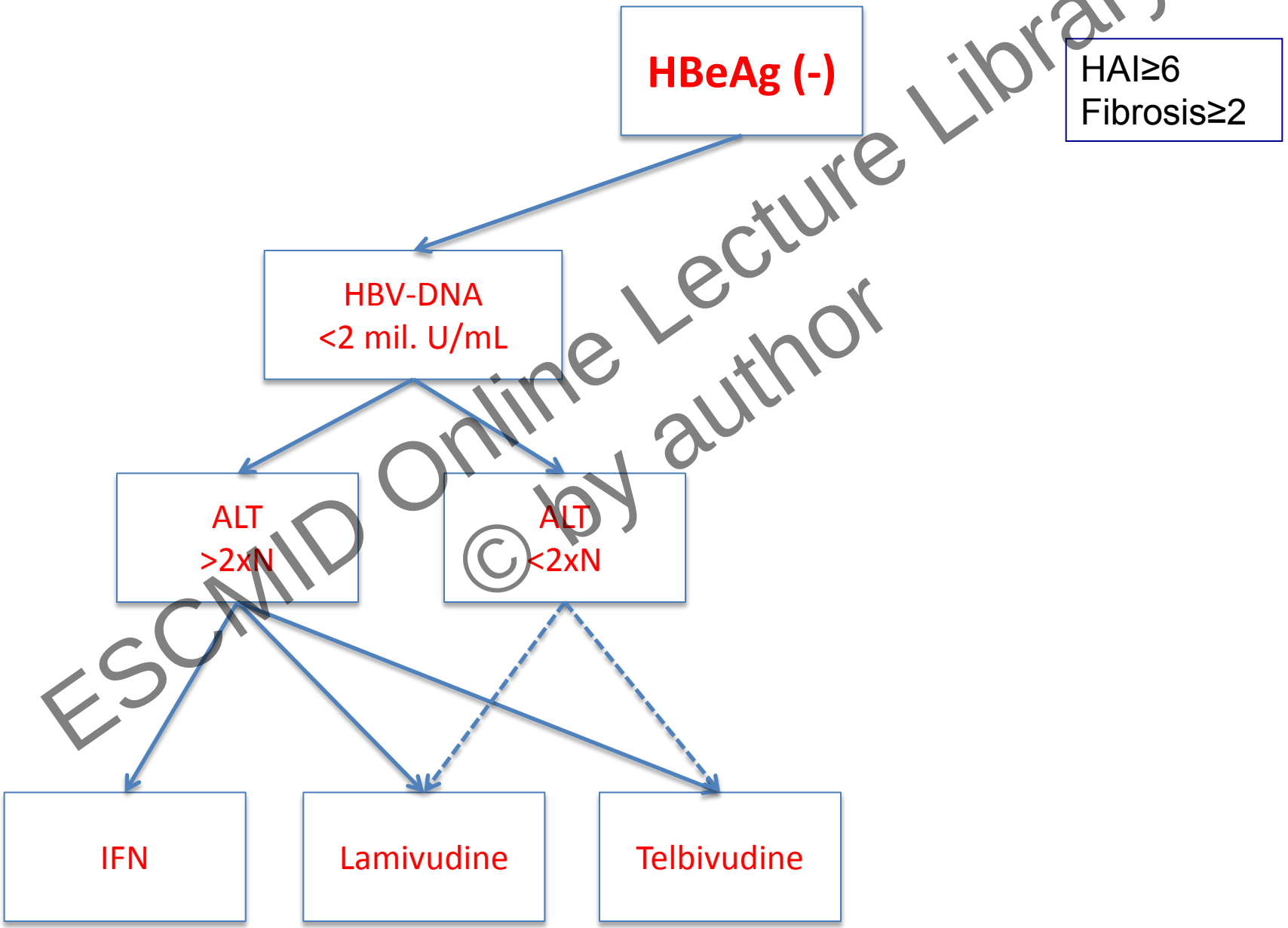


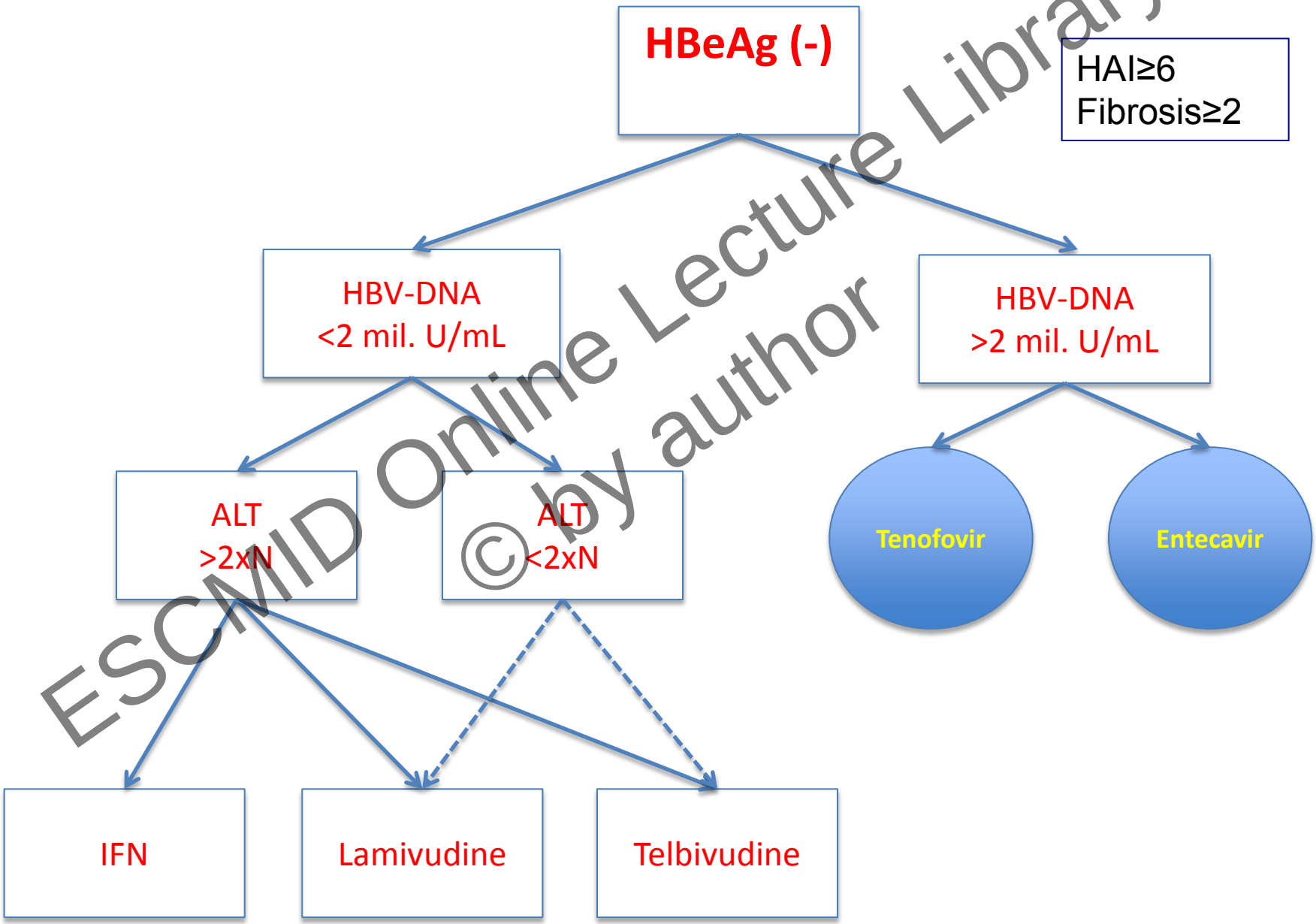

Barth RE, et al. Int J Infect Dis 2010

- Middle East is a moderately endemic part for HBV.
- The predominant genotype is D and associates with a low rate of response to interferon treatment.
- The problem is complicated by hepatitis D virus in some patients.
- In Turkey, HBsAg prevalence is around 4%.

- Although the drugs are reimbursed to all patients, there is a viral load-based stratification.
  - Lamivudine and telbivudine are reimbursed for those with a “low” viral load (<2 million U/L)
  - tenofovir and entecavir are reimbursed for “high” viral load.
- Interferon is paid for those with low viral load and high (>2xnormal) ALT levels.

- To treat;
  - HBV DNA ≥ 10 000 ($10^4$) copies/ml (2.000 IU/ml) and
  - A liver biopsy with HAI≥6 or fibrosis ≥2





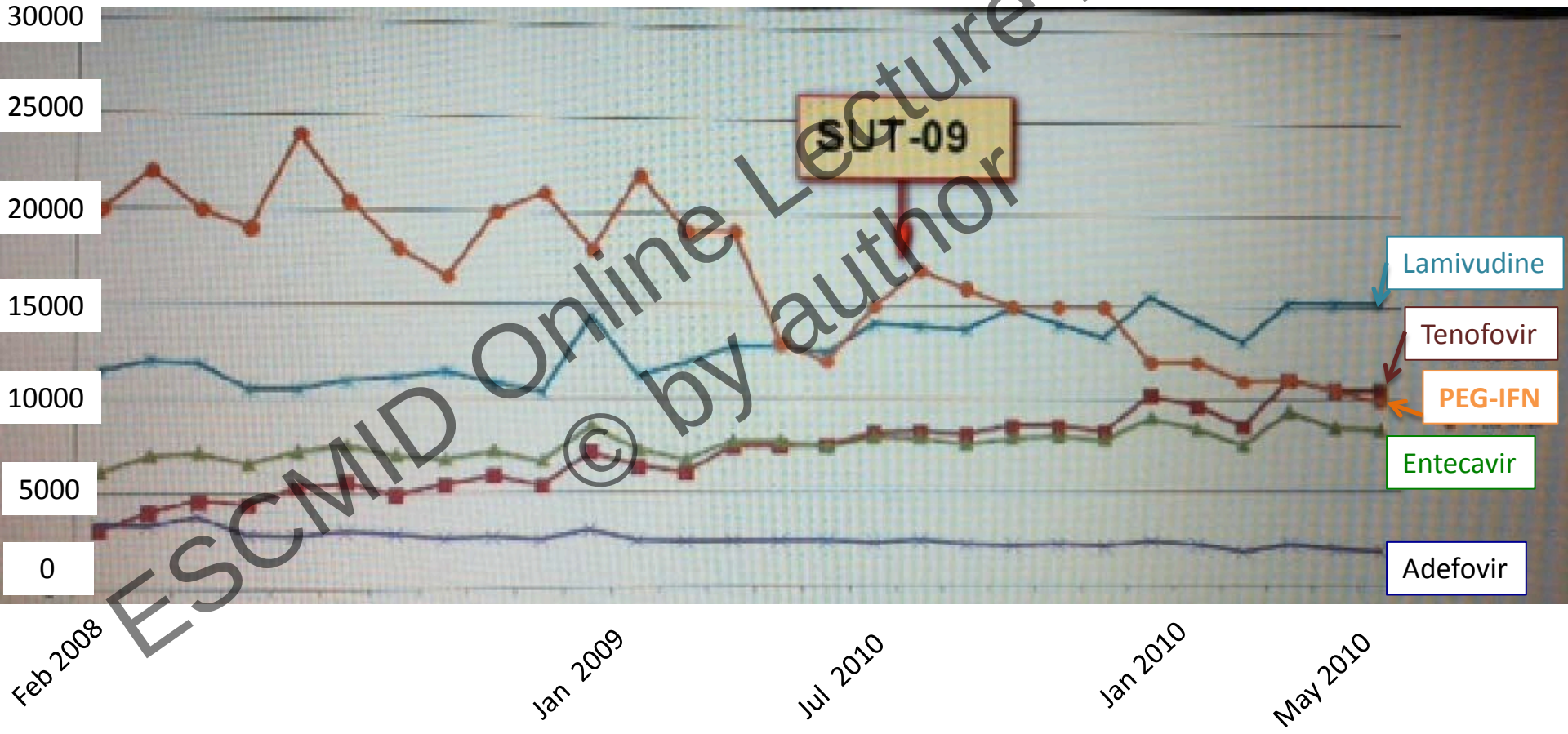
# HBeAg(+)

| | |
|---|---|
| >200 milion U/mL | TDF, ETV |
| 2-200 milion U/mL | IFN*, TDF, ETV |
| <2 milion U/ml | IFN*, LAM, LdT |

* If ALT> 2xULN

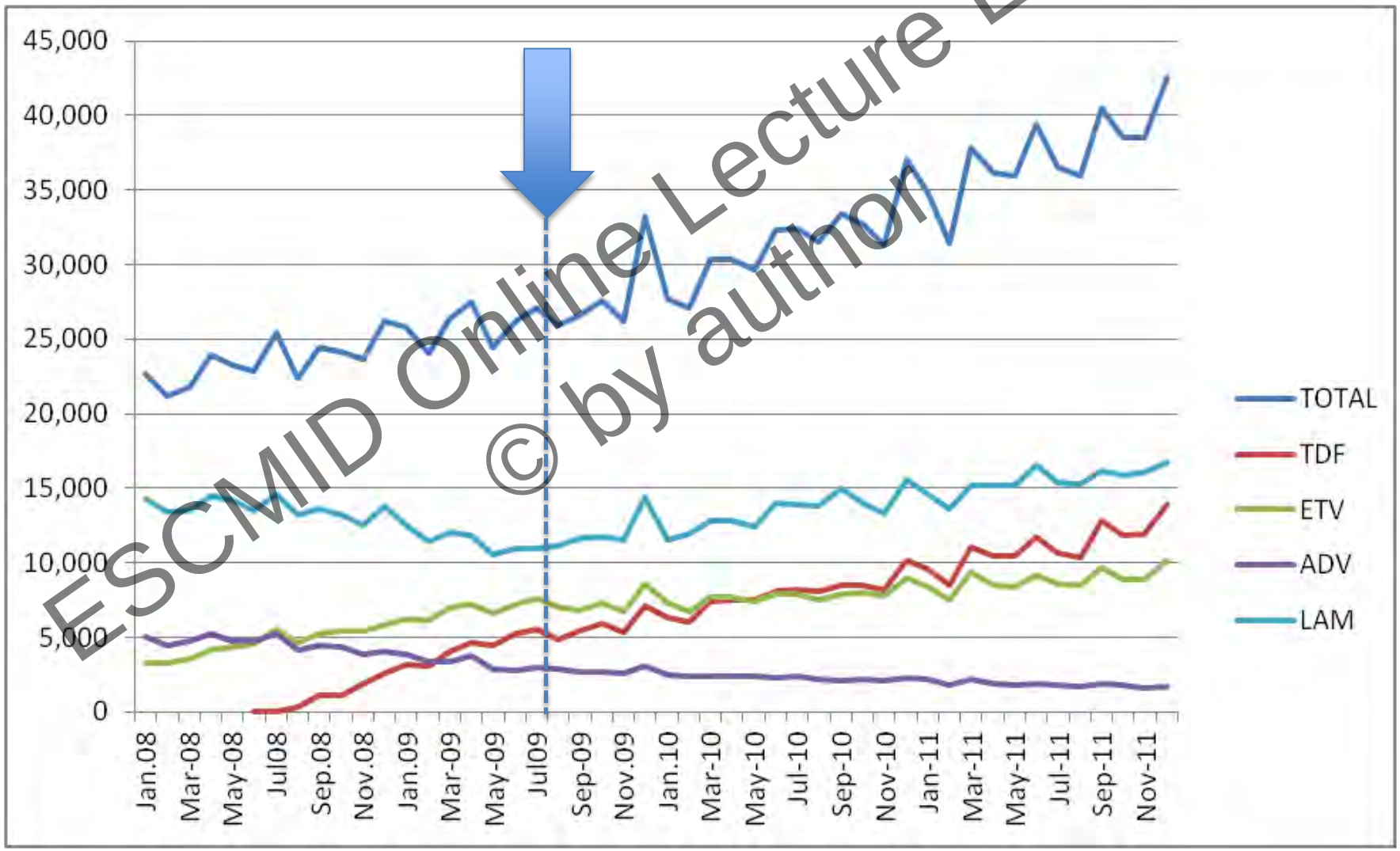
# Duration

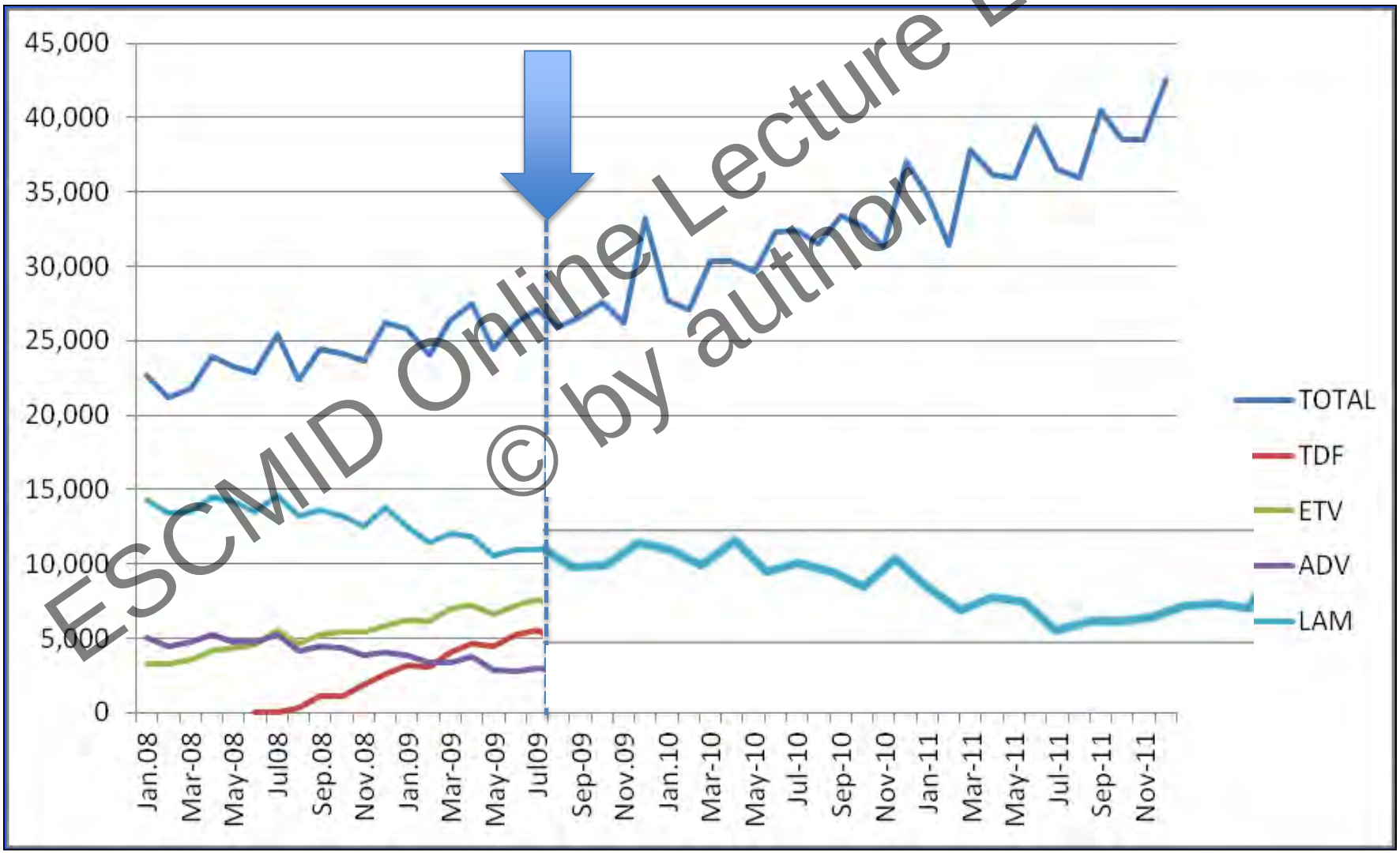
- Interferons: 48 weeks
- Oral antivirals:
  - HBeAg(+): 12 months after e seroconversion
  - HBeAg(-): till HBsAg (-)

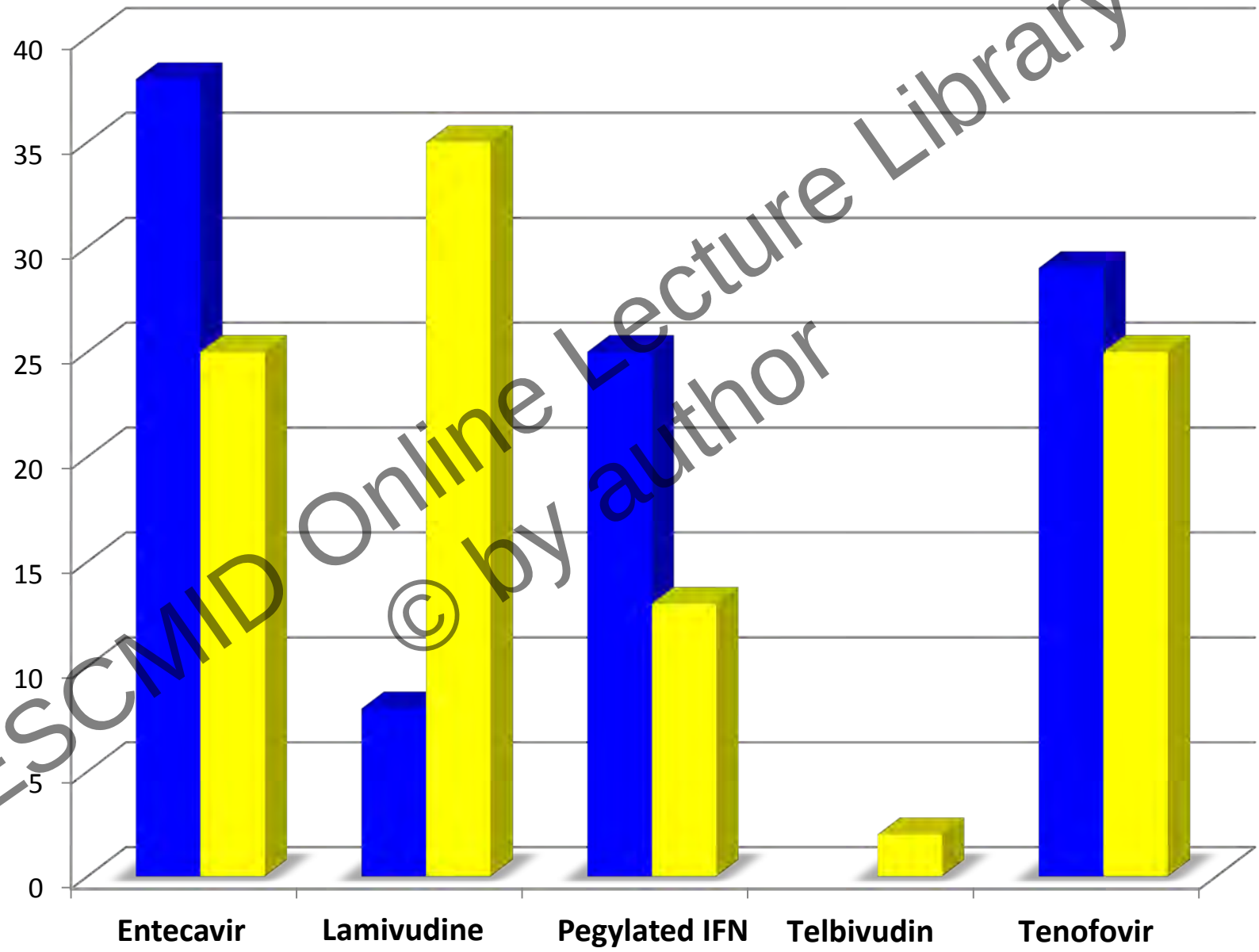





Thanks to Prof Oguz Karabay



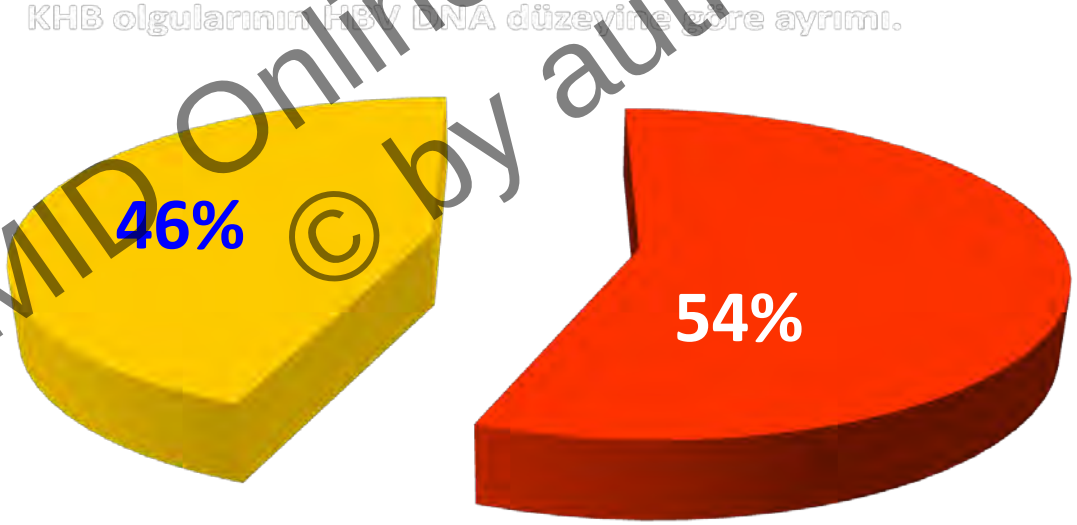







Realist Study Group's Cohort, Turkish Viral Hepatitis Congress, 2012

- Approximately, in half of HBV cases in Istanbul, HBV-DNA <2 000 000 IU/mL
  - 213/466 (46%)




Realist Study Group's Cohort, Turkish Viral Hepatitis Congress, 2012

# In LAM Using Patients;

- Undetectable HBV-DNA at 6$^{th}$ month: 53%



Realist Study Group's Cohort, Turkish Viral Hepatitis Congress, 2012

# Q5

- What happens if a patient has detectable HBV-DNA after 6 months of lamivudine therapy?
  - A. I don’t use lamivudine anymore
  - B. I switch to tenofovir, it is reimbursed
  - C. I recommend to switch to tenofovir, it is not reimbursed/not available
  - D. I add adefovir, tenofovir is not reimbursed/not available

# Cost-Effectiveness

- Lamivudine, if fails (add or) switch to tenofovir
- Start with tenofovir or entecavir

- LAM 40 EUR
- LdT 175 EUR
- TDF 180 EUR
- ETV 240 EUR
- ADV 380 EUR

| Patients 35% HBeAg (+) | 10–year Outcomes | | |
|---|---|---|---|
| 1000 patients | **ETV** | **LAM** | **LAM→LAM+TDF** |
| Compensated Cirrhosis | 54.4 | 198 | 78 |
| Decompensated Cirrhosis | 2.7 | 8.9 | 3.6 |
| HCC | 16.3 | 66 | 23.8 |
| Death | 29 | 107.8 | 44.1 |

Ozdemir O, et al. VHSD 2012, SS-02

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REVIEW ARTICLE

# Treatment of chronic hepatitis B virus infection in resource-constrained settings: expert panel consensus

Steven T. Wiersma[1], Brian McMahon[2], Jean-Michel Pawlotsky[3], Chloe L. Thio[4], Mark Thursz[5], Seng Gee Lim[6], Ponsiano Ocama[7], Gamal Esmat[8], Mendy Maimuna[9], David Bell[10], Marco Vitoria[11], Irina Eramova[12], Daniel Lavanchy[13] and Geoff Dusheiko[14]

# Recommendations-General

- Viral hepatitis (B and C) should be recognized as a major public health threat like HIV, malaria and tuberculosis
- More precise data should be obtained
- Comprehensive HBV programmes should be developed in all countries, especially in areas of high endemicity

# Recommendations

- All blood donors and HIV-positives should be screened by HBsAg
- All HBsAg-positive subjects should be screened for HIV
- All compensated and decompensated cirrhotics should be screened and (if HBsAg positive) should be treated

# Recommendations

- Reliable and sensitive quantitative HBV-DNA assays should be implemented
- Liver biopsy or a non-invasive test may be considered

# Recommendations

- Because HBV-DNA testing and liver biopsy are not widely available in most resource constrained countries;
- Treatment should be largely restricted to
  - Cirrhotic patients (compensated or decompensated)
  - Patients with active disease documented by elevated transaminases.

- Tenofovir or entecavir should be the first-line monotherapy.
- Tenofovir should be available
- Co-infection should be checked at baseline

If testing HBV DNA concentrations are not available:

(a) monitor compliance in all patients,

(b) for treatment with **entecavir**, measure ALT activities every 6 months,

(c) for treatment with **tenofovir**: measure baseline serum creatinine, spot urine protein creatinine ratio if possible and ALT and serum creatinine every 6 months.

# Conclusions

- The management problem of the countries with limited resource can be summarized as
  - **diagnostic** (virology, especially HBV-DNA measurement, liver biopsy)
  - **therapeutic** (unavailability of drugs, high cost of drugs, absence of reimbursement) constrains.
- The absence of screening policy for viral hepatitides (and HIV), and absence of local guidelines for HBV management are the other challenges.

# Conclusions

- Strategies for increasing access to HBV treatment need to be structured
- Patients with cirrhosis (compensated or decompensated) due to HBV infection (if HBsAg is positive practically) should be treated with priority.

# Conclusions

- Quantitative HBV DNA assays and liver biopsy (or alternatively a non-invasive test) should be provided.
- Tenofovir or entecavir should be the first-line monotherapy.
- If these drugs are not available, lamivudine, adefovir or telbivudine can be used by close monitoring and an access to the monitoring of viral resistance should be maintained.