Treatment Algorithm in Chronic Viral hepatitis: An update in 2009

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An algorithm is a step by step list of directions that need to be followed to solve a problem.

The instructions should be simple enough so that each step can be done without thinking about it.

*Wikipedia*
Guidelines for viral hepatitis

• Provide an evidence-based approach to management of patients with chronic viral hepatitis

• Written to assist physicians and other healthcare providers with:
  - Recognition of CVH
  - Diagnosis of CVH
  - Management/treatment of patients with CVH

• International and national guidelines are available
Progress in Chronic Hepatitis C treatment during the last 20 years

Cure of HCV infection?
Registration trials in chronic hepatitis C treatment - The rates of sustained viralogical responses*

- PegIFN 2a + Ribavirin (Fried 2002) - 48 weeks treatment: 81%
- PegIFN 2a + Ribavirin (Hadziyannis 2004) - 24 weeks treatment: 47%
- PegIFN 2b + Ribavirin (Manns 2001) - Total: 81%

* HCV RNA negative and ALT normal at 6 months after the treatment
Anti-HCV +, HCV genotype 1 (4,5,6)
HCV RNA – viral load by quantitative assay

≥F2 fibrosis → Liver biopsy suggested → F0-F1 fibrosis
Consider no treatment

Treat with pegIFN and RBV*

HCV RNA at 12 week

Complete EVR (HCV RNA -) → Continue treatment for Total 48 weeks

Partial EVR (HCV RNA >2log) → Determine HCV RNA at week 24 - qualitative

No EVR (HCV RNA <2log) → Stop treatment

HCV RNA at w48 and w 72 → To establish SVR-follow up

*RBV: 1000mg/d for <75kg, 1200mg/d for >75kg)
EVR: Early viral response
SVR: Sustained viral response

Anti-HCV +, HCV genotype 1 (4,5,6)
HCV RNA – viral load by quantitative assay

No biopsy – Biopsy is optional. Treatment can be initiated if there is no contraindications. …TASL proposal and Turkish Health Authorities (“SUT”) decision…

Treat with pegIFN and RBV*

HCV RNA at 12 week

- Complete EVR (HCV RNA -)
  - Continue treatment for Total 48 weeks
  - HCV RNA at w48 and w 72 To establish SVR-follow up

- Partial EVR (HCV RNA >2log
  - Determine HCV RNA at week 24 - qualitative
  - HCV RNA -
  - HCV RNA +

- No EVR (HCV RNA <2log
  - Stop treatment

TASL modifications 2009…

*RBV: 1000mg/d for <75kg, 1200mg/d for >75kg
EVR: Early viral response
SVR: Sustained viral re
SVR and baseline fibrosis score (n:242)

SVR; F0-1 vs F3-4 (p<0.05).

Cakaloglu et al. 2007
Pretreatment liver biopsy findings (n: 492)

- F4: 6%
- F3: 21%
- F2: 23%
- F1: 37%
- F0: 13%

F0-1 patients 50%

HAI 7.6±3.1 (1-16)

Cakaloglu et al. 2007
Sustained virological response and baseline fibrosis score, N=537

- F0-1, n=178: 76%
- F2, n=173: 68%
- F3, n=106: 42%
- F4, n=80: 41%

Power; Abadir et al AASLD 2005.
Anti-HCV +, HCV genotype 2,3
HCV RNA – viral load by quantitative assay

Liver biopsy optional

Treat with pegIFN and RBV*

Determine HCV RNA at week 24 - qualitative

HCV RNA -

HCV RNA at week 48 to establish SVR-follow up

HCV RNA +

Treatment failed “nonresponder”

*RBV: 800mg/day
EVR: Early viral response
SVR: Sustained viralological response

New Schedule for Rapid Responders
HCV-1 (Low Viral Load)

PEG-IFN α-2b 1.5 μg/kg QW + ribavirin 800-1,400 mg/day

Week 4 - qualitative HCV-RNA

Negative
- Treat for 24 wks
  85-92% SVR

Positive
- Week 12 - quantitative HCV-RNA
  - > 2 log ↓
    - Treat for 48 wks
      85-90% SVR
  - < 2 log ↓
    - Stop
      (or shift to suppressive therapy)

EU approval in 2005
Evolution of CHB guidelines
To provide an evidence-based approach to management of patients with chronic hepatitis B (CHB)…

Do we follow the guidelines?

Percentage of physicians

France
Germany
Italy
Spain
Turkey

5 = Extremely influential
4
3
2
1 = Minimally influential
Goals of therapy

- To improve quality of life and survival by preventing progression to:
  - Cirrhosis
  - Decompensated cirrhosis
  - End-stage liver disease
  - HCC
  - Death

- Goal can be achieved if HBV replication is suppressed in a sustained manner
  - The accompanying reduction in histological activity of CHB lessens the risk of cirrhosis and HCC

- HBV infection cannot be entirely eradicated due to persistence of intrahepatic cccDNA

Indication for treatment

- Based mainly on the combination of 3 criteria:
  - HBV DNA levels
  - Serum ALT levels
  - Histological grade and stage

- Patients should be considered for treatment when:
  - HBV DNA levels >2000 IU/mL (10,000 copies/mL) and/or
  - Serum ALT levels are >1 x ULN, and
  - Liver biopsy shows moderate to severe active necroinflammation and/or fibrosis (e.g. at least grade A2, stage F2 by METAVIR scoring)

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol 50. (2009),
Treatment strategies

- **Finite treatment of with PEG IFN-α or nucleoside analogues (NAs)**
  - Intended to achieve sustained off-treatment virological response
  - Mainly recommended for HBeAg(+) patients with greatest chance of seroconversion
    - High baseline ALT >3 x ULN
    - HBV DNA <10^7 IU/mL and
    - High HAI score in liver biopsy (≥ Metavir A2-Knodell/Ishak 6-7)
  - 48-week course of PEG IFN-α
  - NA therapy is dependent on time to HBe seroconversion

_EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),_
Finite treatment with NAs in HBeAg(+) patients

- Use the most potent agents with the highest genetic barrier to resistance

- NA therapy can be stopped 24 to 48 weeks after HBe seroconversion

- HBsAg should be checked every 6 months following HBe seroconversion
  - HBsAg loss rarely observed in NA-treated patients

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),
Long-term therapy with NAs

- HBV DNA levels should be monitored:
  - At Week 12
  - Then every 12 to 24 weeks

- HBV DNA monitoring is critical to detect treatment failure

- HBV DNA reduction to undetectable levels (<10–15 IU/mL) should ideally be achieved to avoid resistance

- NAs are cleared by the kidneys, and appropriate dosing adjustments are recommended for patients with reduced creatinine clearance
  - Intensive monitoring (monthly in the first 3 months) may be required

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),
## Definition of response

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAs</strong></td>
<td>Primary non-response</td>
<td>Decrease in serum HBV DNA $&lt;1\log_{10}$ IU/mL from baseline at month 3 of therapy</td>
</tr>
<tr>
<td></td>
<td>Virological response</td>
<td>Undetectable HBV DNA* within 48 weeks of therapy</td>
</tr>
<tr>
<td></td>
<td>Partial virological response</td>
<td>Decrease in serum HBV DNA $&gt;1\log_{10}$ IU/mL from baseline, but detectable HBV DNA*. Partial virological response should be assessed at Week 24 or 48</td>
</tr>
<tr>
<td></td>
<td>Virological breakthrough</td>
<td>On-therapy increase in serum HBV DNA of $&gt;1\log_{10}$ IU/mL compared to nadir</td>
</tr>
<tr>
<td><strong>IFN-α</strong></td>
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<td>Decrease in serum HBV DNA to $&lt;1\log_{10}$ IU/mL from baseline at month 3 of therapy</td>
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<td>Virological response</td>
<td>HBV DNA $&lt;2000$ IU/mL at Week 24 of therapy</td>
</tr>
<tr>
<td></td>
<td>Serological response</td>
<td>HBe seroconversion in HBeAg(+) patients</td>
</tr>
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</table>

* by real-time PCR.

_EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),_
### EASL compared to other international guidelines

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<tr>
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<tr>
<td><strong>HBV DNA treatment threshold</strong></td>
<td></td>
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<tr>
<td>- HBeAg(+) (IU/mL)</td>
<td>2,000</td>
<td>20,000</td>
<td>20,000</td>
</tr>
<tr>
<td>- HBeAg(-) (IU/mL)</td>
<td>2,000</td>
<td>2,000–20,000</td>
<td>2,000</td>
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<td><strong>ALT treatment threshold</strong></td>
<td>&gt;ULN for the laboratory</td>
<td>&gt;2 x ULN</td>
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<td><strong>Main factor in decision to treat</strong></td>
<td>HBV DNA, ALT and liver biopsy</td>
<td>ALT</td>
<td>HBV DNA and ALT</td>
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<td><strong>Biopsy</strong></td>
<td>Consider in certain groups</td>
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<tr>
<td><strong>Recommended therapy HBeAg(+) patients</strong></td>
<td>PEG IFN-α or NAs (Entecavir or Tenofovir recommended)</td>
<td><strong>Tenofovir and Entecavir or PEG IFN-α are preferred as initial treatments</strong></td>
<td>Adefovir, Entecavir, Lamivudine, IFN-α or PEG IFN-α preferred (Entecavir or Lamivudine when ALT &gt;5 x ULN)</td>
</tr>
<tr>
<td><strong>Recommended therapy HBeAg(-) patients</strong></td>
<td>As above</td>
<td>As above</td>
<td>As above but Lamivudine not recommended/cautioned due to high resistance rate</td>
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## EASL compared to other international guidelines

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<td>Biopsy evidence needed to treat</td>
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<td><strong>Recommended therapy, HBeAg(+) patients</strong></td>
<td>PEG IFN-α or NAs (Entecavir or Tenofovir recommended)</td>
<td>Tenofovir, Entecavir Lamivudine or PEG IFN-α</td>
<td>Tenofovir and Entecavir superior to ADV and LMV. PEG IFN-α not preferred if age &gt;50 yrs and ALT&lt;2 x ULN, or HBV DNA &gt;2x10⁶ IU/ml</td>
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<tr>
<td><strong>Recommended therapy, HBeAg(-) patients</strong></td>
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**Main factor in decision to treat**

- HBV DNA, ALT and liver biopsy
- HBV DNA, ALT (only in HBeAg(+) patients)
- HBV DNA, ALT and biopsy

**Biopsy evidence needed to treat**

- NAs or Peg-IFN-α
- Peg-IFNs
  - <50 years of age
  - ALT>2xULN
  - HBV DNA <2x10^6 IU/ml

**Recommended therapy, HBeAg(+) patients**

- PEG IFN-α or NAs (Entecavir or Tenofovir recommended)
- Tenofovir, Entecavir
- Lamivudine or PEG IFN-α

**Recommended therapy, HBeAg(-) patients**

- As above
- As above

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**“SUT” modification in 2009**

If HBV DNA <10^7 IU/ml

Lamivudine first line medication

At w24 determine HBV DNA (-) continue with lamivudine

HBV DNA detectable by PCR;
- antiviral response failure
- resistance development

“add on” or switch to Tenofovir DF
“SUT” modification in 2009

If HBV DNA $<10^7$ copy/ml

\[ \text{Lamivudine} \quad \text{first line medication} \]

At w24 determine HBV DNA ( - ) continue with lamivudine

HBV DNA detectable by PCR;
- antiviral response failure
- resistance development

“add on” or switch to Tenofovir DF
Compensated and Decompenated Cirrhosis

**Compensated**
- Detectable HBV DNA
- Treat
  - **Preferred Treatment**
    - Tenofovir DF*
    - Entecavir*
    - De novo Combination therapy may play a role

**Decompensated**
- Detectable HBV DNA
- Treat
- Candidates for Transplant

PegIFN in well-compensated pts

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),
Treatment failure

- **Primary non-response**
  - Check compliance
  - In adefovir-treated patients, switch rapidly to Baraclude or tenofovir
  - In compliant patients, check for resistance and formulate a rescue strategy

- **Partial response**
  - Check compliance
  - In patients treated with lower potency drugs switch to a more potent drug, or add a more potent drug without cross-resistance

- **Virological breakthrough**
  - As early as possible, identify viral load increase and adapt treatment
  - Identify resistance profile and adapt treatment accordingly

*EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),*
Resistance

In case of resistance, initiate appropriate rescue therapy using:

- The most potent antiviral agent with minimal risk of inducing multiple drug-resistant strains

Adding on a drug without cross-resistance is the only efficient strategy

_EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009)_
Cross-resistance data (*in vitro*)

<table>
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<tr>
<th></th>
<th>Lamivudine</th>
<th>Telbivudine</th>
<th>Entecavir</th>
<th>Adefovir</th>
<th>Tenofovir</th>
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<tbody>
<tr>
<td><strong>Wild type</strong></td>
<td>S</td>
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<tr>
<td><strong>M204I</strong></td>
<td>R</td>
<td>R</td>
<td>I</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><strong>L180M+M204V</strong></td>
<td>R</td>
<td>R</td>
<td>I</td>
<td>S</td>
<td>S</td>
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<tr>
<td><strong>A181T/V</strong></td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
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<tr>
<td><strong>N236T</strong></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>I</td>
</tr>
<tr>
<td><strong>L180M+M204V/I ±169T±V173L ± M250V</strong></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><strong>L180M+M204V/I ±T184G±S202I/G</strong></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
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Summary

- The new EASL guidelines provide clinicians with best practice on how to treat patients with CHB
- Treatment initiation should be based on:
  - Patient’s health
  - HBV DNA and ALT levels
  - Assessment of liver damage
- Use a potent agent with a high barrier to resistance
- Tenofovir and Entecavir are recommended as first-line agents
- HBV treatment knowledge has increased significantly in recent years
- New guidelines recognise that many patients are at significant risk of disease progression – so recommendations have evolved
There was an old hepatologist who lived in a shoe
He had so many tests he didn't know what to do
There was e, surface, core and DNA too
But now we have “x”, it's there just for you

Koretz RL. Hepatitis: Facts and Fables. In “Current Hepatology” Volume 10,

Year 2008;
There was an old hepatologist who lived in a shoe
He had so many medications he didn't know what to do
There was IFN, lamivudine, adefovir, pegIFN and entecavir too
But now we have telbivudine and tenofovir, they'r there just for you.