Efficacy & safety of drug treatment of Chronic Hepatitis ‘B’ infection

Prof Brig Gen Md Mokhlesur Rahman
Prof & Head
Dept of Gastroenterology
AFMC & CMH Dhaka
• Australia antigen was discovered by Prof. Blumberg – 1967
• He was awarded nobel prize – 1977
Schematic Representation of HBV

- DNA polymerase
- HBV DNA
- Outer lipid envelope containing HB surface antigen
- Inner protein core (HBcAg)
- HBeAg
- HBsAg
Significance of Markers of HBV

- **HBsAg**  – Infection
- **HBeAg**  – Replication
- **HBV DNA**  – Replication
- **Anti HBs**  – Immunity
- **Anti HBe**  – Seroconversion of HBeAg
- **Anti HBc (IgM)**  – Acute infection/reactivation
- **Anti HBc (IgG)**  – Remote past infection
Prevalence of HBV in Bangladesh

5.5%-7.8%

Khan M et al. J Gastro Hepato 2004;19:S419–S430
HBV infection

- Acute: < 6 months
- Chronic: > 6 months
HBV infection

- Childhood infection - > 95% chronic
- Adult infection - > 95% acute
Pathogenesis

HBV infection is an immune – based disorder
Clinical manifestation

• Acute hepatitis  – Jaundice
• Chronic hepatitis  – Asymptomatic
Chronic Hepatitis B - Consequences

Liver disease progression over time

20–30 years

Normal ▶ Cirrhosis ▶ Cirrhosis ▶ HCC

HBV ▶ ACUTE / CHRONIC HEPATITIS B ▶ CIRRHOSIS ▶ ESLD ▶ HEPATOCELLULAR CARCINOMA

Liver damage = the result of attempts, usually unsuccessful, to clear infected hepatocytes as part of the immunoclearance stage of disease
Replication cycle of Hepatitis 'B'
Stages of hepatitis ‘B’ viral infection

- Stage 1: Immune tolerance stage
- Stage 2: Immune clearance stage
- Stage 3: Inactive carrier stage
- Stage 4: Reactivation stage
Stages of HBV infection

- HBeAg
- Anti-HBe
- HBV-DNA
- ALT

- immune tolerance
- immune clearance
- inactive carrier
- reactivation

Contd..
Stages of chronic hepatitis ‘B'

Immune tolerance:

- HBsAg +ve > 6 months
- HBeAg +ve, Anti HBe -ve
- Serum HBV DNA > 20,000 i.u./ml
- Persistent normal ALT
- Liver biopsy - normal or minor change.
Stages of chronic hepatitis ‘B'

Immune clearance (HBeAg +ve CHB):
- HBsAg +ve > 6 months
- HBeAg +ve, Anti HBe -ve
- Serum HBV DNA > 20,000 i.u./ml
- Persistent or intermittent elevation of ALT
- Liver biopsy - Chronic hepatitis (HAI≥4)
Stages of chronic hepatitis ‘B'

Inactive HBV carrier:

- HBsAg +ve > 6 months
- HBeAg -ve, Anti HBe +ve
- Serum HBV DNA < 2000 i.u./ml
- Persistent normal ALT
- Liver biopsy - Absence of significant hepatitis (HAI < 4)
Stages of chronic hepatitis 'B'

Reactivation (HBeAg -ve CHB):

- HBsAg +ve > 6 months
- HBeAg -ve, Anti HBe +ve
- Serum HBV DNA > 2000 i.u./ml
- Persistent or intermittent elevation of ALT
- Liver biopsy - Chronic hepatitis (HAI ≥ 4)
Risk factors for development of Cirrhosis

- Older age
- Male sex
- High viral load
- HBV genotype C
- Coinfection with HCV, HIV, HDV
- Heavy alcohol consumption
- Aflatoxin
- Smoking
Risk factors for HCC

- Older age
- Male sex
- Family history of HCC
- Cirrhosis of liver
- Core promoter mutation
- Coinfection with HCV, HIV, HDV
- History of reversion from anti-HBe to HBeAg
- Presence of HBeAg & high viral load is an independent risk factor for HCC
• Persistent seropositivity for HBeAg & HBV DNA > 2000 i.u./ml are significant risk factors for Cirrhosis and HCC

- Ileoje UH et al. Gastroenterol 2006;130:678-686
Positivity for HBeAg is Associated with an Increased Risk of HCC – Taiwanese Data
Persistence HBV DNA Associated With Increased Risk of HCC and Cirrhosis

Long-term follow-up of untreated HBsAg positive individuals in Taiwan

**Cumulative Incidence of Cirrhosis at Year 13 Follow-up**

<table>
<thead>
<tr>
<th>Baseline HBV DNA (copies/mL)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 300</td>
<td>4.5</td>
</tr>
<tr>
<td>300-9999</td>
<td>5.9</td>
</tr>
<tr>
<td>10,000-99,999</td>
<td>9.8</td>
</tr>
<tr>
<td>100,000-99,999</td>
<td>23.5</td>
</tr>
<tr>
<td>≥ 1 million</td>
<td>36.2</td>
</tr>
</tbody>
</table>

**Cumulative Incidence of HCC at Year 13 Follow-up**

<table>
<thead>
<tr>
<th>Baseline HBV DNA (copies/mL)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 300</td>
<td>1.3</td>
</tr>
<tr>
<td>300-9999</td>
<td>1.4</td>
</tr>
<tr>
<td>1000-9999</td>
<td>3.6</td>
</tr>
<tr>
<td>10,000-99,999</td>
<td>12.2</td>
</tr>
<tr>
<td>≥ 100,000</td>
<td>14.9</td>
</tr>
</tbody>
</table>

Retrospective study of 309 patients over mean follow-up of 5.7 years

Proportion of patients surviving

Survival Probability (%)

WITH HBsAg seroconversion

WITHOUT HBsAg seroconversion

P<0.001

Treatment of CHB

Ref:
AASLD guideline - 2009
APASL guideline - 2008
EASL guideline - 2008
BGS Guideline - 2011
Goals of HBV therapy

• **Long term goals:**
  – Improve survival
  – Prevention of cirrhosis and HCC
  – Prevention of complication
Goals of HBV therapy

- **Short term goals:**
  - Biochemical: Normalisation of ALT
  - Serological: HBeAg seroconversion
  - Virological: Undetectable serum HBV DNA
  - Histological: Reduction of necro-inflammatory score

**HBsAg seroconversion** – Close to cure
TREATMENT ENDPOINTS IN CHB

- Undetectable Serum HBV DNA
- HBeAg Loss & Seroconversion
- HBsAg Clearance
- cccDNA Clearance
- Normal ALT
- Decreased HAI and Fibrosis Score
TARGETED THERAPY CHRONIC HEPATITIS 'B'
Indications of treatment

HBeAg positive CHB

- ALT > 2 X ULN
- HBV DNA > 20,000 IU/ml
- Active necroinflammation or fibrosis
Indication of treatment

- HBV DNA > 2000 IU/ml in HBeAg –ve
- Compensated cirrhosis with detectable DNA may be considered for treatment even if ALT is normal & DNA is < 2000 IU/ml.
- Treatment should be started as early as possible if there is hepatic decompensation.
Indication of treatment

- Immunotolerant patient < 30 yrs of age with persistently normal ALT & high HBV DNA level without any suspicion of liver disease & without a family history of HCC or cirrhosis do not require immediate liver biopsy or treatment.
- Follow up is mandatory
Definition of response

- **Biochemical response:**
  - Decrease in serum ALT to normal range

- **Virological response:**
  - Decrease in serum HBV DNA to undetectable level by PCR assays within 48 weeks of NUCs therapy.
  - In Interferon therapy virological response is defined as HBV DNA conc < 2000 IU/ml at 24 weeks of therapy.

- **Serological response:**
  - Loss of HBeAg & development of antiHBe
Definition of response

- Primary non-response:
  < 1 log10 IU/ml decrease in HBV DNA from baseline at 12 weeks of therapy
- Partial virological response:
  Decrease in HBV DNA > 1 log10 IU/ml but detectable by RT-PCR assay at 24 weeks of therapy.
- Virological breakthrough:
  Increase in HBV DNA level of > 1 log10 IU/ml compared to nadir DNA level on therapy after achieving virologic response during continued therapy
- Viral rebound: Increase in viral DNA to > 20,000 IU/ml or above pretreatment level after achieving virologic response during continued treatment
- **Histological response:**
  - Decrease in histological activity index by at least 2 points & no worsening of fibrosis score compared to pre-treatment liver biopsy.

- **Complete response:**
  - Biochemical response, virological response & loss of HBsAg
• Virological relapse:
  - Increase in serum HBV DNA of 1 log10 IU/ml after discontinuation of treatment in at least 2 determinations > 4 weeks apart
Resistance

- **Genotypic resistance:**
  - Detection of mutation that confer resistance to NUC

- **Phenotypic resistance:**
  - Mutation detected decreases susceptibility to NUC (increase MIC)
Drugs available for treatment of CHB

• Interferon : Standard, Pegylated
• Nucleotide analogue : Adefovir, Tenofovir
• Nucleoside analogue : Lamivudine, Entecavir, Telbivudine, Emtricitabine
History of antiviral drug development

- Interferon – 1989
- Lamivudine – 1998
- Adefovir – 2002
- Entecavir – 2005
- Pegylated Interferon – 2005
- Telbivudine – 2006
- Tenofovir – 2008
Adult dose of the drugs

- Interferon alfa 2a – 5 MU/d or 10 MU tiw
- Pegylated Interferon alfa 2a – 180 mcg / wk
- Entecavir – 0.5 mg / d
- Tenofovir – 300 mg/d
- Telbivudine – 600 mg/d
- Lamivudine – 100 mg/d
- Adefovir – 10 mg/d
Mechanism of action of Interferon

- Antiviral
- Anti proliferative
- Immunomodulatory
Mechanism of action of Nucleoside/ tide Analogue (NUC)

• Inhibit priming of reverse transcriptase

• Inhibit viral minus strand DNA synthesis (RNA dependent DNA polymerase activity)

• Inhibit viral plus strand DNA synthesis (DNA dependent DNA polymerase activity)
Preferred 1\textsuperscript{st} line drugs

- Pegylated Interferon alfa 2a/2b
- Tenofovir
- Entecavir
Interferon Therapy

- **Advantages**
  - No resistance so far
  - Durable off-treatment response
  - Higher rate of HBsAg clearance
    (11-12% in 4 yrs)
  - Finite duration of course (6-12 months)
Disadvantages:

- High initial cost
- Parenteral administration
- Increased side effects
- Contraindicated in the decompensated disease
- Response varies according to genotype

(genotype A & B > C & D)
Response to Interferon alfa 2a therapy

- 33% HBeAg seroconversion (control – 12%)
- 20-40% response in relapsed cases
- Seroconversion is sustained in 80%-90% cases after 4-8 yrs follow up
- Delayed clearance of HBsAg – 12% - 65% within 5 yrs of HBeAg loss

Peginterferon (alfa 2a/2b)

• Higher seroconversion than standard interferon (33% vs 25%; p > 0.05)
• Higher combination response (HBeAg loss, HBV DNA reduction & normal ALT) 24% VS 12%; P=0.036

Ref: CooksleyWG et al. J Viral Hepatol 2003;10:298-305
Side effects of interferon

- Flu-like symptoms
- Fatigue
- Bone marrow suppression
- Major depression, suicidal tendency
- Hypothyroidism
- Hyperthyroidism
- Mild ALT flare
Nucleoside/Nucleotide Analogue (NUCs)

- Advantages:
  - Oral administration
  - Low initial cost
  - Potent antiviral effect
  - Good tolerance
Nucleoside/Nucleotide Analogue (NUCs)

- Disadvantages:
  - Duration of therapy indefinite - ? life long
  - Resistance rate is high except newer drugs like Entecavir & Tenofovir
  - Relapse rate is high after stopping
  - Lower rate of HBeAg & HBsAg seroconversion
Response to treatment at 1 yr in HBeAg positive patient

<table>
<thead>
<tr>
<th>Drugs</th>
<th>HBeAg seroconversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN</td>
<td>30</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>22</td>
</tr>
<tr>
<td>Adefovir</td>
<td>12</td>
</tr>
<tr>
<td>Entecavir</td>
<td>21</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>23</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>21</td>
</tr>
</tbody>
</table>
Response to treatment at 1 yr in HBeAg positive patient

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Undetectable HBV DNA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN</td>
<td>25</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>39</td>
</tr>
<tr>
<td>Adefovir</td>
<td>21</td>
</tr>
<tr>
<td>Entecavir</td>
<td>67</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>60</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>74</td>
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</table>
Response to treatment at 1 yr in HBeAg positive patient

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Normalisation of ALT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN</td>
<td>39</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>66</td>
</tr>
<tr>
<td>Adefovir</td>
<td>48</td>
</tr>
<tr>
<td>Entecavir</td>
<td>68</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>77</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>69</td>
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</table>
Response to treatment at 1 yr in HBeAg negative patient

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Normalisation of ALT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN</td>
<td>38</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>74</td>
</tr>
<tr>
<td>Adefovir</td>
<td>72</td>
</tr>
<tr>
<td>Entecavir</td>
<td>78</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>74</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>77</td>
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</table>
Response to treatment at 1 yr in HBeAg negative patient

<table>
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<tr>
<th>Drugs</th>
<th>Undetectable HBV DNA (%)</th>
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<tbody>
<tr>
<td>PEG-IFN</td>
<td>63</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>72</td>
</tr>
<tr>
<td>Adefovir</td>
<td>51</td>
</tr>
<tr>
<td>Entecavir</td>
<td>90</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>88</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>91</td>
</tr>
</tbody>
</table>
Lamivudine

- L-Nucleoside analogue
- Potent inhibitor of reverse transcriptase
- HBeAg seroconversion:
  - 1 year - 18%
  - 2 year - 26%
  - 3 year - 40%
  - 5 year - 35%-65%

Leung N. Hepatol Int 2008
Lamivudine (contd..)

• Combination therapy using lamivudine with adefovir, telbivudine and IFN has no significant efficacy advantage

Leung N. Hepatol Int 2008
Lamivudine (contd..)

- **Undetectable HBV DNA:**

<table>
<thead>
<tr>
<th>Years</th>
<th>HBeAg +ve</th>
<th>HBeAg -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36%</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td>39%</td>
<td>57%</td>
</tr>
<tr>
<td>3</td>
<td>20%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Leung N. Hepatol Int 2008
## Lamivudine Resistance

<table>
<thead>
<tr>
<th>Year</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
</tr>
</tbody>
</table>

Leung N. Hepatol Int 2008
Side effects of Lamivudine

• Very safe & well tolerated
• Mild rise of ALT may occur
Adefovir Dipivoxil

- Acyclic adenine nucleotide analogue
- Potent inhibitor of HBV reverse transcriptase
Adefovir Dipivoxil

- **HBeAg Seroconversion**: 

<table>
<thead>
<tr>
<th>Years</th>
<th>HBeAg +ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12%</td>
</tr>
<tr>
<td>2</td>
<td>29%</td>
</tr>
<tr>
<td>3</td>
<td>40%</td>
</tr>
</tbody>
</table>

Leung N. Hepatol Int 2008
Adefovir Dipivoxil (HBeAg -ve CHB)

- ALT Normalisation - 69%
- Undetectable HBV DNA (<200 IU/ml) - 67%
- Improvement in necroinflammation - 83%
- Regression of Fibrosis - 73%

Hadziyannis SJ et al. Gastroenterology 2006
Adefovir Dipivoxil

- There was reversible increase in serum creatinine of > 0.5 mg/dl (Maximum 1.5 mg/dl) reported in 3% of patients when therapy was extended to 5 years.

Hadziyannis SJ et al. Gastroenterology 2006
Adefovir Dipivoxil

- **Adefovir resistance:**

<table>
<thead>
<tr>
<th>Year</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
</tr>
</tbody>
</table>

Lampertico P et al. Gastroenterology 2006
Side effects of Adefovir

- Nephrotoxicity – 3% after 4 - 5 yrs

Serum creatinine should be tested every 3 months
Entecavir

- Cyclopentyl guanosine analogue
- Potent selective inhibition of priming, DNA dependent DNA synthesis and RNA dependent DNA synthesis (reverse transcription) function of the HBV polymerase
- It is superior to Lamivudine in reducing in HBV DNA & lack of resistance
Entecavir

• HBeAg seroconversion

<table>
<thead>
<tr>
<th>Year</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
</tr>
</tbody>
</table>

Chang TT et al. NEJM 2006
Entecavir

- **Undetectable DNA:**

<table>
<thead>
<tr>
<th>Year</th>
<th>HBeAg +ve</th>
<th>HBeAg -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67%</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>80%</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>89%</td>
<td>NA</td>
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</table>

Chang TT et al. NEJM 2006
# Entecavir Resistance

<table>
<thead>
<tr>
<th>Year</th>
<th>Resistance (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Side effects of Entecavir

• Safety profile is similar to Lamivudine
Telbivudine

- L-nucleoside analogue
- Potent & specific anti HBV activity
- It is more potent than Lamivudine & Adefovir
Telbivudine

**HBeAg Seroconversion:**

<table>
<thead>
<tr>
<th>Year</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
</tr>
</tbody>
</table>

# Telbivudine

## Undetectable DNA:

<table>
<thead>
<tr>
<th>Year</th>
<th>HBeAg +ve</th>
<th>HBeAg -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60%</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>56%</td>
<td>82%</td>
</tr>
</tbody>
</table>

# Telbivudine Resistance

<table>
<thead>
<tr>
<th>Year</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
</tr>
</tbody>
</table>
Side effects of Telbuvudine

- Myopathy
- Peripheral neuropathy

Peripheral neuropathy is more common when combined with pegIFN
Tenofovir

- Acyclic adenine nucleotide analogue
- It has strong and early suppression of HBV including Lamivudine resistant mutants
- It is more potent than Adefovir
## Response to Tenofovir at 1 yr (%)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tenofovir</th>
<th>Adefovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA loss</td>
<td>76</td>
<td>13</td>
</tr>
<tr>
<td>ALT normalisation</td>
<td>68</td>
<td>54</td>
</tr>
<tr>
<td>HBe seroconversion</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>HBsAg</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
Tenofovir Resistance

- No resistance detected so far in 5 yrs
Side effects of Tenofovir

- Renal impairment
- Osteomalacia
- Deceased bone density
- Fanconi syndrome
Treatment of Chronic Hepatitis B in special groups

Pregnancy:

- Telbivudine & Tenofovir are category B drugs
- Lamivudine, Adefovir & Entecavir are category C drugs
- IFN based therapy is contraindicated
- Who are already on therapy can continue treatment with cat B drugs
- Cat B – no risk in animal studies but unknown in human
- Cat C – Teratogenic in animal but unknown in human
- No firm recommendation can be made on the use of nucleoside (tide) analogue in prevention of transmission from viraemic mother
Pediatric Patient

- IFN – 6 MU/m² thrice weekly
- Lamivudine – 3 mg/kg/d
- Adefovir – 0.3 mg/kg/d in age 2 – 10 yrs.
  - 10 mg/d in age >11 yrs.
- PegiIFN and newer Nucleoside /tide analogue are not recommended till now.
- Long term safety and drug resistance are more important.
Patients with Renal failure

- All antivirals can be used with dose modification
- All NUCs can be used with in renal transplant cases
- Entecavir is preferred
Co-infection with HCV

- Higher incidence of cirrhosis, HCC and mortality in co-infection with HCV, HDV & HIV virus.
- Dominant virus should be identified and treated.
- If HBV dominant, treatment of HBV should be aimed.
- If HCV is dominant, IFN + Ribavirin can achieve SVR similar to monoinfection with HCV.
Co-infection with HDV

- Inj. IFN 9 MU TIW for 12 months
- PegIFN 180 microgram/ wk for 12 months
- Lamivudine is ineffective
Co-infection with HIV

- If CD4 count > 500 cells/µl & HIV infection does not require treatment, IFN, Adefovir, Telbivudine monotherapy is the treatment of choice.
- If HIV infection requires treatment, Tenofovir or Lamivudine/ Tenofovir combination should be included in HAART.
- IFN is preferred because of absence of resistance.
- Both Lamivudine and Tenofovir are active against HBV & HIV.
- If CD4 count is < 500 cells/cmm and liver disease is active, HBV should be treated first.
Decompensated Liver Disease

- IFN – contraindicated
- Treatment should be started as early as possible
- Lamivudine, Entecavir, Telbivudine and Tenofovir are effective.
Patient on immunosuppressive drugs or chemotherapy

- Reactivation and / decompensation occur in 20 – 50% cases.
- Lamivudine & Entecavir are effective.
- Prophylactic use of lamivudine should be started 1 wk before start of chemotherapy and continued at least 12 wks after the end of chemotherapy.
Patient With Acute Severe Hepatitis

• > 95-99% of adult with severe HBV infection will recover spontaneously
• Lamivudine, Entecavir or Tenofovir may be used
• Duration - at least 3 months after seroconversion to anti HBS or 6 months after HBe seroconversion without HBsAg loss
Liver Transplantation

• Liver transplantation has become a cost – effective treatment of liver failure and HCC with excellent 5 – yr survival.
• Lamivudine, entacavir and adefovir can be used before transplantation.
• Combination of lamivudine + low dose I.M. HB1g prophylaxis (400-800 U daily for 1 wk, then monthly reduces recurrence rate of HBV to < 5%.
• 5-yr patient survival - 85%
• 5-yr graft survival – 80%.
Treatment of resistant HBV

• Patients failed to respond to IFN alfa may be treated with NUCs
• In case of primary nonresponse therapy should be changed to more potent antiviral like Entecavir or Tenofovir at wk 12
• In partial virological response at wk 24, change to a more potent drug or add nucleoside analogue to nucleotide analogue & vice versa
In patients receiving Entecavir or Tenofovir with a partial virological response at wk 48 may be added the other drug but long term safety of combination of Entecavir & Tenofovir in unknow
• In case of viral breakthrough rescue therapy by adding- on a second drug without having coss-resistance
## Treatment options after NA failure

<table>
<thead>
<tr>
<th>Resistance to</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entecavir</td>
<td>Add adefovir</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>Add tenfovir</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Add adefovir</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>Add tenfovir</td>
</tr>
</tbody>
</table>

Rapti I et al Hepatology 2007
Lampertico P et al Hepatology 2006
## Treatment options after NA failure

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<td>or</td>
</tr>
<tr>
<td></td>
<td>Add tenofovir</td>
</tr>
<tr>
<td></td>
<td>Or</td>
</tr>
<tr>
<td></td>
<td>Switch to entecavir 1 mg/d</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Add Lamivudine</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>Add Entecavir</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
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<td>Switch to entecavir</td>
</tr>
<tr>
<td></td>
<td>or</td>
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<tr>
<td></td>
<td>Switch to tenofovir + emtricitabine</td>
</tr>
</tbody>
</table>

Switching to IFN based therapy is an option
Duration of Treatment

For Interferon
- 6 months for HBeAg positive patients
- 12 months for HBeAg negative patients
Duration of Treatment

For NUCs:

- In HBeAg positive patients:
  - Treatment can be stopped when HBeAg Seroconversion with undetectable HBV-DNA has been documented on two separate occasions at least 6 months apart
Duration of Treatment

In HBeAg negative patient:
- It is not clear how long treatment should be continued but treatment discontinuation can be considered if undetectable HBV DNA has been documented on three separate occasions 6 months apart
Patient monitoring & follow-up

- Every 3-6 monthly
- ALT, PT, HBeAg, Anti HBe, HBV DNA, USG to be done at each visit
Who should be treated with what?

Direct antivirals
- Immunocompetent
- Younger patients
- NA-failures/resistant
- High ALT
- Low HBV DNA
- Active liver lesions
- Compensated liver disease
- IFN/PEG-IFN non-responders

Interferon-based
- Immunocompetent
- Younger patients
- NA-failures/resistant
- High ALT
- Low HBV DNA
- Active liver lesions
- Compensated liver disease
- IFN/PEG-IFN non-responders

NA treatment should not be prescribed until the PATIENT understands that they CANNOT be stopped abruptly for any reason.
Conclusions

• IFN, Entecavir & Tenofovir are 1\textsuperscript{st} line drugs
• NUCs have good antiviral effect but cannot eliminate HBsAg & cccDNA
• NUCs have high resistance rate except Entecavir & Tenofovir
• IFN – based treatment has no resistance & higher HBsAg clearance rate but costly
Conclusions

• All drugs are safe & effective & can reduce the progression of disease and even prevent or delay cirrhosis & HCC
• But none are suitable to eradicate the disease
• We are looking for new drugs