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Presents

Hepatitis B Virus Infection: Clinical Practice Guidlines

Clinical Practice Guidelines

- Who to treat?
- What treatment?
- When to stop treatment?

HBV genotypes (8)

Genotype	Region	Comments
A	Northern America	More sensitive to IFN
	Northern Europe	↑ALT more frequently
	India, Africa	More rapid 3TC resistance
B	Asia	More benign
		More sensitive to IFN
C	Asia	More HCC
D	**Southern Europe**	**Less response to IFN**
	Middle East, India	
E	West & South Africa	
F	Central & South America	
G	USA and Europe	
H	Central America, California	

Kramvis et al. J Viral Hepat 2005; 12: 456-64.
Schaefer et al. Hepatol Res 2007; 37 (suppl): 20-6.

Transmission of HBV

Perinatal transmission

Perinatal

- 90% of infected infants become chronically infected

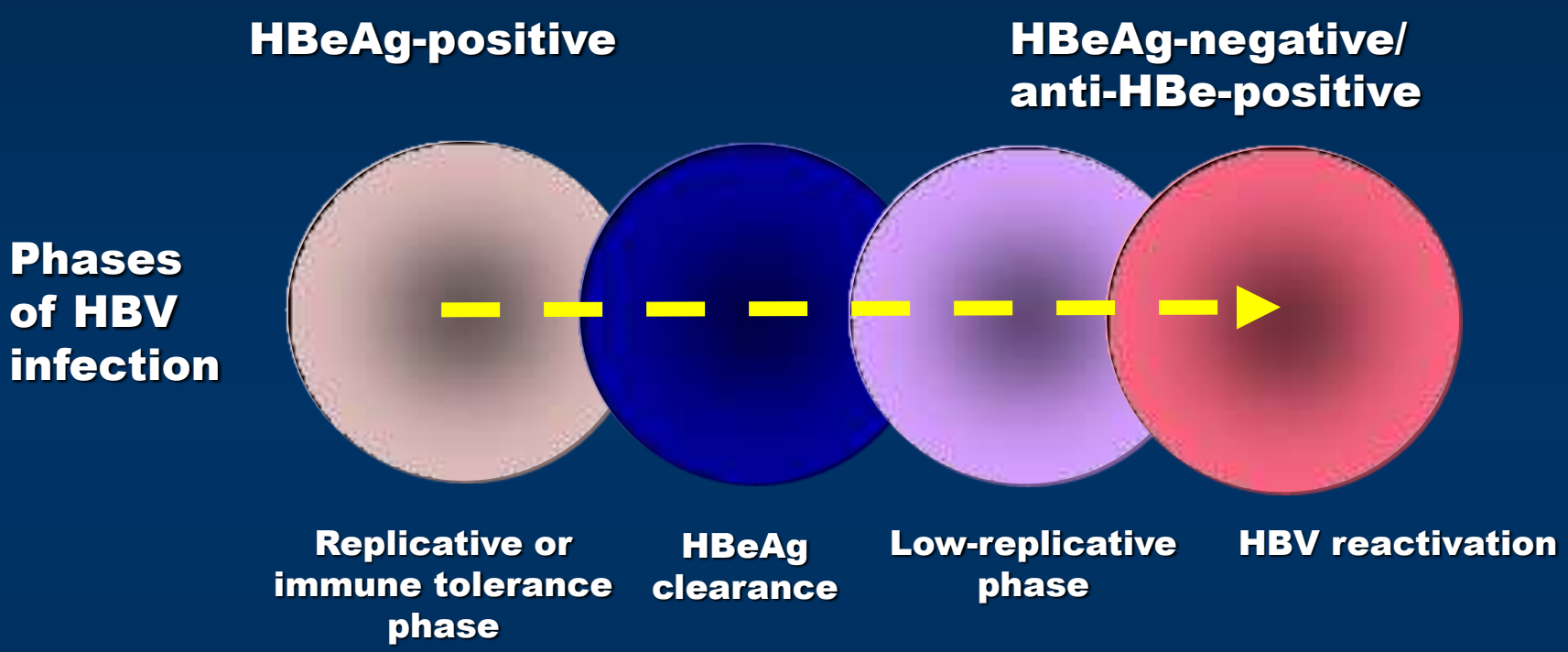
Horizontal transmission

- 6% of people infected over the age of 5 become chronically infected

Recipient

Child-to-child
Contaminated needles
Sexual contacts
Healthcare worker
Blood transfusion

Natural History of HBV: Development of HBeAg-negative CHB



Brunetto. *J Hepatol* 1991

HBeAg-Negative CHB Characteristics

- Growing prevalence
- Liver disease typically advanced
- Male
- Age range 36-45 years
- Sustained spontaneous remission is rare
- Persistent or intermittent HBV replication
- Fluctuations in ALT and viremia levels
- Severe liver necroinflammation
- Progressive fibrosis
  - ~40% of patients in some studies have cirrhosis

1. Hadziyannis et al. *N Engl J Med*. 2003;348:800-807.
2. Fattovich. *Sem Liver Dis*. 2003;23:47-58.

HBV: Factors Associated With Increased Risks of Progression to Cirrhosis

Host Factors	Virus Factors	Environmental Factors
Older age* (longer duration)	High levels of HBV replication*	Concurrent infection (HCV*, HDV, HIV)
Male*	Genotype (C > B)*	Alcohol consumption*
Immune status	HBV variant (core promoter)	Diabetes mellitus†
		Obesity†

*Supported by strong evidence.
†Further studies needed.
Yim JY, Lok AS-F. *Hepatology*. 2006;43:S173-S181.

Who to treat?

Hepatitis B Virus infection: Who to treat?

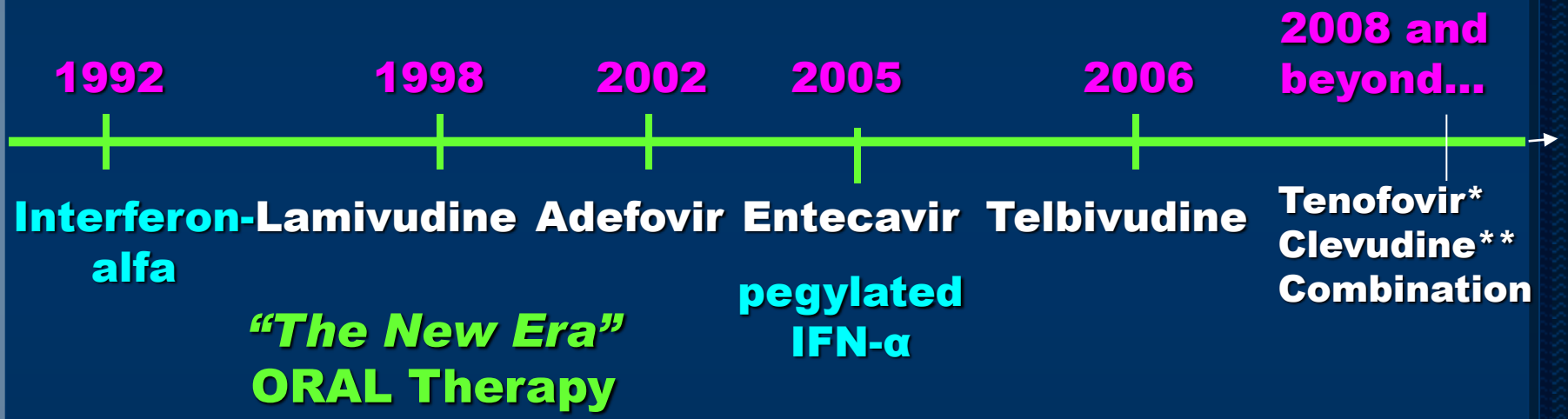
- Those with elevated HBV DNA [>20,000 IU/mL for HBeAg(+) and 2,000 IU/mL for HBeAg(-)], plus
- Elevated ALT, and/or significant disease on liver biopsy.

Goals of Antiviral Treatment of Chronic Hepatitis B

- **Sustained suppression of HBV replication:**
  - ↓ serum HBV DNA to $<10^5$ copies/ml.
  - HBeAg to anti-HBe seroconversion.
  - HBsAg to anti-HBs seroconversion.
- **Remission of liver disease:**
  - Normalization of serum ALT levels.
  - ↓ necroinflammation in liver.
- **Improvement in clinical outcome:**
  - ↓ risks of developing cirrhosis, liver failure and HCC.
  - ↑ survival.

What treatment?

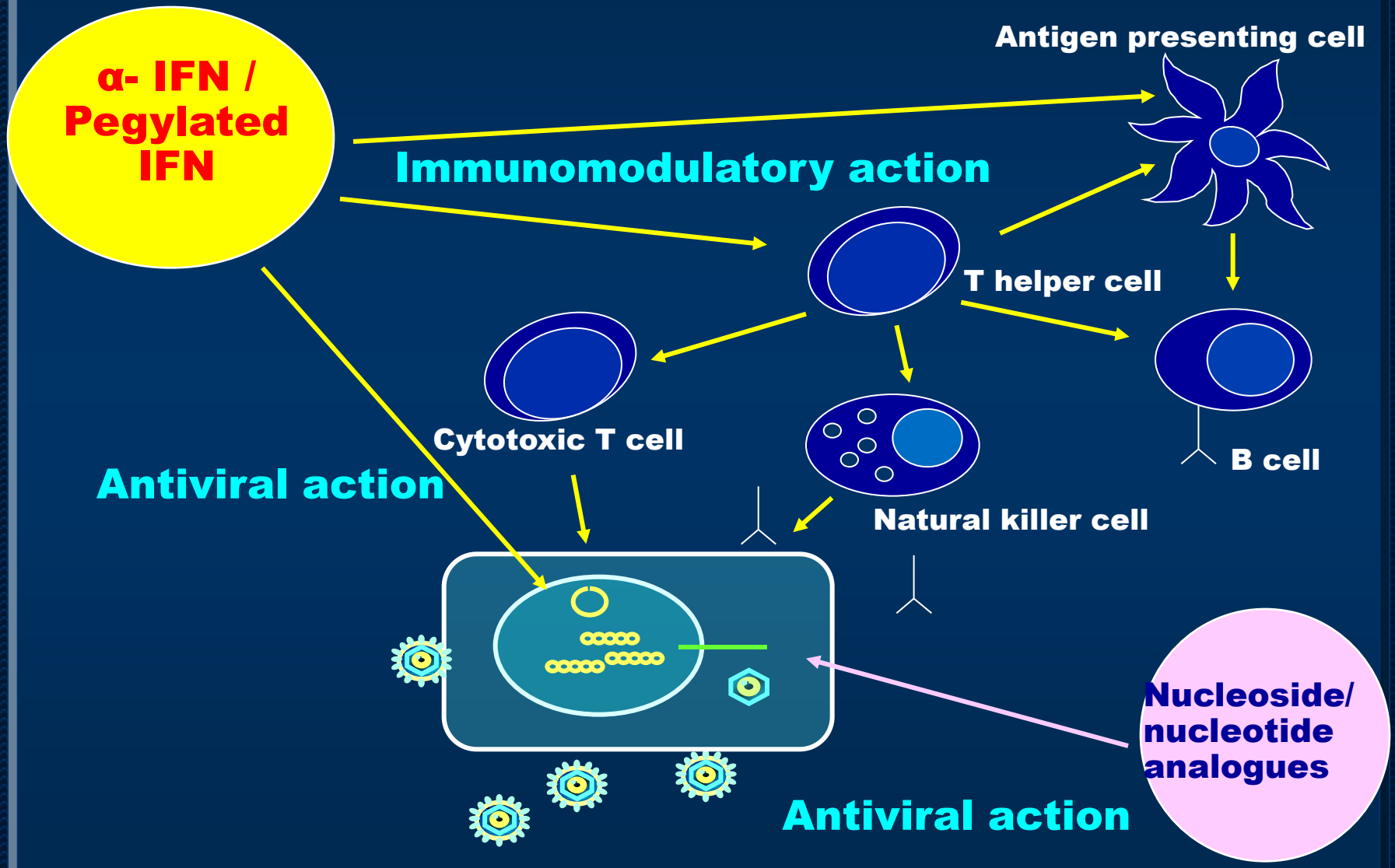
Therapy for Chronic Hepatitis B



Nucleos(t)ide Analogues

- **First-line oral antiviral agents:**
  - Adefovir (Hepsera®) 10 mg daily.
  - Entecavir (Baraclude®) 0.5 -1 mg daily.
  - Tenofovir 300mg daily.
- **Second-line oral antiviral agents:**
  - Lamivudine (Epivir-HBV®) 100 mg daily.
  - Telbivudine (Tyzeka™) 600 mg daily.

Treatment Options for CHB



Antiviral Therapy: A Matter of Choice
Case Features Should Determine Approach

IFN/Peg-IFN	Nucleos(t)ide Analoges
-Poor tolerability in elderly & those with comorbid illness.	-Any age, minimal adverse events.
-Less effective for high level Viremia.	-Baseline viremia generally not an issue.
-Chance for SVR determined by baseline ALT.	-ALT elevation not required for viral suppression.
-Response genotype dependent.	-Viral suppression independent of genotype.
-Contraindicated with decompensated disease.	-Can be used safely in decom-pensated disease.
-Limited usefulness in special populations.	-Appropriate in certain settings.

Antiviral Therapy: A Matter of Choice
Case Features Should Determine Approach

IFN/Peg-IFN	Nucleos(t)ide Analoges
-Short-term, finite duration (48 wks).	-Long-term maintenance (years).
-Long-term benefit in ~1/3 pts.	- Benefit is more with maintenance.
-HBsAg seroconversion achievable.	-Monitored closely.
-No resistance.	-Risk of resistance, and cross-resistance.
-Prior exposure to NAs not a barrier to tx.	-Use in combination.

Treatment Algorithm

Treatment Algorithm
Patients with Compensated Disease

HBeAg Positive

HBV DNA <20,000 IU/mL

- No treatment
- Monitor every 6–12 months

HBV DNA ≥20,000 IU/mL

ALT Normal

- Monitor ALT every 3-12 months (immune tolerant)
- Consider biopsy, if age >35–40, and treat if significant disease

ALT Elevated

- Treat to HBeAg SC
- Entecavir, tenofovir, and peginterferon are first-line options

*1 IU = 5.6 copies; #Normal ALT for men = 30 U/ml and for women = 19 U/ml.

Keeffe EB, et al. *Clin Gastroenterol Hepatol.* 2008.

Treatment Algorithm
Patients with Compensated Disease

HBeAg Negative

HBV DNA <2,000 IU/mL

- No treatment
- Monitor every 6–12 months

HBV DNA ≥2,000 IU/mL

ALT Normal

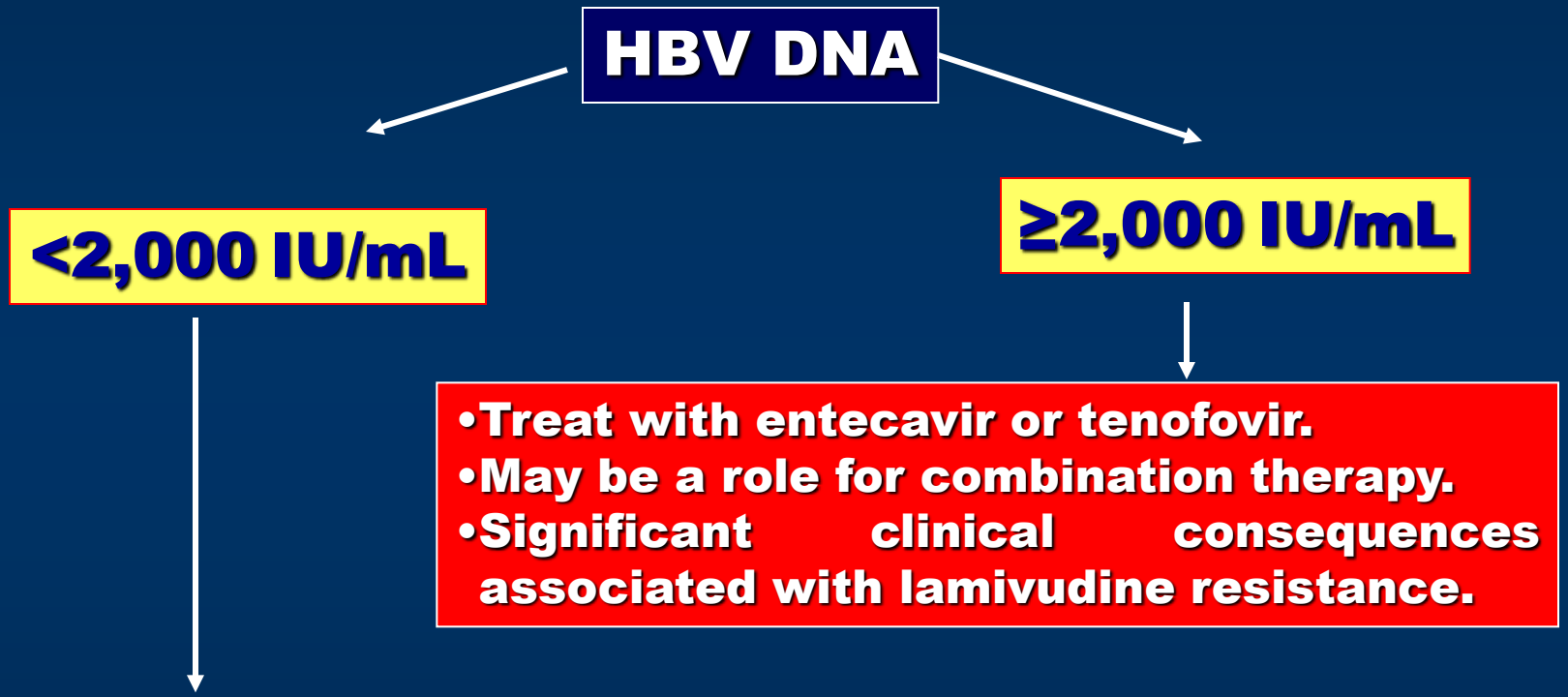
- Monitor ALT and HBV DNA, or
- Consider biopsy, since ALT often fluctuates, and treat if significant disease

ALT Elevated

- Treat long-term
- Entecavir, tenofovir, and peginterferon are first-line options

Keeffe EB, et al. *Clin Gastroenterol Hepatol.* 2008.

Treatment Algorithm
Patients with Compensated Cirrhosis



Keeffe EB, et al. *Clin Gastroenterol Hepatol.* 2008.

Decompensated Cirrhosis (HBeAg+ or HBeAg-)

Treatment

HBV DNA <2.000 IU/ml (10^4 cop/ml) or ≥ 2.000 IU/ml (≥10^4cop/ml)

Adefovir
Lamivudine
Adefovir + Lamivudine or possibly entacavir

Liver transplantation

Keeffe et al., Cl Gast. and Hep., 2006; 4: 936-962.

Treatment of Decompensated Cirrhosis

- **Measurements of Response:**
  - Viral suppression ✓
  - Biochemical improvement ✓
  - Decrease in CTP score ✓

    (Alb, bil, PT, ascites, encephalopathy)
  - Decrease clinical complications ±
  - Decrease need for transplant ±
  - Decrease HCC ?
  - Improve survival ±

Treatment of HBV: Special Cases

- **Chemotherapy:** Prophylactic treatment to prevent HBV reactivation (Rx from 1 wk before to 6-12 mo after).[1]
  - % with hepatitis: 53% untreated vs. 14% lamivudine-treated.
- **Third trimester of pregnancy:** Treatment to reduce rate of vertical transmission.[2] Use in women with HBV DNA >10^8 c/mL.

[1]Kohrt H, et al. *Aliment Pharmacol Ther.* 2006;24:1003-1016.
[2]Xu WM, et al. *Hepatology*. 2004;40:272A-273A.

HBV/HCV Co-infection:

- In HCV dominant disease, interferon (IFN) plus ribavirin treatment has been well studied and has proven efficacy. In HBV dominant disease, IFN with or without lamivudine is reasonable.
- Other HBV treatment agents such as adefovir and entecavir can be used on a case-by-case basis.

When to Stop Treatment?
Traditional Endpoints

Therapeutic Endpoints

- HBeAg seroconversion is KEY in wild type.
- Sustained suppression of HBV DNA to low or undetectable levels.
- ALT normalization.
- Reduced necroinflammation on biopsy.

When to Alter Treatment?

1)-Inadequate Response

2)-Development of Resistance

Responses to Anti-HBV Therapy

- **Virologic response:**
  - Decrease in serum HBV DNA to undetectable level, and loss of HBeAg in HBeAg+ patients.
- **Primary non response:**
  - Decrease in serum HBV DNA by <2 log IU/mL after at least 24 weeks of therapy.
- **Virologic relapse:**
  - Increase in serum HBV DNA by 1 log IU/mL after discontinuation of treatment in at least 2 determinations > 4 weeks apart.

Lok *et al Hepatology*. 2007; 45:507-539

Chronic Hepatitis B:
Rates of Antiviral Drug Resistance

Drug	Resistance, %
Interferon	• None
Lamivudine	◆23 at Yr 1 ◆~70 at Yr 5
Adefovir	◆0 at Yr 1 ◆30 at Yr 5
Entecavir	◆1.2 in naive at Yr 5 ◆46 in LAM-r at Yr 5
Peginterferon α-2a	• None
Telbivudine	◆25 in HBeAg+ at Yr 2 ◆11 in HBeAg- at Yr 2
Tenofovir	◆0 at Yr 2

Management Roadmap According to 24 Week Virologic Response

Week 24: Early predictors of efficacy

Complete response
<60 IU/mL
(<300 copies/mL)

→ **Continue**
Monitor every 6 months

Partial response
60-2,000 IU/mL

→ **Add*** ***another drug*** or
Continue***
Monitor every 3 months

Inadequate response
>2,000 IU/mL
(>10,000 copies/mL)

→ **Add**
another drug *without cross resistance*
Monitor every 3 months

***Depends on
- Genetic barrier to resistance of drug used
- Level of residual viremia
- Degree of viral load reduction

Keeffe et al. Clin Gastroenterol Hepatol 2007;5:890-97

Egyptian Guidelines for Management of Hepatitis B

Advisory Board

- Gamal Esmat
- Imam Waked
- Gamal Shiha
- Taher El-Zanaty
- Amr Fateen
- Yosery Taher
- Ayman Yosery
- Sameh Labib

A) For patients who have HBeAg (– ve)

1) ALT ≥ 2 ULN) and DNA > 10,000 copies/ml (2000 IU/ml)

No need for liver biopsy

Treatment

2) ALT is 1-2 ULN **OR** HBV/ DNA < 10,000 copies/ml (2000 IU/ml)

Liver biopsy is recommended

Treatment if ≥A2 or ≥ F2 (Metavir)

3) If ALT is normal and PCR > 100,000 copies/ml (20.000IU/ml)

Liver biopsy is recommended if age≥40 yrs

Treatment if ≥A2 or ≥ F2

B) For patients who have HBeAg (+ ve):

- The same but the cut off value for HBV DNA is 100,000 copies/ml (20,000 IU/ml), instead of 10,000 copies/ml (2000 IU/ml) in case of HBeAg -ve patients.

Medications

A-Patients who have HBeAg +ve or patients who have Delta virus infection will be treated by:

Peg IFN
for 6 months

HBeAg Seroconversion

Stop therapy

If no HBeAg Seroconversion

Treatment can then be switched to antiviral till seroconversion. Then for 6-12 months after HBeAg serconversion

B) Naive patients who have HBeAg – ve:

- 1-Viral load > 100,000 copies/ml treated with:

Entecavir (Baraclude: 0.5 mg O.D)

- 2-Viral load < 100,000 copies/ml treated with:

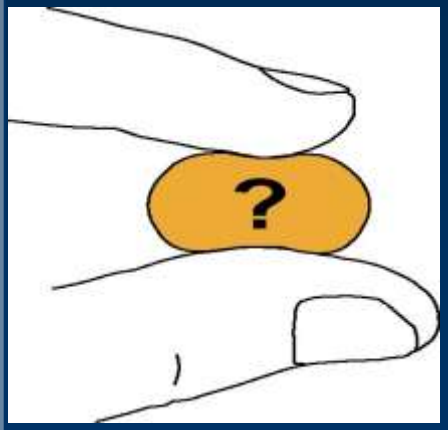
Lamivudine (zeffix 100 mg O.D.) for 6 months

- Then recheck for HBV DNA by PCR at 24 weeks (6months):
- If < 1000 copies/ml → continue on

lamivudine

- But if after 6 months PCR > 1000 copies /ml add → ***Adefovir (hepsera: 10 mg O.D.)***

C) Special groups:



Cirrhotic patients

Pregnant women

Co-infected patients with HCV

Cirrhotic patients:

- Cirrhotic patients with detectable viremia will receive combined therapy from the start *(Lamivudine & Adefovir).*

Pregnant women:

Lamivudine **is the only drug which could be used in pregnant women and should be used during the last trimester in HBV-DNA positive ladies even if they do not have liver disease to decrease chance of new-born infection. After labour, re-evaluate the condition and consider treatment according to the previous guidelines.**

Co-infected patients with HCV:

Patients fulfilling the inclusion criteria for HBV treatment and have co-infection with HCV (HCV RNA positive by PCR) are recommended to use:

(*Peg IFN+ribavirin+antiviral* therapy according to the previous criteria).

D) Follow up:

- I) **Monthly** visits for receiving medications & follow up for side effects and relapsing symptoms.
- II) Checking liver enzymes every **3 months.**
- III) Serum creatinine is done every **3 months** in those receiving *Adefovir*.
- IV) Liver function tests, CBC, AFP, Abdominal U/S and HBV/DNA by quantitative PCR every **6 months.**
- Patients with positive viremia after **one year** of therapy are considered non responders and must be revaluated.

Treatment of CHB
Summary

Preferred initial therapy:

- Entecavir, tenofovir and PEG-IFN α 2a.

When to start therapy:

- Elevated HBV DNA [>20,000 IU/mL for HBeAg(+) and 2,000 IU/mL for HBeAg(-)] plus elevated ALT, and/or significant disease on liver biopsy.

When to stop or alter therapy:

- HBeAg(+): HBeAg seroconversion and (-) HBV DNA.
- HBeAg(-): ?long-term therapy.
- Inadequate VR (≥2,000 IU/mL) at Week 24.
- Development of antiviral drug resistance.


Thank You