HBV Treatment Guidelines

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- A 29 Y old lady diagnosed as chronic HBV 3 years ago during her pregnancy , no treatment was offered at that time except for ALT monitoring every 3 months by her GP.
- Now, referred to liver specialist as she wants to be pregnant again

Family history and other histories:

- Parents alive and non reactive for HBs Ag
- One brother tested and is HBs Ag reactive
- Patient denies any other risk factor for HBV infection , feels unusual fatigue , no abnormal findings in physical examination

Laboratory investigations

- Total bilirubin: 0.7 mg/dl
- ALT: 210 IU/L
- Serum albumin : 4.2 gm/dl
- Hb :12 gm/dl
- PLT,WBC: N
- PT:12 sec
- HBs Ag : reactive
- HBe Ag : reactive
- HBV DNA: 26000 IU/ml

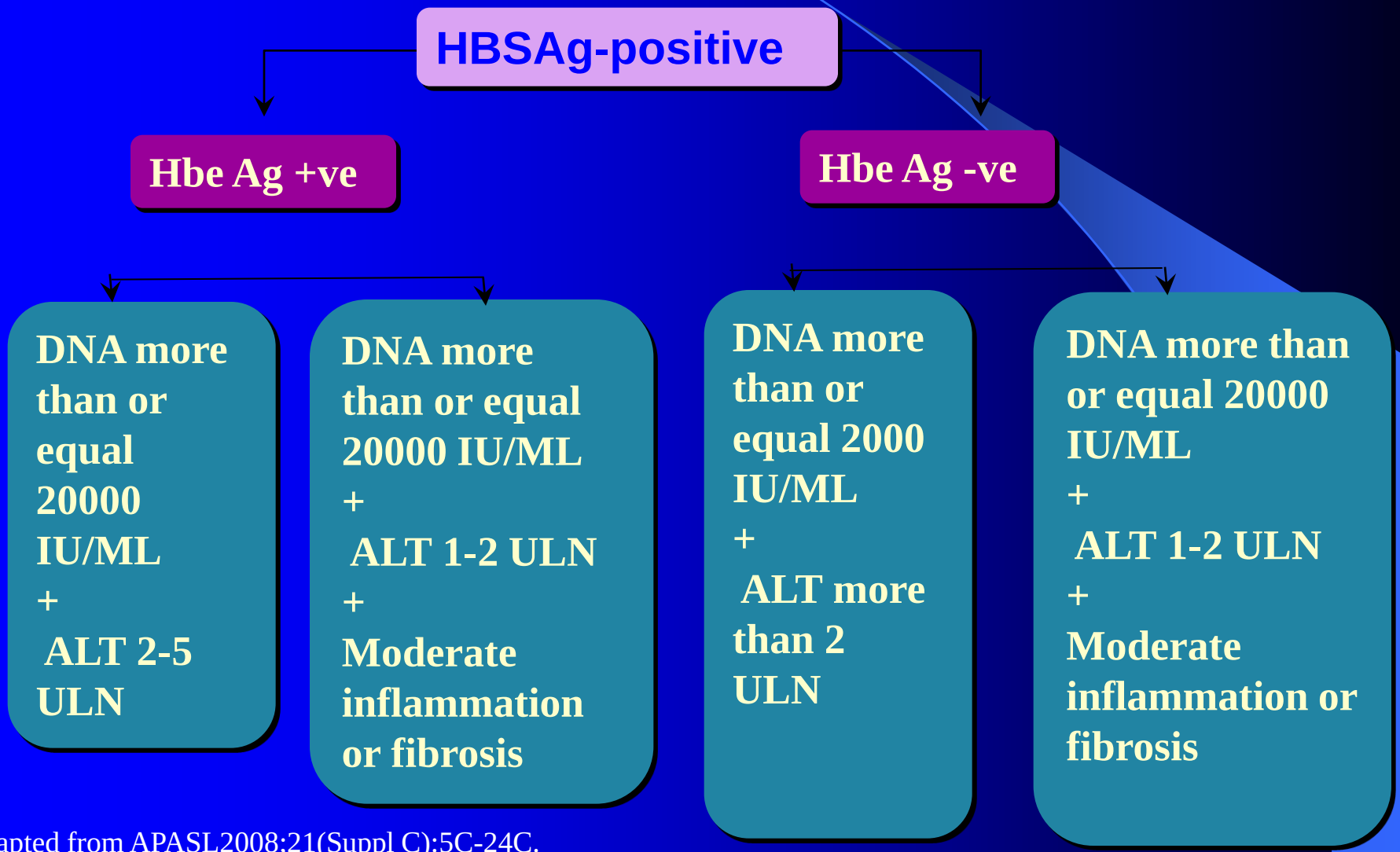
Repeated viral markers after 3 months:

- HBs Ag : reactive
- HBe Ag : reactive
- HBV DNA: 39000 IU/ml
- ALT: 290 IU/L

Liver biopsy: liver architecture is intact but there is significant lobular hepatitis with stage I,II fibrosis

IS THIS LADY INDICATED FOR TREATMENT?

APASL Guidelines of treatment in chronic hepatitis B



Adapted from APASL2008;21(Suppl C):5C-24C.

The 2009 (AASLD) guidelines

- **HBeAg positive**
  - HBV DNA > 20,000 IU/mL and ALT > 2 x ULN*
  - Consider biopsy if age > 40 yrs, ALT 1-2 x ULN, or family history of HCC; treat if moderate to severe necroinflammation and/or fibrosis.

- **HBeAg-negative patients**
  - HBV DNA > 2,000 IU/mL and ALT > 2 x ULN*
  - HBV DNA ≥ 2000 IU/mL and ALT 1-2 x ULN: consider biopsy and treat moderate to severe necroinflammation and/or fibrosis.

EASL 2010 Guidelines

- The decision to treat depends on pattern of disease, HBV-DNA level, and presence or absence of significant necro-inflammation and hepatic fibrosis.
- HBV-DNA thresholds of 20000, 2000 and 2000 IU/ml, are often used for HbeAg+ve chronic hepatitis, HbeAg –ve chronic hepatitis and cirrhosis respectively, for initiating therapy .

What are the available treatment options?

Standard Treatments for Chronic Hepatitis B

- **Interferon**

Peginterferon alfa-2a (Pegasys) 180 mcg/week x 24-48 weeks

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

- **Liver transplantation** (decompensated chronic hepatitis B with cirrhosis)

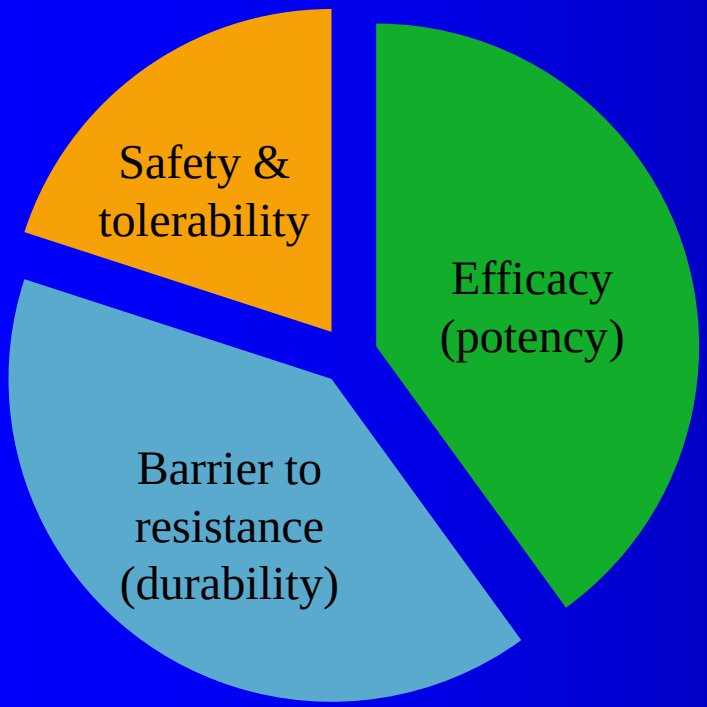
Current Guideline Recommendations for First-line Therapy

- Peginterferon alfa-2a
  - Exceptions: pregnancy, chemotherapy prophylaxis, decompensated cirrhosis, acute infection
- Entecavir
- Tenofovir

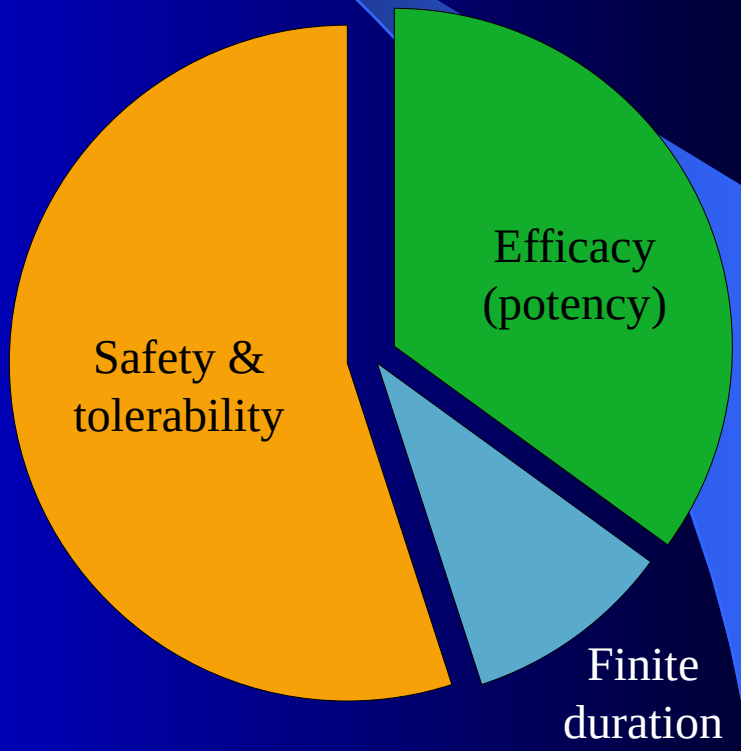
EASL. J Hepatol. 2009;50:227-242. Liaw YF, et al. Hepatol Int. 2008;2:263-283. Lok AS, et al. Hepatology. 2009;50:661-662.

Factors Driving Selection of Initial Therapy

Nucleos(t)ide Analogues



Peginterferon



Only two treatment strategies available – we need to select the best for each patient

INTERFERON

Aim for off-treatment immune control and HBsAg clearance

Durable response through dual MoA: Immunomodulatory and antiviral

Finite therapy

NUCLEOSIDE ANALOGS

Aim for on-treatment viral suppression

Maintained suppression through continued therapy

Long-term therapy (potentially life-long for some)

MoA: Mode of action

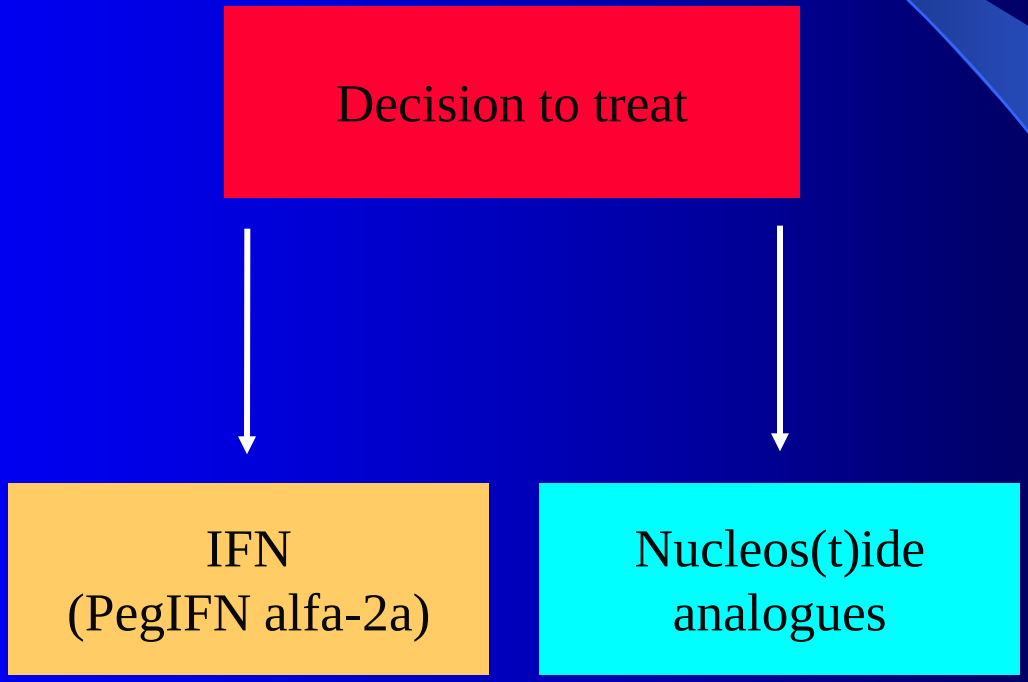
Recommended Dosing of Anti-HBV Agents

Agent	Route	Recommended Dosing	
		Adult	Children
Interferon alfa	SQ	5 MU daily or 10 MU 3 x per wk	6 MU/m^2 3 x per wk (max: 10 MU)
Peginterferon alfa-2a	SQ	180 µg/wk	Not approved
Lamivudine	PO	100 mg QD*†	3 mg/kg/day (max: 100 mg/day)
Adefovir	PO	10 mg QD*	Not approved‡
Entecavir	PO	▪ 0.5 mg QD (no previous LAM) ▪ 1.0 mg QD (if refr/resist to LAM)*	Not approved
Telbivudine	PO	600 mg QD*	Not approved
Tenofovir	PO	300 mg QD*	Not approved

*Dose adjustment needed if eGFR < 50 mL/min. †Persons coinfected with HIV should receive 150 mg BID. Should only be used in combination with other antiretrovirals. ‡Approved for ages 12 and older.

Lok AS, et al. Hepatology. 2009;50:661-662.

The First Branch Point in Choosing With What to Treat



PegIFN vs Nucleos(t)ide Analogues

PegIFN		Nucleos(t)ide Analogues	
Pro	**Con**	**Pro**	**Con**
▪ Finite course of therapy ▪ No resistance ▪ Higher rate of HBeAg loss in 1 yr ▪ Higher rate of HBsAg loss with short duration therapy*	▪ SQ administration ▪ Frequent AEs ▪ Contraindicated in patients with cirrhosis, in pregnancy, with acute hepatitis B, and who are immunosuppressed	▪ PO administration ▪ Infrequent AEs ▪ Safe for patients with decompensated disease†	▪ Need for long-term or indefinite therapy ▪ Potential for drug resistance

*Particularly for HBeAg-positive patients with genotype A infection.
†Recent case report of lactic acidosis in severe liver failure.

Lok AS. Hepatology. 2010;52:743-747. Buster EH, et al. Gastroenterology. 2008;135:459-467.
Lange CM, et al. Hepatology. 2009;50:2001-2006.

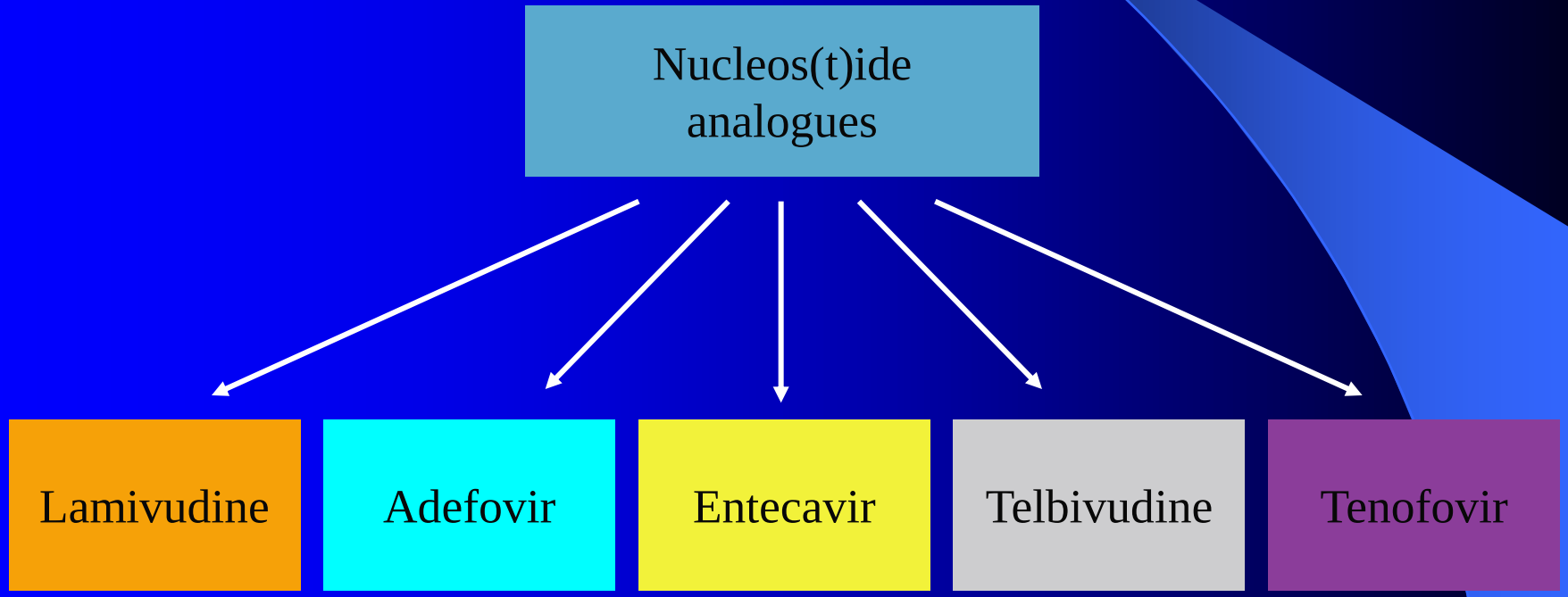
When to Consider PegIFN

- Favorable predictors of response[1,2]
  - Low HBV DNA*
  - High ALT*
  - Genotype A or B > C or D[3-5]
- Specific patient demographics[1,2]
  - Generally young people
    - Young women wanting pregnancy in near future
  - Absence of comorbidities
- Patient preference[1,2]
- Concomitant HCV infection

*Also predictive of response to nucleos(t)ide analogues.

1. Lok AS, et al. Hepatology. 2009;50:661-662. 2. Lok AS. Hepatology. 2010;52:743-747.
3. Janssen HL, et al, Lancet. 2005;365;123-129. 4. Lau GK, et al. N Engl J Med. 2005;352:2682-2695. 5. Flink HJ, et al. Am J Gastroenterol. 2006;101:297-303.

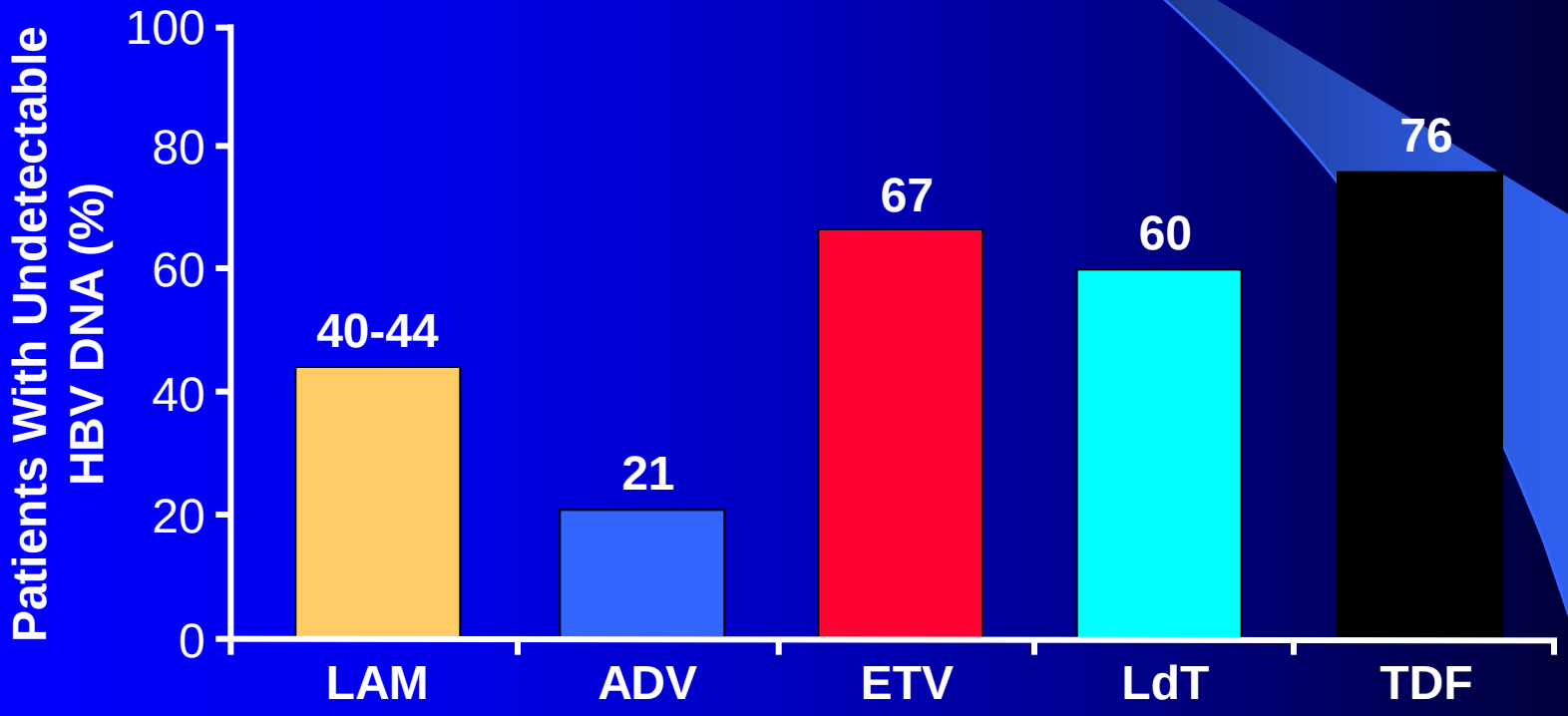
The Second Branch Point in Choosing With What to Treat



Antiviral therapy is a matter of choice!!

Virologic Response in HBeAg+ Patients (Undetectable* HBV DNA at Wk 48-52)

Not head-to-head trials; different patient populations and trial designs

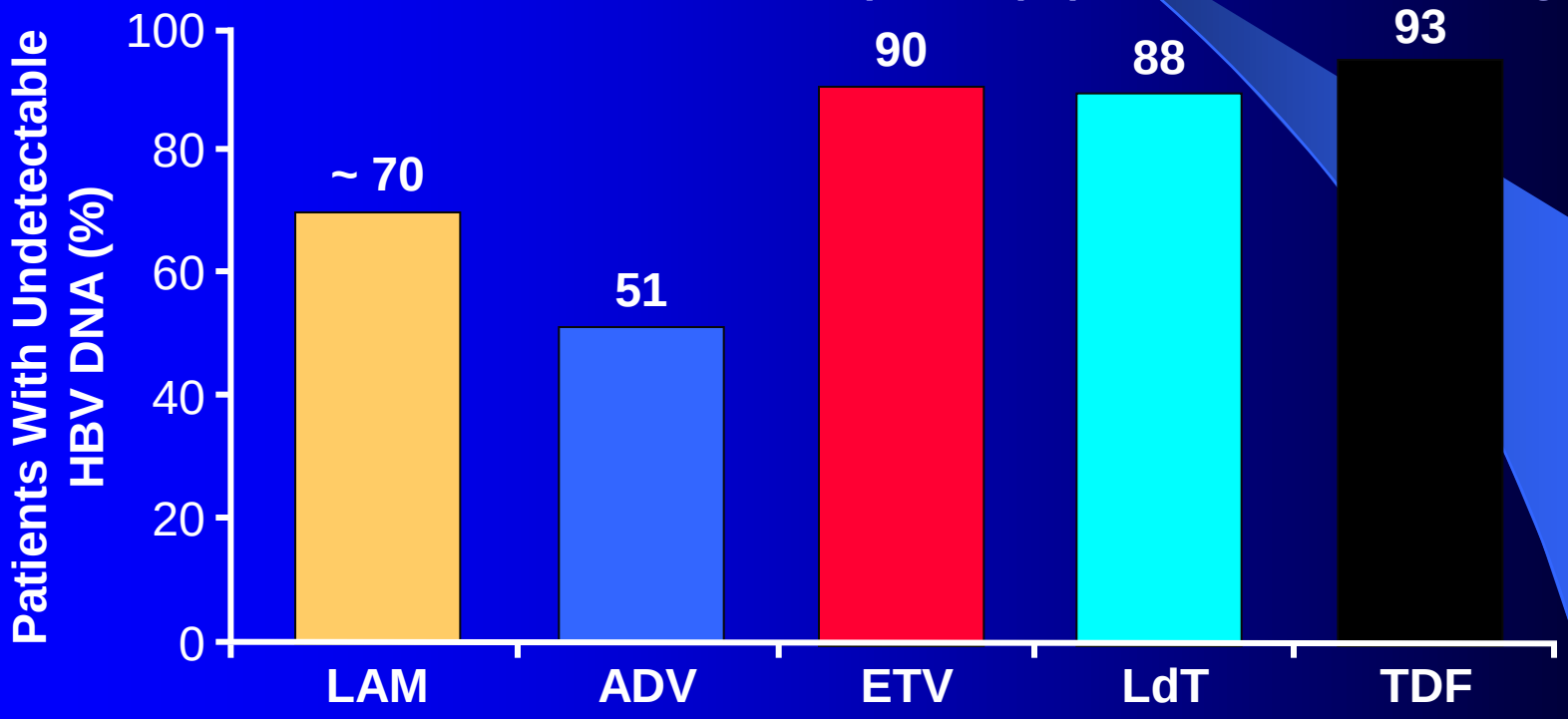


*By PCR based assay (LLD ~ 50 IU/mL) except for some LAM studies.

Adapted from Lok AS, et al. Hepatology. 2007;45:507-539.
Heathcote EJ, et al. AASLD 2007. Abstract LB6.

Virologic Response in HBeAg- Patients (Undetectable* HBV DNA at Wk 48-52)

Not head-to-head trials; different patient populations and trial designs

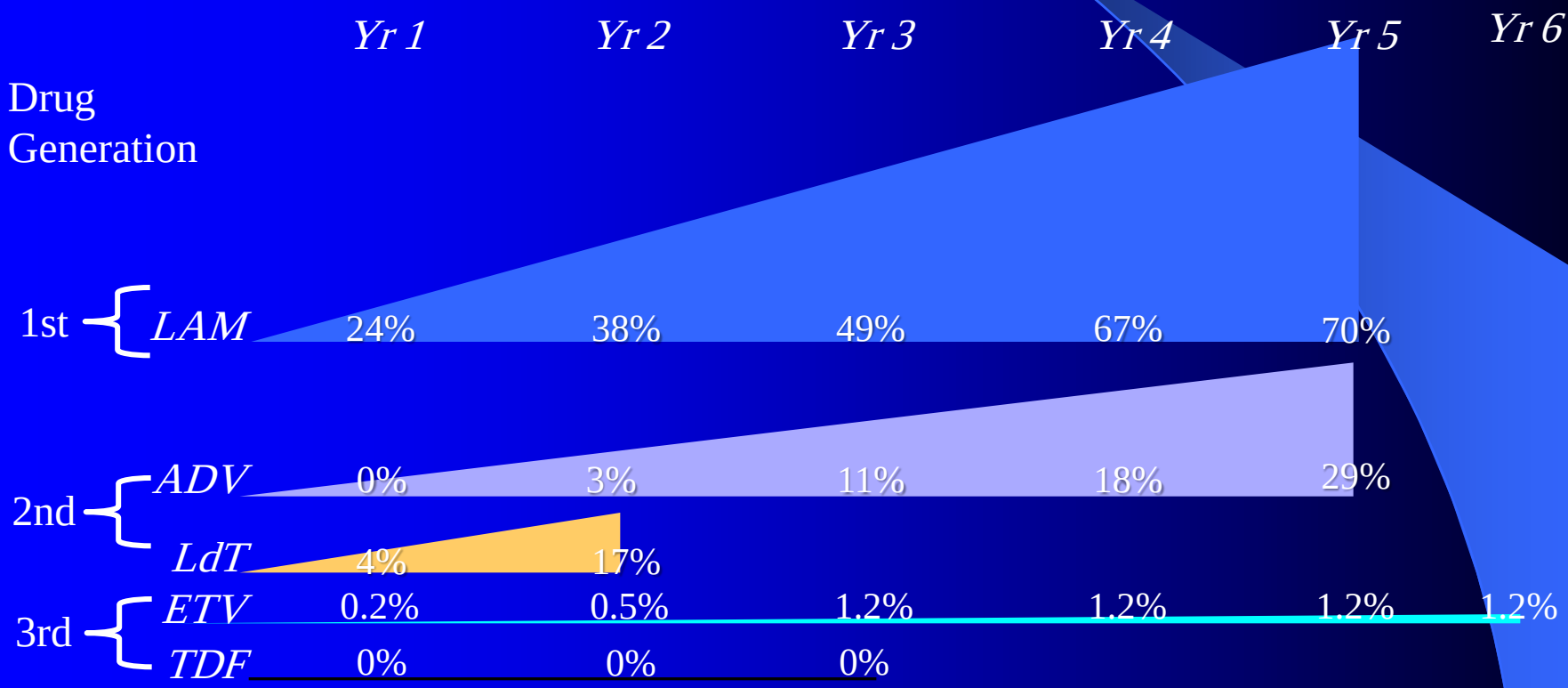


*By PCR based assay (LLD ~ 50 IU/mL) except for some LAM studies.

Adapted from Lok AS, et al. Hepatology 2007;45:507-539.
Marcellin P, et al. AASLD 2007. Abstract LB2.

Cumulative Rates of Resistance With Oral Agents in Nucleos(t)ide-Naive Patients

Not head-to-head trials; different patient populations and trial designs



EASL. J Hepatol. 2009;50:227-242. Tenny DJ, et al. EASL 2009. Abstract 20.
Marcellin P, et al. AASLD 2009. Abstract 481. Heathcote E, et al. AASLD 2009. Abstract 483.

Therapy selected

- Patient mentioned her wish to become pregnant in the not too distant future, she wanted to try finite treatment.
- Peg Interferon 180 Mcgm weekly started for 1 year.

On-Treatment Monitoring and Response Evaluation

Monitoring of Patients Receiving (Peg)IFN Therapy

Time Point	Monitoring
Every 4 wks	▪ Blood counts ▪ Liver panel
Every 12 wks	▪ TSH ▪ HBV DNA levels
Every 24 wks	▪ HBeAg/anti-HBe (if initially HBeAg positive)
Every 12 wks during first 24 wks	▪ Blood counts ▪ Liver panel ▪ TSH ▪ HBV DNA ▪ HBeAg/anti-HBe (if initially HBeAg positive)

Lok AS, et al. Hepatology. 2009;50:661-662.

Monitoring of Patients Receiving Nucleos(t)ide Analogue Therapy

Time Point	Monitoring
Every 12 wks	▪ Liver panel ▪ Serum creatinine (if receiving TDF or ADV)
Every 12-24 wks	▪ HBV DNA levels
Every 24 wks	▪ HBeAg/anti-HBe (if initially HBeAg positive)
Every 6-12 mos	▪ HBsAg in HBeAg-negative patients with persistently undetectable HBV DNA

Lok AS, et al. Hepatology. 2009;50:661-662.

- During treatment with Peg Interferon

month	ALT	DNA by PCR
3 M (12 w)	32	<60 IU/ml
6 M (24 w)	18	<60 IU/ml
12 M (48 w)	18	<60 IU/ml

- No HBe Ag seroconversion is seen.

Defining treatment response?

Phases of response of chronic HBV to treatment

1. **Phase 1 : decrease viral replication and viral DNA.**
2. **Phase 2 : Seroconversion to Hbe negative.**
3. **Phase 3 : loss of HBs Ag and the apperance of anti HBs.**

Definitions of Respone to anti-HBV Treatment

- ***Complete virologic response*** is defined as HBV DNA levels < 60 IU/mL (< 300 copies/mL)
- ***Partial virologic response*** is defined as residual HBV DNA levels < 2000 IU/mL (< 4 $\log_{10}$ copies/mL) at week 24.
- ***Inadequate virologic response*** is defined as residual HBV DNA levels ≥ 2000 IU/mL (≥ 4 $\log_{10}$ copies/mL) at week 24

Definition of Response to Antiviral Therapy

Response	Definition
Primary nonresponse*	**↓ in serum HBV DNA by < 2 $\log_{10}$ IU/mL after ≥ 24 wks of therapy**
Biochemical response	↓ in serum ALT to within the normal range
Virologic response	↓ in serum HBV DNA to undetectable levels by PCR and loss of HBeAg in patients who were initially HBeAg positive
Histologic response	↓ in histology activity index by ≥ 2 points and no worsening of fibrosis score compared to pretreatment liver biopsy
Complete response	Fulfill criteria of biochemical and virologic response and HBsAg loss

*Not applicable to interferon therapy.

Lok AS, et al. Hepatology. 2009;50:661-662. Chronic Hepatitis B: Update 2009, Lok ASF, McMahon BJ, www.aasld.org.

What are the on treatment predictors?

Predictors of HBsAg Loss in HBeAg-Positive Patients

- Race: whites > nonwhites[1]
- Genotype[1-3]
  - Nucleos(t)ide analogues: A and D
  - Peginterferon: A
- Decline in HBsAg level during first 24 wks with nucleos(t)ide analogues[1]
- HBeAg negative at or within 26 wks of completing peginterferon treatment[3]

1. Heathcote EJ, et al. EASL 2009. Abstract 909. 2. Gish RG, et al. J Viral Hepat. 2010;17:16-22.
3. Buster EH, et al. Gastroenterology. 2008;135;459-467.

Utility of on-treatment markers for predicting treatment response

- HBeAg level
  - No commercially assay currrently available
  - Applicable to HBeAg-positive only
- HBsAg level
  - Appropriate for both HBeAg-positive and -negative
  - Reflects cccDNA in infected cells
  - Initial findings on clinical utility are encouraging
- HBV DNA level
  - Does not differentiate between responders and relapsers

Wong, Chan. Drugs 2009

HBV DNA as on treatment predictor

- The benefit of monitoring the viral load during treatment is probably limited.
- DNA decline improves prediction of sustained response, and it is recommended to discontinue therapy in patients in whom an HBV DNA decline of 2 log10 at week 24 is not achieved .
- In parallel with HBV DNA, quantitative assays for HBeAg and HBsAg have become available

HBe Ag Levels as on treatment predictor

- Monitoring serum HBeAg levels during treatment may help to predict the probability of subsequent HBeAg loss or seroconversion.
- At 24 weeks of therapy, high HBeAg levels had a greater negative predictive value (96%) compared with HBV DNA levels at the same time point

HBsAg level as a key to response-guided therapy in future treatment paradigms

- Serum HBsAg levels probably reflect intrahepatic cccDNA, the key replicative intermediate .
- On-treatment reduction of HBsAg may reflect the reduced intrahepatic cccDNA concentrations..
- HBsAg is the only viral marker that remains detectable in the serum of CHB patients who become HBeAg negative

Benefits of on-treatment HBsAg monitoring

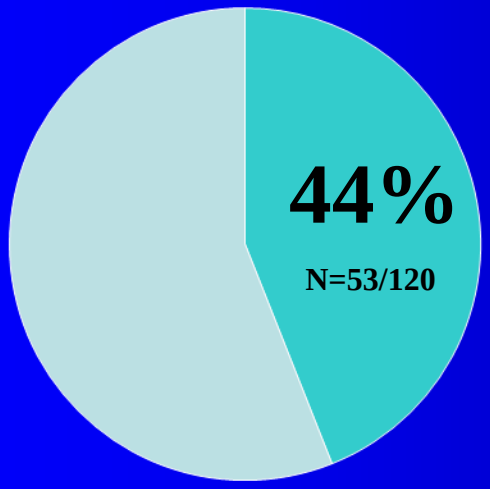
- Week 12 HBsAg decline
  - ≥10% decline is an early sign of future success
  - Helps motivate the patient
- Week 24 HBsAg decline
  - Greater chance of sustained immune control and HBsAg clearance

Marcellin et al. APASL 2010

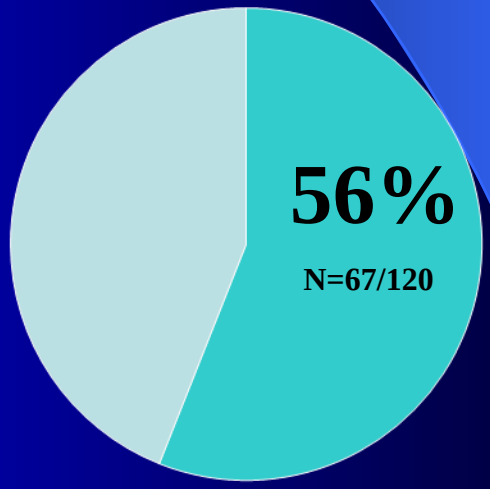
Proportion of patients who achieved a≥10% decline in HBsAg increased by Week 24

% HBeAg-negative patients achieving HBsAg decline ≥10%

Week 12:
Patient motivation



Week 24:
Predict with more confidence



Marcellin et al. APASL 2010

HBsAg reduction at Week 24 is an early sign of future HBsAg clearance

HBeAg-negative patients

45% **HBsAg clearance 5 years post-treatment**

43% **HBV DNA ≤10,000 copies/mL 1 year post- treatment**

Among HBeAg-negative patients who achieved HBsAg decline ≥10% from baseline at Week 24 of treatment*

SUSTAINED IMMUNE CONTROL

*56% of patients achieved HBsAg decline ≥10% at Week 24

Marcellin et al. APASL 2010

- After 6 months of pegylated Interferon treatment , she become pregnant and her ALT is normal and HBV DNA : < 60 Iu/ml , however No HBeAg seroconversion occured

Third trimester of pregnancy

- ALT: 24 IU/L
- HBV DNA:60 IU/ml
- HBeAg :reactive

questions

- Will you add lamivudine in this stage?
- How will you treat the newborn for prevention of HBV transmission?
- Can she feed her new born?

- No therapy was given
- The newborn was given both active and passive immunization
- The baby started on breast feeding.

EASL 2010 recommendations

Pregnancy and Breastfeeding

- Vertical transmission (mother to infant) of infection occurs in 65-90% of pregnancies where the mother is HBeAg positive and in about ten percent of HBsAg positive, HBeAg negative mothers,Most (>90%) of infected infants become chronic carriers.
- Infants born to HBsAg positive mothers are vaccinated from birth, sometimes in combination with Hepatitis B specific Immunoglobulin (HBSIg) 200 i.u intramuscularly [IIa,B],This reduces vertical transmission by approximately ninety percent.
- There is some evidence that lamivudine may further reduce vertical transmission if given to women with a high HBV-DNA viral load in the third trimester [Ib, A], However, if HBSIg is not available, vaccination alone prevents vertical transmission in 66-100% [IIa, B]. Infants should be tested for hepatitis B (HBsAg and anti-HBs) 4-6 weeks after the final dose of vaccine [IV, C].
- Infected mothers should continue to breast feed as there is no additional risk of transmission.

- At 4.5 months post pregnancy she developed again unusual fatigue

Lab investigations:

- HBs Ag : reactive
- HBe Ag: reactive
- HBV DNA: 29000 IU/ml
- ALT: 310 IU/ml
- Total bilirubin: 1.3 mg/dl

questions

- What are the possible causes of flare in ALT level and reappearance of HBV DNA?
- Would you consider treatment?
- If yes

1. Pegylated interferon
2. Oral antiviral

- A significant increase in liver inflammation occurs often after pregnancy. This may be due to a reactivation of the immune system after delivery."
- A significant increase in liver disease activity within six months after the mothers gave birth. Based on characteristics such as the mother's status as having chronic liver disease or being an HBV carrier, the authors stated that it was not possible to predict during pregnancy which women would experience liver disease exacerbations. This means that regardless of the status of HBV infection, pregnant women who have been infected with HBV are susceptible to its resurgence following delivery.
- Likely due to the immunologic changes that accompany a woman as she gestates and produces a new human being, the Hepatitis B virus can flourish in a pregnant woman's body. Because so many people have antigens to HBV, this possibility must be known to expectant mothers and their caregivers.

- She started on lamivudine 100 mg/day

month	ALT	eAg	HBV DNA
3 M	100	+VE	Less than 60 IU/ml
6 M	21	+VE but level decrease markedly	Less than 60 IU/ml
12 M	21	Non reactive and HBe Ab +VE	Less than 60 IU/ml
18 M	18	HBeAG:non reactive HBeAb:reactive	Less than 60 IU/ml

Questions

- How would you define the above response?
- When you will stop the treatment?

What are the endpoints of treatment?

Therapeutic strategy defines which endpoint is appropriate for determining success

- **PEG-IFN**

  Aim for sustained response after a finite course of therapy through immunologically mediated control HBV DNA ≤10,000 copies/mL for HBeAg-negative HBeAg seroconversion for HBeAg-positive

- **NAs**

  Aim for maintained suppression of viral replication

  Undetectable levels of HBV DNA are needed to prevent resistance

End-points of Hepatitis B therapy

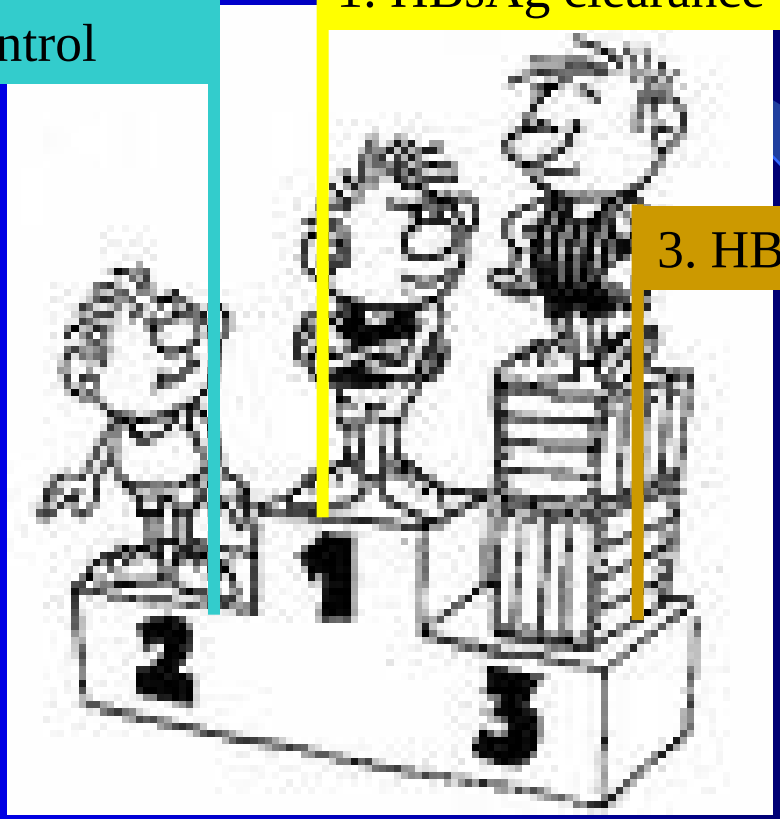
- Sustained **HBsAg-loss** or seroconversion to **anti-HBs** (ideal end-point)
- In HBeAg-positive patients:
  - durable HBe-seroconversion (satisfactory end-point)
- In HBeAg-positive patients without HBs seroconversion and in HBeAg-negative patients:
  - maintained undetectable HBV-DNA (NUCs)
  - sustained undetectable HBV-DNA after (PEG) IFN

EASL Clinical Practice Guidelines: Management of chronic Hepatitis B. Journal of Hepatology 2009;50:227-242

Relevance of efficacy endpoints

2. Inactive HBsAg carrier status
Sustained immune control

1. HBsAg clearance



3. HBV DNA suppression

HBV DNA <2,000 IU/ml (10,000 copies/mL) without therapy
normal ALT, HBsAg <?

Guidelines
HBsAg clearance is the "Ideal endpoint"

- AASLD, EASL and APASL guidelines all acknowledge the importance of HBsAg clearance
  - "Key role in the natural history of chronic HBV infection"
- EASL guidelines (*J Hepatol* 2009)
  - "... is associated with a complete and definitive remission of the activity of CHB and an improved long-term outcome"

AASLD guidelines (2009)

- Recommend that patients with chronic hepatitis B who are HBe Ag +ve , treatment should be continued until the patient achieves seroconversion and has completed at least 6 months of additional treatment after the apperance of anti Hbe.
- In patients with Hbe Ag -ve form of the disease , treatment should be continued until the patient has achieved HBs Ag clearance

- HBs Ag seroclearance represent the preferred end point of therapy of chronic hepatitis B

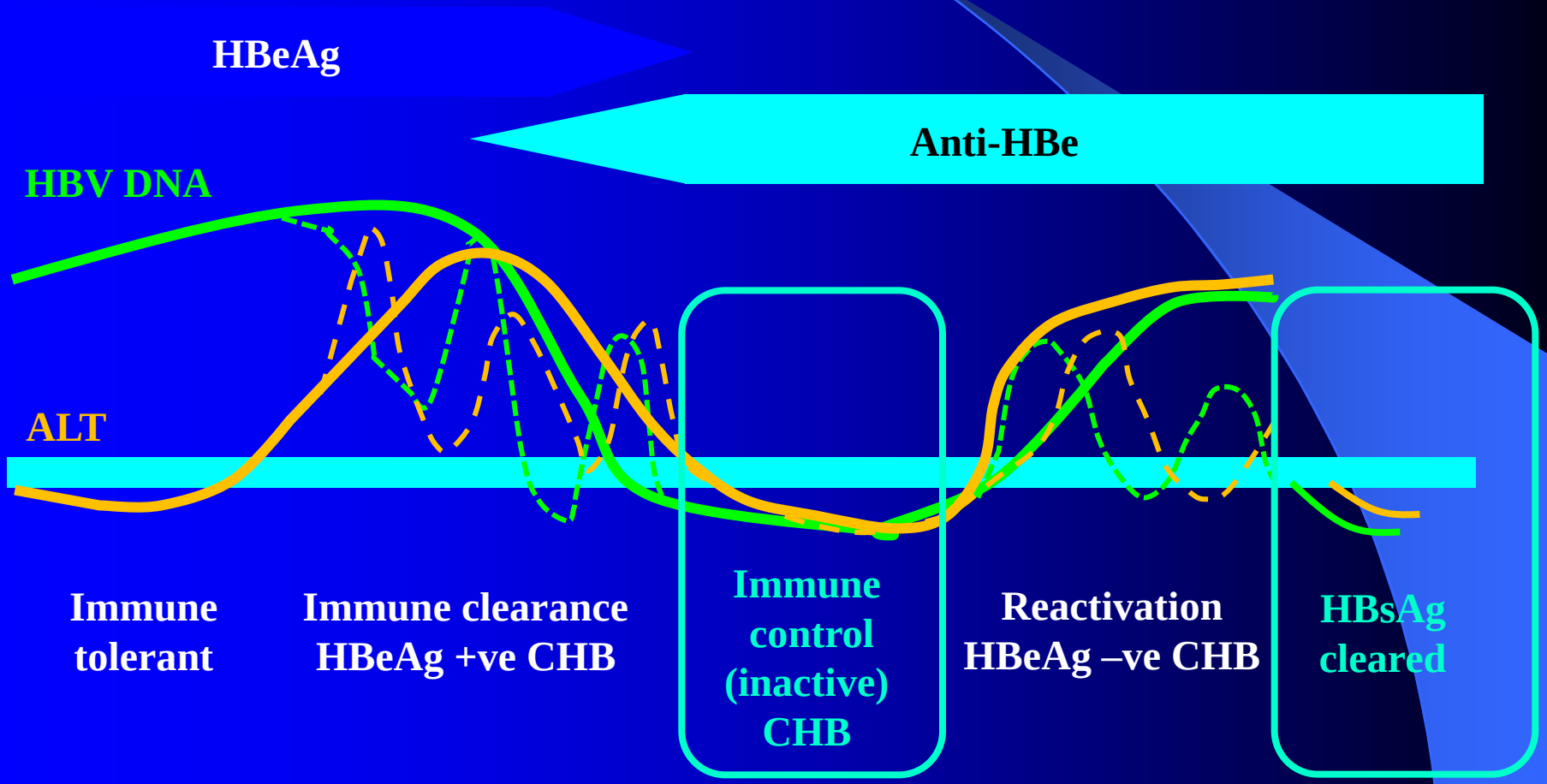
Why is HBs Ag the best end point?

- Serum HBsAg levels probably reflect intrahepatic cccDNA, the key replicative intermediate .
- HBs Ag seroclearance represent the preferred end point of therapy of chronic hepatitis B as it is believed to represent successful immunological control of active HBV replication.
- serum HBsAg loss comes as close to clinical cure and is clearly associated with improved outcomes, provided that HBsAg clearance occurs before the development of cirrhosis
- HBsAg is the only viral marker that remains detectable in the serum of CHB patients who become HBeAg negative.

HBeAg seroconversion as an end point of treatment

- HBeAg seroconversion is frequently used as a primary endpoint in HBeAg-positive patients treated with PEG-IFN.
- Most patients enter an inactive carrier state after achieving HBeAg seroconversion, characterized by low or undetectable HBV DNA levels and normalization of ALT levels.
- Long-term follow-up studies have demonstrated that HBeAg seroconversion is associated with increased survival and a reduced risk of developing HCC .

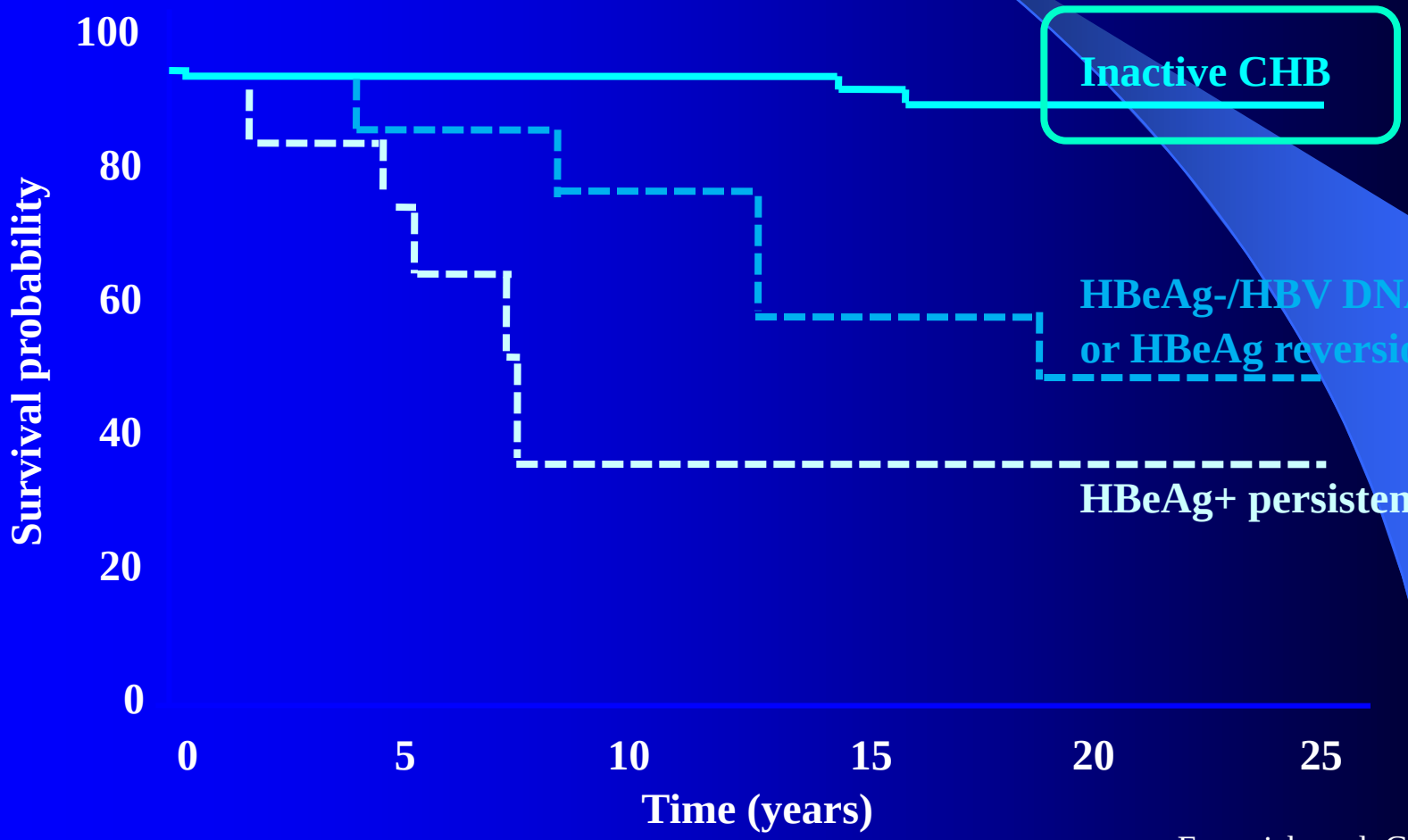
Inactive disease is what we want to achieve



Lok et al. Arch Intern Med 2006

Inactive CHB is associated with good prognosis

25-year survival rates in untreated CHB



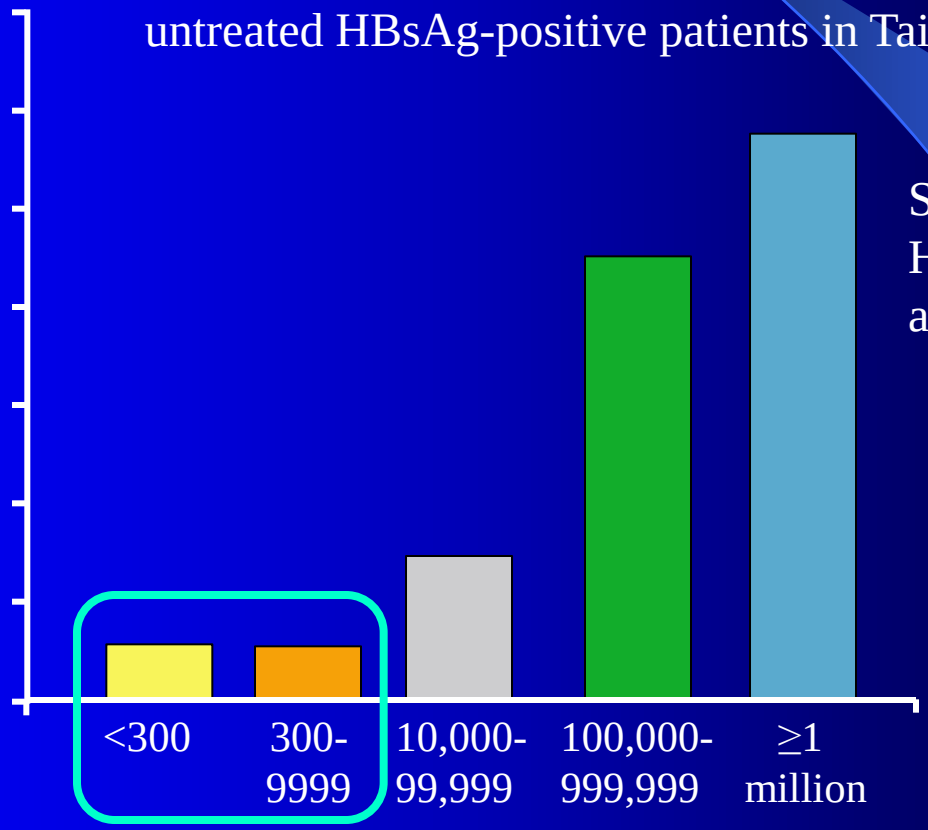
Fattovich et al. Gut 2008

suppression of HBV DNA as an end point of treatment

- HBeAg seroconversion is by definition not possible in HBeAg-negative patients.
- Thus, suppression of HBV DNA to low or undetectable levels in combination with normalization of ALT is considered the most important treatment goal.
- Response to therapy is defined by the sustained presence of an HBV DNA level below 2,000 IU/mL according to the European guidelines.

HBV DNA <10,000 copies/mL is associated with low HCC risk

REVEAL: long-term follow-up (mean, 11.4 yrs) of untreated HBsAg-positive patients in Taiwan (N=3,653)



Similar low risk of HCC for <300 and <10,000 cp/mL

Chen et al. JAMA 2006

- She achieved HBeAg seroconversion.
- Stop the treatment according to the current guidelines

AASLD Guideline Recommendations for Duration of NA Treatment

"32. Duration of nucleoside analogue treatment

a. HBeAg-positive chronic hepatitis B—Treatment should be continued until the patient has achieved HBeAg seroconversion and undetectable serum HBV DNA and completed at least 6 mos of additional treatment after appearance of anti-HBe. (I)

- *Close monitoring for relapse is needed after withdrawal of treatment. (I)*

b. HBeAg-negative chronic hepatitis B—Treatment should be continued until the patient has achieved HBsAg clearance. (I)"

Lok AS, et al. Hepatology. 2009;50:661-662.

Treatment stopped

Follow up at 12 months:

- ALT:12
- HBV DNA: less than 60 IU/ml

Maintaining the response


THANK YOU

NEPTUNE: PegIFN alfa-2a Administered for 24 vs 48 Wks in HBeAg+ Patients

24 wks inferior to 48 wks of pegIFN alfa-2a therapy, regardless of dose, in randomized, double-blind phase IV study

HBeAg Seroconversion 6 Mos After Rx, %	24 Wks (n = 282)	48 Wks (n = 262)	OR (95% CI)	*P* Value
Overall	18.4	30.9	2.17 (1.43-3.31)	.749
Genotype B	29	36	1.44 (0.75-2.78)	.215
Genotype C	13	31	3.29 (1.76-6.15)	.960
ALT > 1-2 x ULN	11	19	NR	--
ALT > 2-5 x ULN	20	36	NR	--
ALT > 5-10 x ULN	34	53	NR	--

*For noninferiority; ie, nonsignificance = not noninferior.

Liaw Y-F, et al. AASLD 2010. Abstract 215.

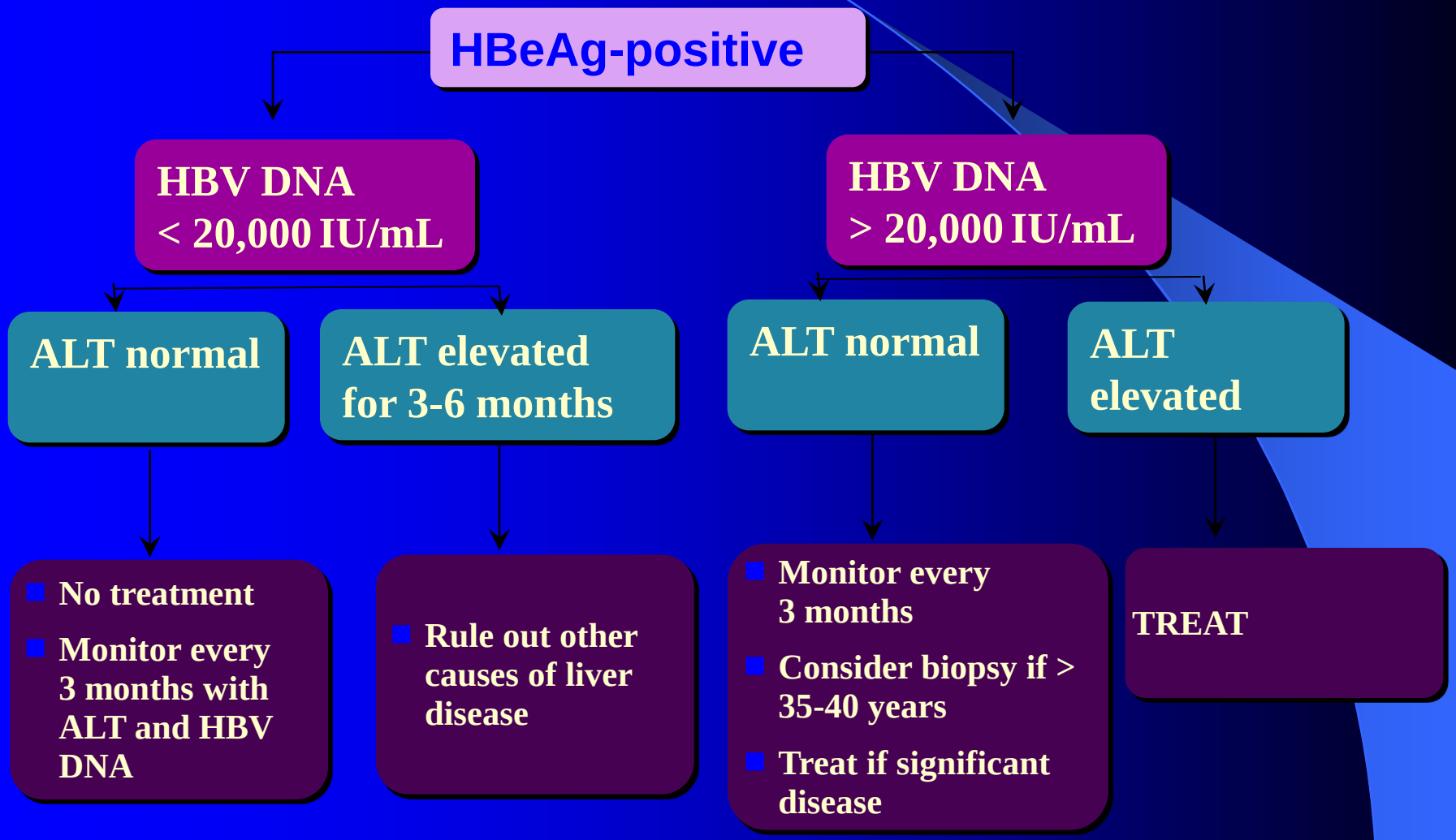
Safety of Extending PegIFN alfa-2a From 48 to 96 Wks in Genotype D HBeAg- Pts

PegBeLiver: higher virologic/serologic response rates observed 1 yr posttreatment in HBeAg-negative pts (94% genotype D) treated with pegIFN alfa-2a for 96 vs 48 wks[1]

Safety Outcome[2]	PegIFN Alfa-2a 48 Wks (n = 51)	PegIFN Alfa-2a 96 Wks (n = 77)	*P* Value
Treatment discontinuation, %	20	26	.52
Any treatment-related adverse event, %	82	79	.82
Any serious adverse event, %	14	12	.79
Treatment-related serious AE %	4	3	1.00
Dose modification, %	29	21	.30
Death, n	1	0	1.00
Laboratory abnormalities, %			
Increased ALT	4	3	1.00
Neutropenia	24	16	.36
Thrombocytopenia	12	10	.77
Anemia	8	5	.71

1. Lampertico P, et al. EASL 2010. Abstract 98. 2. Lampertico P, et al. AASLD 2010. Abstract 135.

Algorithm for Selecting HBeAg-Positive Patients for Treatment



Adapted from CASL Consensus Guidelines. *Can J Gastroenterol* 2009;21(Suppl C):5C-24C.

Tolerability and Safety: Nucleos(t)ide Analogues vs Peginterferon

Nucleos(t)ide Analogues

- Safe at all stages of disease, including decompensated cirrhosis
- Safe in immunocompromised populations
  - Selected drugs probably safe in pregnancy
- Reported toxicities are rare

Peginterferon

- Contraindications
  - Decompensated cirrhosis
  - Pregnancy
  - Chemotherapy prophylaxis
  - Acute HBV infection
- Not recommended
  - Cirrhosis
- Adverse effects common

Lok AS, et al. Hepatology. 2007;45:507-539. Lok AS, et al. Hepatology. 2009;50:661-662.

- The suppression of serum HBV DNA during treatment appears to be the best predictor of improved long-term patient outcomes.
- Failure to reduce HBV DNA levels by 1 log10 IU/mL or more after 12 weeks of treatment is considered an indication of therapeutic failure.
- Complete viral response after 6 months of oral therapy correlates with reductions in resistance, HBeAg seroconversion, and continued negativity of therapy at 1–2 years.

- Monitoring patients during treatment is an important means of assessing drug safety, compliance, and treatment responses.
- Early monitoring of HBV DNA is of particular value to detect primary treatment failure and predict outcomes of continued therapy (e.g., improved liver histology, reduced likelihood of disease progression, the development of drug resistance).