

Hepatitis B Putting Experts into Practice

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Case # 1 - HBV



- A 57-year-old Indian female was diagnosed with HBV infection in 1998.
- She had history of jaundice at age of 18.
- She has never received treatment for HBV.
- No family history of liver cancer
- Pt resists being treated because of side effects of medication (4/2007)
- No biopsy has been done at this point

Lab values - 2007

- **ALT:** 29 (Reference range 7-56 U/L)
- **HBV DNA:** Unavailable
- **HbsAg:** Positive
- **HBeAg:** Negative
- **Anti-HBe:** Positive
- **HBV DNA:** 11 million IU/mL.
- **Serum AFP:** 2.1
- **MRI:** Negative for HCC

- What should you do?

What should you do? *HBeAg negative CHB:*

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- A. ALT every 3-6 months
- B. Consider liver biopsy to determine stage and grade
- C. Offer treatment for HBV
- D. Obtain genotype and mutation test

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A.

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B.

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C.

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D.

Treatment Criteria for Chronic Hepatitis B

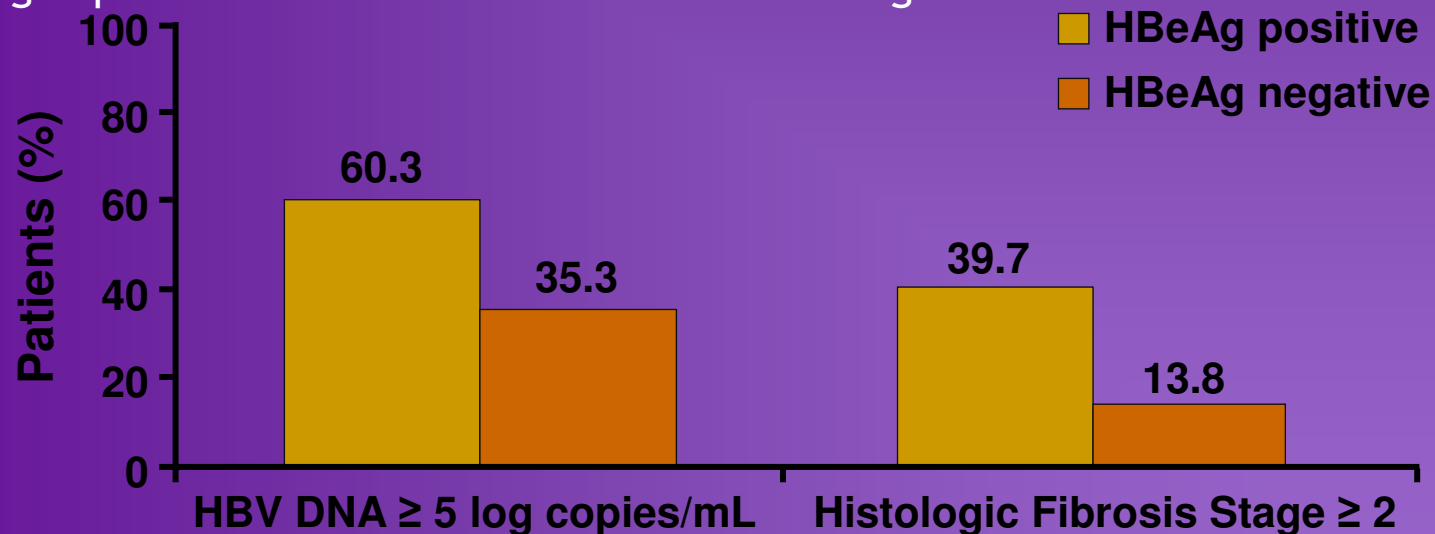
Guideline	HBeAg +		HBeAg-	
	HBV DNA copies/mL	ALT U/L	HBV DNA copies/mL	ALT U/L
US Algorithm 2008*	$\geq 10^5$	>ULN or (+) biopsy	$\geq 10^4$	>ULN or (+) biopsy
EASL 2008	$\geq 10^4$	> ULN	$\geq 10^4$	> ULN
APASL 2008	$\geq 10^5$	>2x ULN	$\geq 10^5$	>2x ULN
AASLD 2007	$\geq 10^5$	>2x ULN or (+) biopsy	$\geq 10^5$	>2x ULN or (+) biopsy

What is a “Normal” ALT Level?

- 9,221 first-time blood donor candidates
- 74% suitable donors after exclusion of anemia, seizure, sexual and other risk
 - 57% determined to be ‘low risk’ for liver disease
 - Negative viral serology
 - BMI < 25
 - Normal serum cholesterol, triglycerides, and glucose levels
 - Absence of concurrent medication use
- Updated healthy ALT ranges determined from the group of low-risk individuals
 - Males: 30 IU/L
 - Females: 19 IU/L

Patients with Normal ALT May Have Significant Fibrosis

- 1387 asymptomatic HBsAg-positive patients with ≥ 1 -year follow-up
 - 189 with persistently normal ALT (PNALT)* included in analysis (HBeAg-: 116)
- 21% of HBeAg-negative patients with PNALT and HBV DNA < 5 log copies/mL had HAI ≥ 3 and/or fibrosis stage ≥ 2

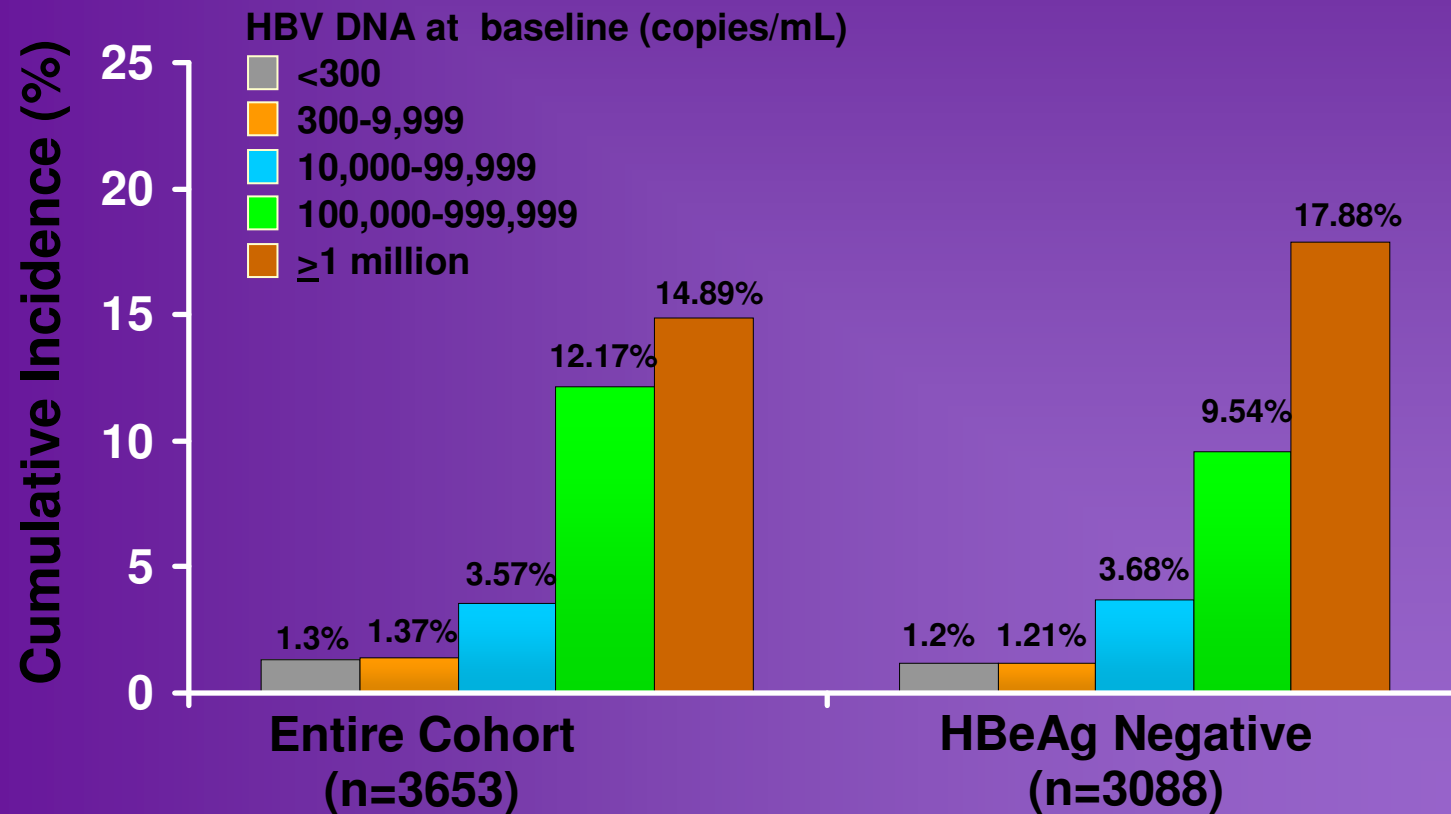


* ≥ 3 ALT values in the previous 1 year prior to baseline liver biopsy that were all ≤ 40 IU/L and remained so until the start of treatment or the last follow-up.

Kumar M, et al. *Gastroenterology*. 2008;134:1376-1384.

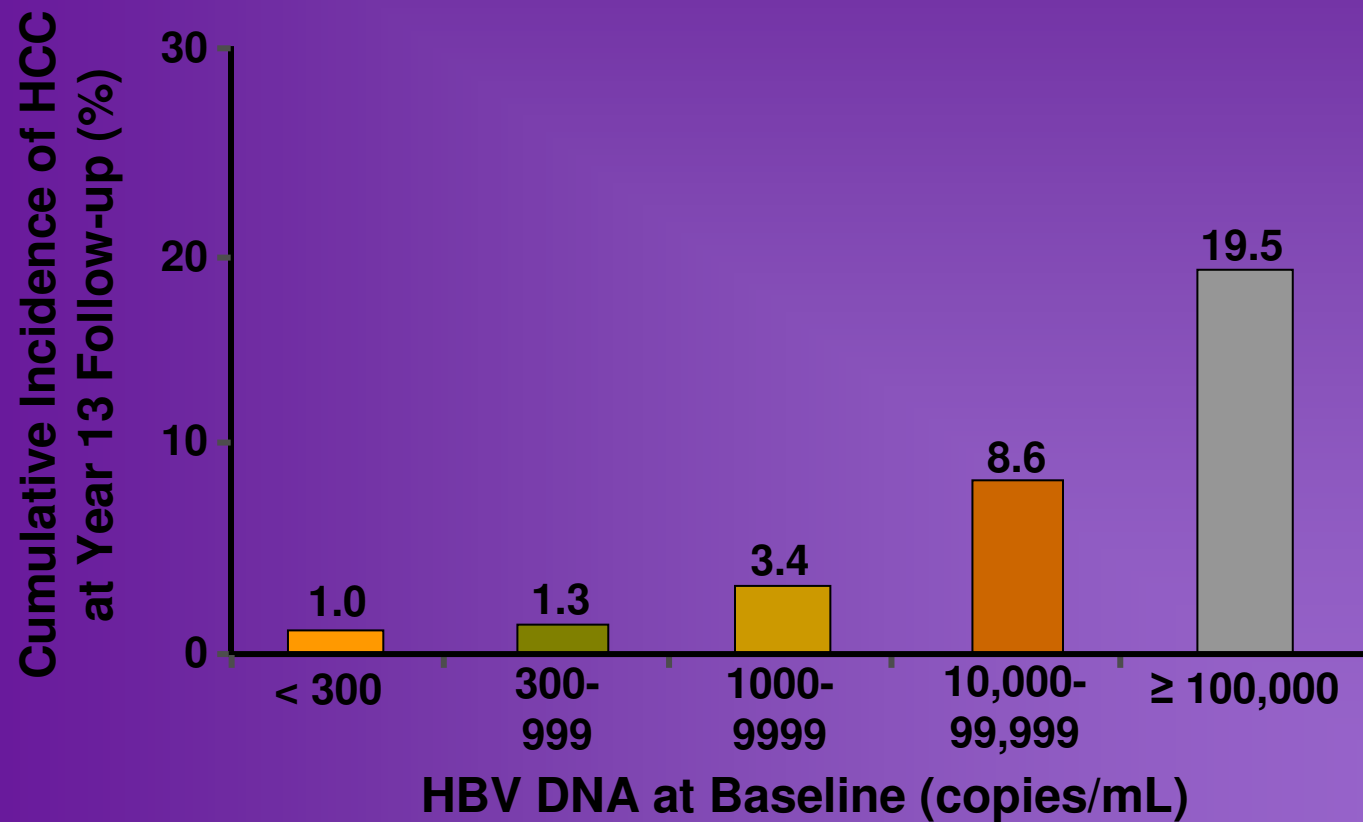
REVEAL: Cumulative Incidence of Hepatocellular Carcinoma by HBV DNA Level at Study Entry

Hepatocellular Carcinoma (13-year follow-up)



Incidence of HCC in HBeAg Negative Patients with Normal ALT

(n = 2966)



Candidates for Therapy Based on ALT Levels

- Revised ALT ULN should be used as criteria for treatment
 - 30 IU/L for men; 19 IU/L for women
- A normal ALT level alone might not be an adequate indicator of who should be treated
 - ALT levels should be considered in conjunction with HBV DNA levels and patient's age

Case # 1 - HBV



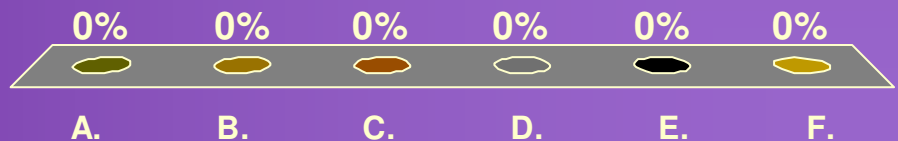
- 06/07: Liver Biopsy: grade 3, stage 2
- Genotype: D
- Precore mutation not detected, BCP mutations detected
- MRI revealed no masses

- What medication is best for this patient?

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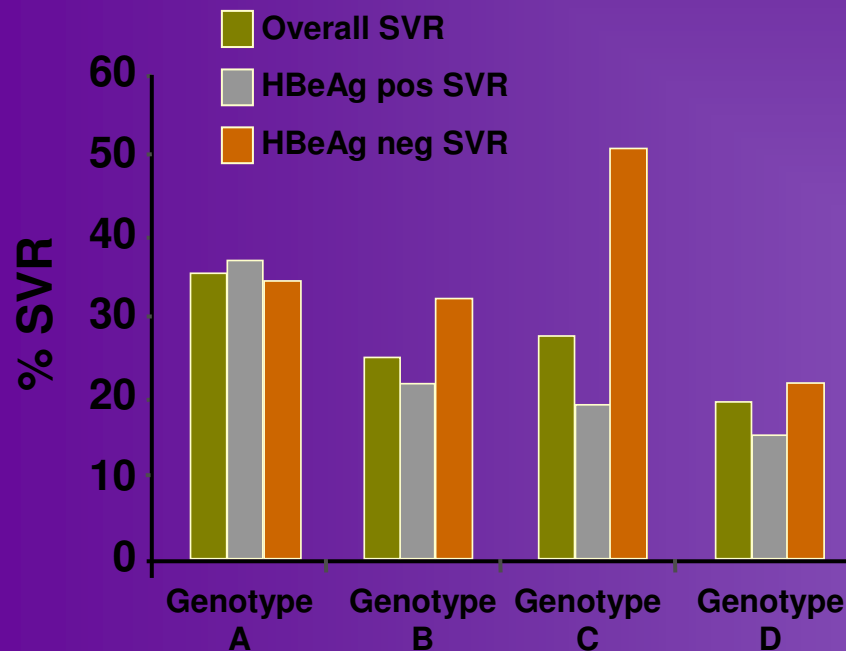
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- A. Pegylated Interferon alfa-2a
- B. Lamivudine
- C. Adefovir
- D. Entecavir
- E. Telbivudine
- F. Pegylated Interferon alfa-2a and Lamivudine



Response to Interferon-Alfa: Multivariate Analysis

SVR by Genotype and HBeAg Status



Independent Predictors for SVR

	OR (95% CI)	P value
HBV genotype		
A vs. D	3.620 (2.316-5.657)	0.0001
B vs. D	2.621 (1.618-4.245)	0.0001
C vs. D	3.184 (2.054-4.936)	0.0001
ALT >5 vs. ≤5 xULN	1.432 (1.056-1.940)	0.02
HBeAg neg. vs. pos.	2.124 (1.527-2.966)	0.0001

Conclusion: Multivariate analysis adjusted for treatment identified genotype D, HBeAg negative status and normal ALT level as independent predictors for failing to achieve SVR

PegIFN:

- High rate of seroconversion with carefully selected patients
 - High ALT
 - Favorable genotype
- Finite course of therapy
- No resistance (ever)
- Side effects are better with HBV
 - No Ribavirin
 - Different patient group

Anti-viral Agents: Safety, Tolerability, Cost and Risk: Benefit

	LAM	ADV	Entecavir	Telbivudine	Tenofovir
Dosing	QD	QD	QD	QD	QD
Tolerability	Well tolerated	Well tolerated, Watch serum Cr	Well tolerated	Well tolerated, Watch CPK	Well tolerated, Watch serum Cr
Pregnancy	C	C	C	B	B
Approximate cost for 1 year	2,500	6,500	8,700	6,000	6,000
Potency	Moderate	Modest	High	High	High
Resistance	High	Moderate	Low	High	Low

Case # 1 - HBV



- June 2008: Started on Hepsera
- Pre-treatment HBV DNA: 4.2 million IU/ml
- October 2008: HBV DNA 158,000 IU/ml
- Dec 2008: HBV DNA 62,900 IU/ml
- Hepsera was continued

- March 2009: HBV DNA 46,500 IU/ml
- June 2009: HBV DNA 56,300 IU/ml
- HBsAg: Pos, HBeAg: Neg, Anti-HBe: Pos, ALT: 23

- What would you do next?

What would you do next?

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- A. Continue same drug for another six months
- B. Add another drug
- C. Switch to another drug
- D. Test for anti-viral resistance
- E. Stop therapy, as it is ineffective

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A.

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D.

E.

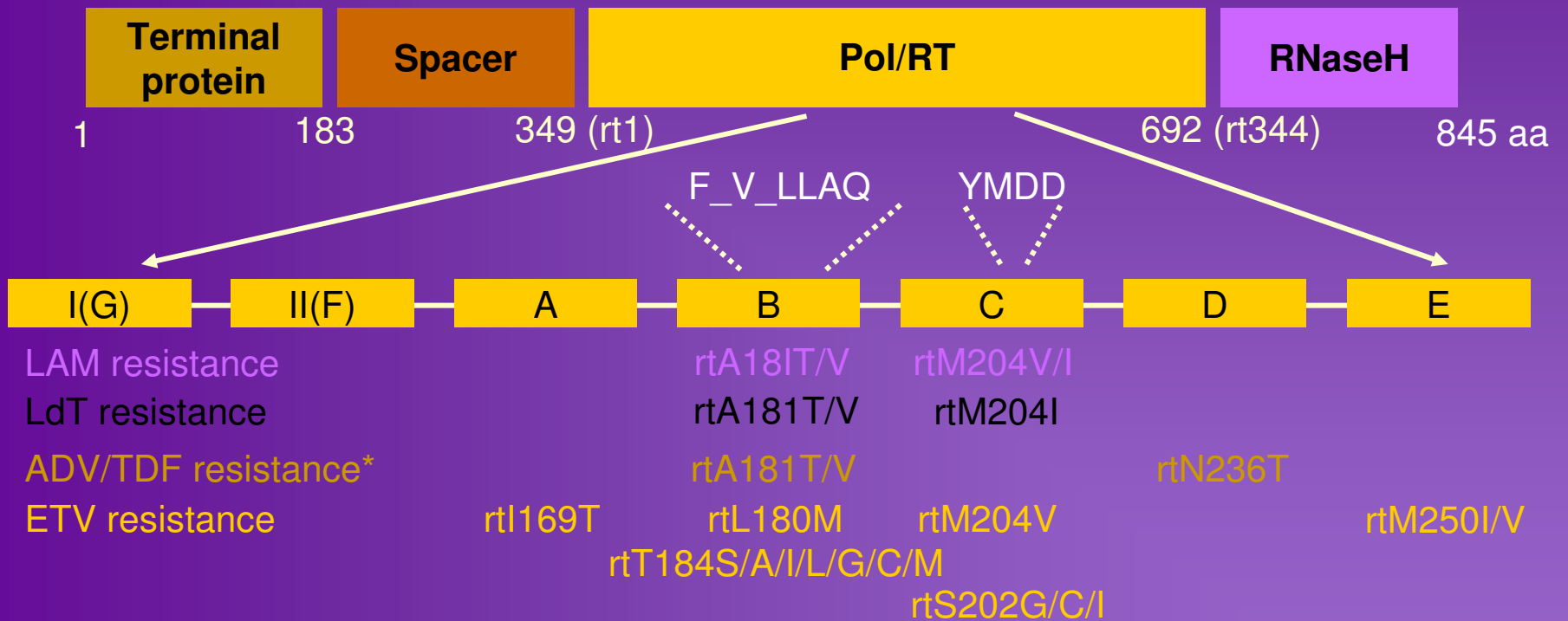
Polymerase Inhibitors:

	Mutation
3TC (lamivudine or Epivir)	NO
LDT (telbivudine or Tyzeka)	NO
FCV (famciclovir or Famvir)	NO
ADV (adefovir or Hepsara)	rtN236T
ETV (entecavir or Baraclude)	NO

Precore and BCP Mutations:

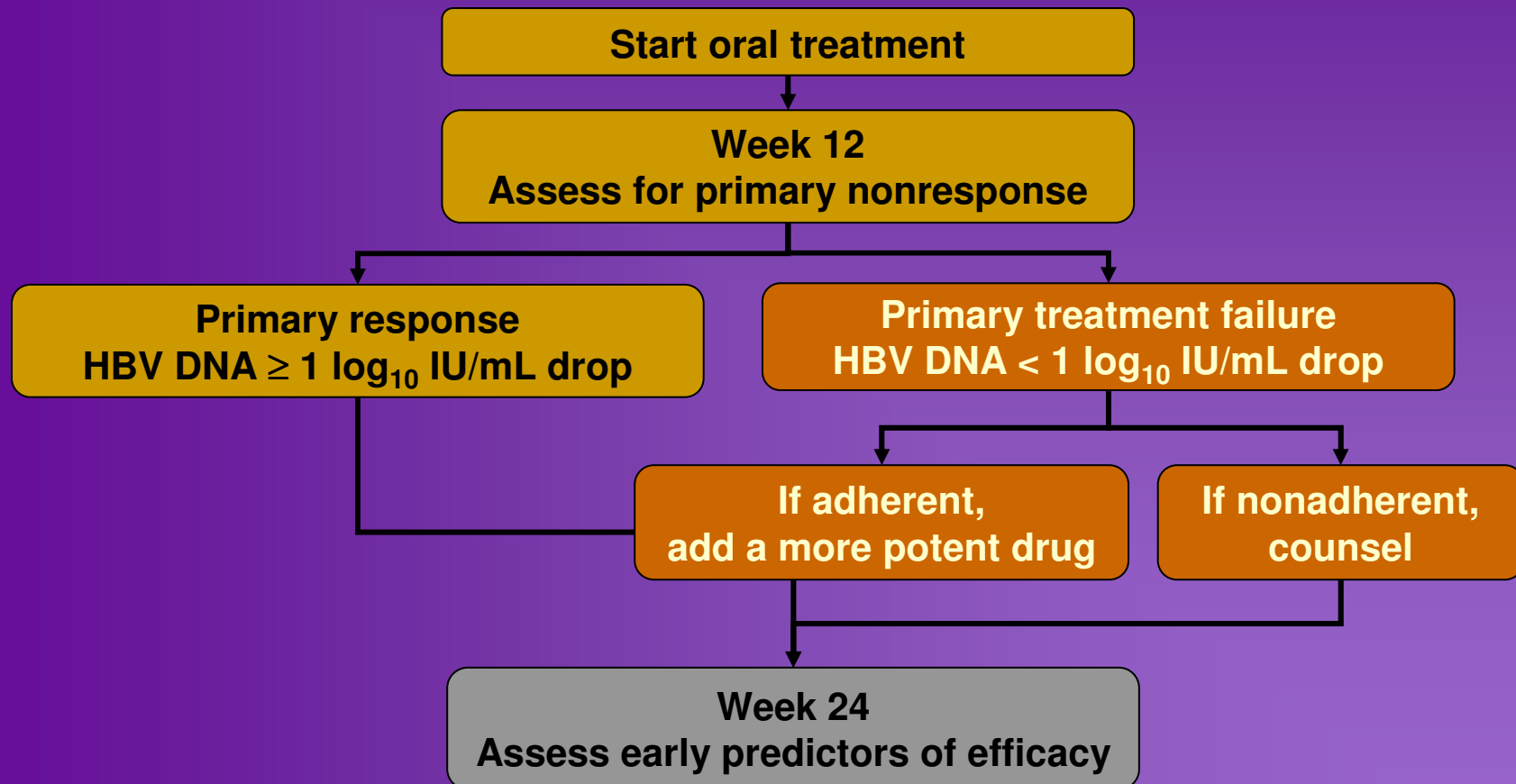
Precore (TAG)	Not Detected
BCP	A1762T,G1764A

HBV Primary Resistance Mutations

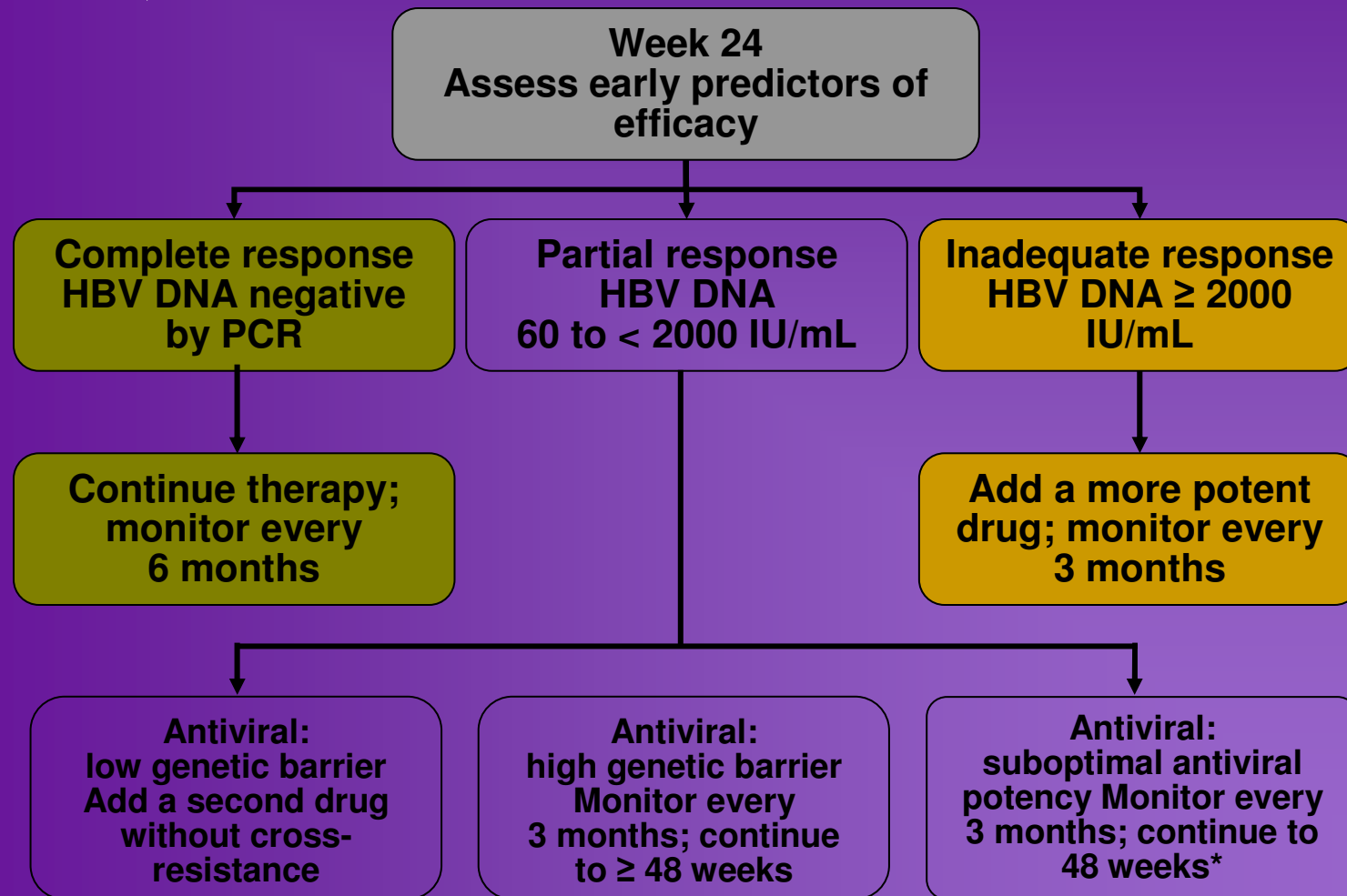


*Based on in vitro data and therapy switch following emergence of genotypic ADV resistance.

HBV Roadmap Concept



HBV Roadmap Concept (cont'd)



Goals of Therapy in Patients With Chronic HBV Infection

- Prevent complications of liver disease
 - Histologic progression to cirrhosis
 - Decompensated liver disease
 - Liver cancer
- Mechanisms to achieve the primary goal:
 - HBeAg and HBsAg seroconversion
 - Long-term suppression of HBV replication

How long to continue therapy?

- Continue therapy until HBsAg negative and anti-HBs positive
- Continue for 3-5 years following undetectable HBV DNA and follow closely thereafter
- Life-long therapy, no stopping!

Duration of HBV Treatment

- HBeAg positive
 - 6-12 months after HBeAg seroconversion to minimize relapse rate
 - Long-term therapy may be required
- HBeAg negative
 - Relapse common after cessation of therapy
 - Long-term treatment currently recommended
- Cirrhosis
 - Long-term therapy

Case # 2 - HBV



- 50 year old Caucasian male
- 1994: while residing in Brazil in a village along the Jura River and developed an acute onset of nausea, vomiting, fatigue, myalgias, arthralgias, and jaundice. Due to the remote area in which he was living, he did not receive any medical care. The symptoms lasted approx. 2-4 weeks.
- 1996: He returned to the US in April 1994 he was diagnosed with chronic Hepatitis B. Lab tests showed positive HBsAg and HBeAg, high liver enzymes. HBV DNA > 10 million copies/ml.
- Liver biopsy : grade 1-2, stage 4 liver disease
- 1997: Therapy was initiated standard interferon. Within 12 weeks of treatment he had become HBV DNA negative. The interferon was discontinued and replaced with Epivir on 10/1997. By 7/1998 he had become HBsAg negative and anti-HBs positive. Therapy was discontinued on November 1, 1998.

- What is the plan for follow up?

What is the plan for follow up?



- A. Follow up with HBV DNA, anti-HBs titer every 6-12 m
- B. Follow with US liver and AFP every 6 months
- C. He needs long-term treatment
- D. Needs HBV therapy if on high dose steroid therapy or immunosuppression in future
- E. Does not need any follow up

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A.

B.

C.

D.

E.

United States Algorithm

Cirrhotics

Cirrhosis	HBeAg	HBV DNA* (copies/mL)	Management
Compensated	+/-	$< 10^4$	Treat or follow
Compensated	+/-	$\geq 10^4$	Treat
Decompensated	+	$\geq 10^3$	Treat with oral antiviral; refer for liver transplant
Decompensated	-	$< 10^3$	Treat with oral antiviral; refer for liver transplant

Lok ASF, MacMahon BJ. Hepatology. 2001;34:1225. Lok ASF, MacMahon BJ. Hepatology. 2004;39:857.


Case # 3 - HBV



- 28/F, born in China
- Incidentally found to be HBsAg positive, asymptomatic
- ALT 50, HBeAg negative, anti-HBe positive, HBV DNA 25,000 IU/ml
- No family history of liver cancer
- She is planning for pregnancy in next 2 yrs

- What would be the next step?

What would be the next step?

- A. She needs HBV therapy now
- B. Liver biopsy, and if advanced disease, then treat
-  C. Defer therapy until family is complete
- D. Start HBV therapy at 36 weeks to prevent HBV transmission to the newborn

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A.

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B.

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C.

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D.

HBV Transmission: When Does It Happen?

- In utero transmission
 - Very rare (< 10%); associated with high HBV DNA levels^[1]
- During amniocentesis
 - Very rare; no transmission reported in 2 case series^[2,3]
- **At birth!**
 - HBeAg-positive mothers: 85%
 - HBeAg-negative mothers: 31%^[4]

Prevention of HBV Transmission by Postnatal Vaccination

- Active plus passive immunization most

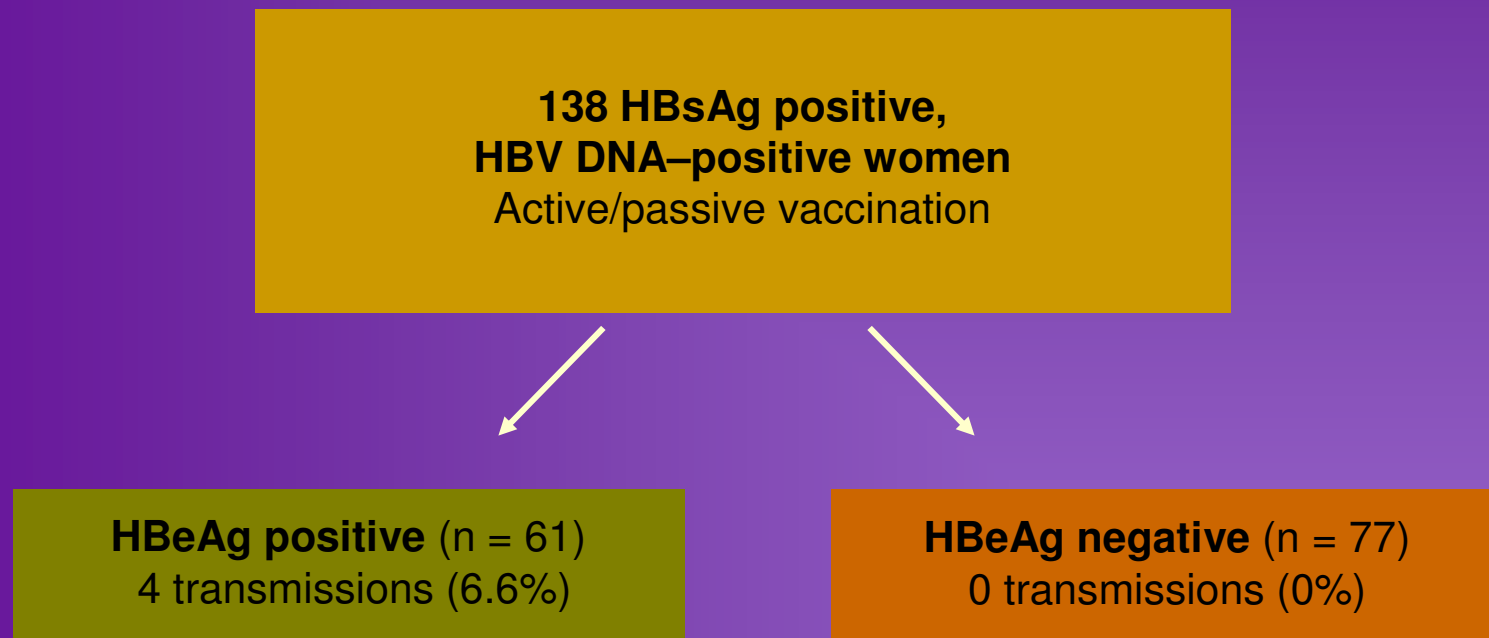
	No Vaccine	Passive Immunization	Passive + Active Immunization
Infants without HBV, %	5	72	95

- Role of maternal HBV DNA on transmission^[2]
 - HBV DNA < 150 pg/mL (1.1×10^7 IU/mL) = 0% transmission
 - HBV DNA > 150 pg/mL = 32% transmission

1. Ranger-Rogez S, et al. Expert Rev Ant Infect Ther. 2004;2:133-145.

2. del Canho R, et al. Vaccine. 1997;15:1624-1630.

Perinatal Transmission of Hepatitis B: Risk Factor HBV DNA



HBV DNA cutoff: 8 log₁₀ copies/mL

Can Antiviral Treatment Reduce Vertical HBV Transmission?

- No complete prevention of transmission, even in case of successful LAM treatment^[1]
- LAM given 1 month before delivery decreased HBV transmission from 28.0% in untreated historical controls to 12.5% (OR: 2.9; 95% CI: 0.29-28.0)^[2]
 - All received standard prophylaxis
 - High maternal viremia associated with vaccination failure

1. Kazim SN, et al. Lancet. 2002;359:1488-1489.

2. van Zonneveld M, et al. J Viral Hepat. 2003;10:294-297.

■ No adverse events noted with LAM

Pregnancy Category of FDA-Approved Treatments for Chronic HBV

Drug	Pregnancy Category
IFN alfa-2b	C
PegIFN alfa-2a	C
Adefovir	C
Entecavir	C
Lamivudine	C
Telbivudine	B
Tenofovir	B

FDA Classification of Drug Safety During Pregnancy

A	Controlled studies in women fail to demonstrate a risk to the fetus and the possibility of fetal harm appears remote
B	Either animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other), and there are no controlled studies in women or studies in women and animals are not available; drugs should be given only if the potential benefit justifies the potential risk to the fetus
D	There is positive evidence of human fetal risk , but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease in which safer drugs cannot be used or are ineffective)
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit; the drug is contraindicated in women who are or may become pregnant

Take Home Points

- Best prevention for transmission is vaccination/HBIG
- Maternal HBV DNA levels are likely associated with increased risk of transmission
- Family planning must be discussed with women of childbearing age before initiating HBV therapy
- Assess necessity of treatment; wait if possible
 - Treatment may be indicated in advanced disease
- Few data exist for safety of HBV treatment during pregnancy
 - Treatment in the third trimester may be considered
- If HBV treatment discontinued for pregnancy, monitor for flare

Recommendations for HBV-Infected Women Who Desire Pregnancy

- Women with mild liver disease, low viremia
 - Pregnancy before treatment
- Women with moderate liver disease, no cirrhosis
 - Treatment before pregnancy; if response, stop treatment before pregnancy
- Women with advanced liver disease
 - Treatment before and during pregnancy; continue treatment after delivery
- Women with mild liver disease, very high viremia
 - Treatment in last trimester with “B” category drug

End of Case Discussions



Hepatitis B: Case 1

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- 2007: ALT 29 (Reference range 7-56 U/L)
HBsAg pos, HBeAg neg, Anti-HBe pos
HBV DNA 11 million IU/mL. Serum AFP 2.1
MRI negative for HCC
- What should you do?

Case 1

What should you do? *HBeAg negative CHB*:

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2. Consider liver biopsy to determine stage and grade
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Case 2

- 50-yr-old caucasian male
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Case 2 - What is the plan for follow up?

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