

Hepatitis B
Putting Experts into Practice
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Case #1

- 38-year-old Asian American male, who moved from China to the US at age of 5 years .
- Recently detected to be HBsAg positive
- Father died from liver cancer a year ago and his sister was recently diagnosed with HBV infection.
- He rarely drinks alcohol and does not smoke.

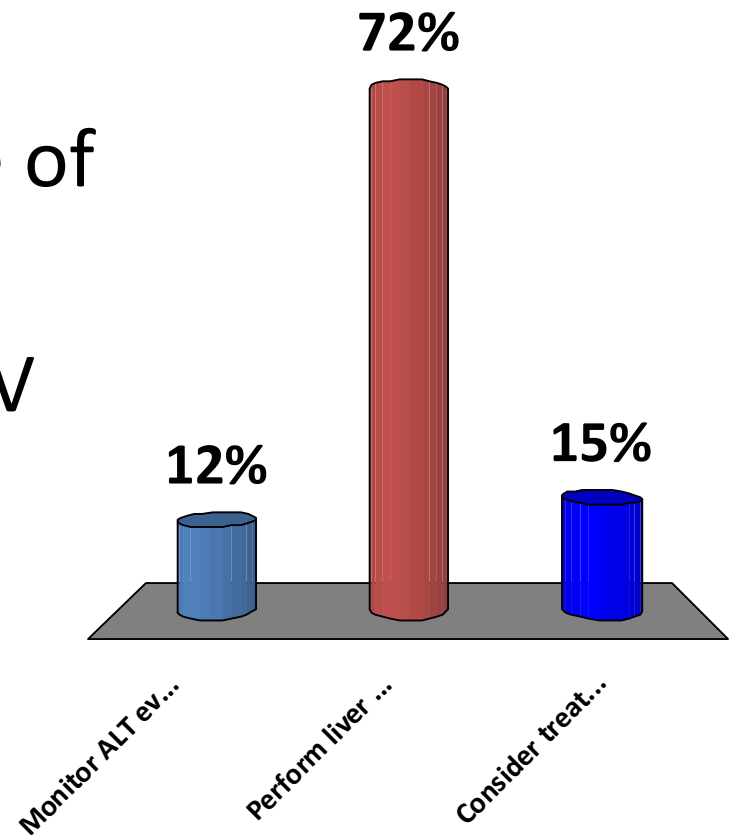
Lab data 02/08

- ALT 38 IU/L. AST 45 IU/L.
- Platelet count 190,000/mm³
- Albumin 4.6 g/dl
- Bilirubin 0.9 mg/dl
- INR 1.1
- Creatinine 0.8 mg/
- HBeAg positive
- HBV DNA level of 22 X10⁶IU/mL
- HBV genotype C

- US liver appears normal

What would you do next?

1. Monitor ALT every 3-6 months
2. Perform liver biopsy to determine grade and stage of liver disease
3. Consider treatment for HBV



Recommendations for Treatment Initiation in HBeAg-Positive Patients

	AASLD 2009 ¹	US Algorithm 2008 ²	EASL 2009 ³
HBV DNA, IU/mL	> 20,000	> 20,000	≥ 2,000
ALT, x ULN ¹	> 2	> 1	> 1
Liver biopsy, ² grade/stage	Moderate/severe necroinflammation and/or significant fibrosis		

¹Persistent (> 3-6 months); specified 30 U/L for men and 19 U/L for women in AASLD and US Algorithm

²Biopsy recommended, but not required; best used selectively

¹Lok A, et al. *Hepatology*. 2009;50:661-662.

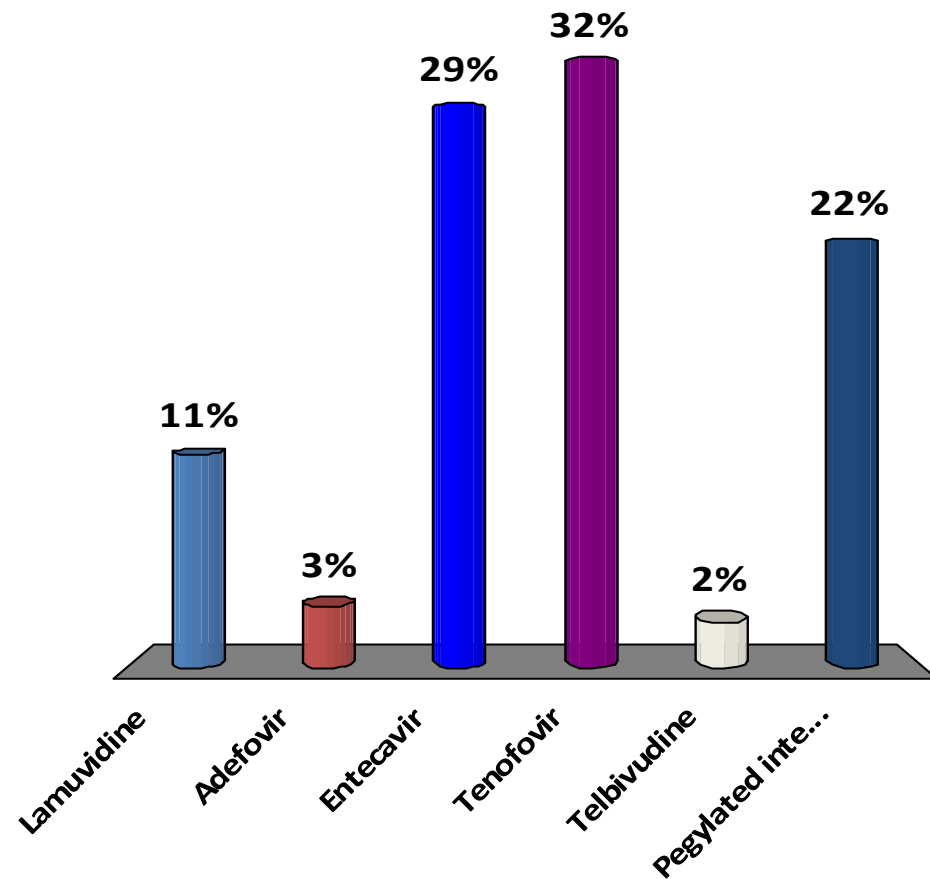
²Keefe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.

³EASL HBV Guidelines. *J Hepatol*. 2009;50:227-242.

Liver biopsy shows grade 2 and stage disease

What treatment is best for this patient?

1. Lamuvidine
2. Adefovir
3. Entecavir
4. Tenofovir
5. Telbivudine
6. Pegylated interferon



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First-line therapy	ETV, TDF pegIFN	ETV, TDF, pegIFN	ETV, TDF, pegIFN

¹Persistent (> 3-6 months); specified 30 U/L for men and 19 U/L for women in AASLD and US Algorithm

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Treatment of HBV 2010

Comparative Efficacy

Drug	HBeAg (+)		HBeAg (-)
	% HBeAg Seroconversion at Yr 1	% HBV DNA Negative at Yr 1*	% HBV DNA Negative at Yr 1*
Interferon	~18	37	60-70
Lamivudine	18	40-44	60-70
Adefovir	12	21	51
Entecavir	21	67	90
Peginterferon α -2a	27	25	63
Telbivudine	23	60	88
Tenofovir [†]	21	76	93

*Interferon and lamivudine: hybridization assay; adefovir, entecavir, and peginterferon: PCR assay.

[†]Licensed for treatment of HIV infection; under review by FDA for treatment of chronic hepatitis B.

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

	LAM	ADV	Entecavir	Telbivudine	Tenofovir
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

03/07/08 Entecavir 0.5 mg daily

06/11/08 (3 month FU)

- ALT 30 IU/L
- HBV DNA 20,000 IU/mL.

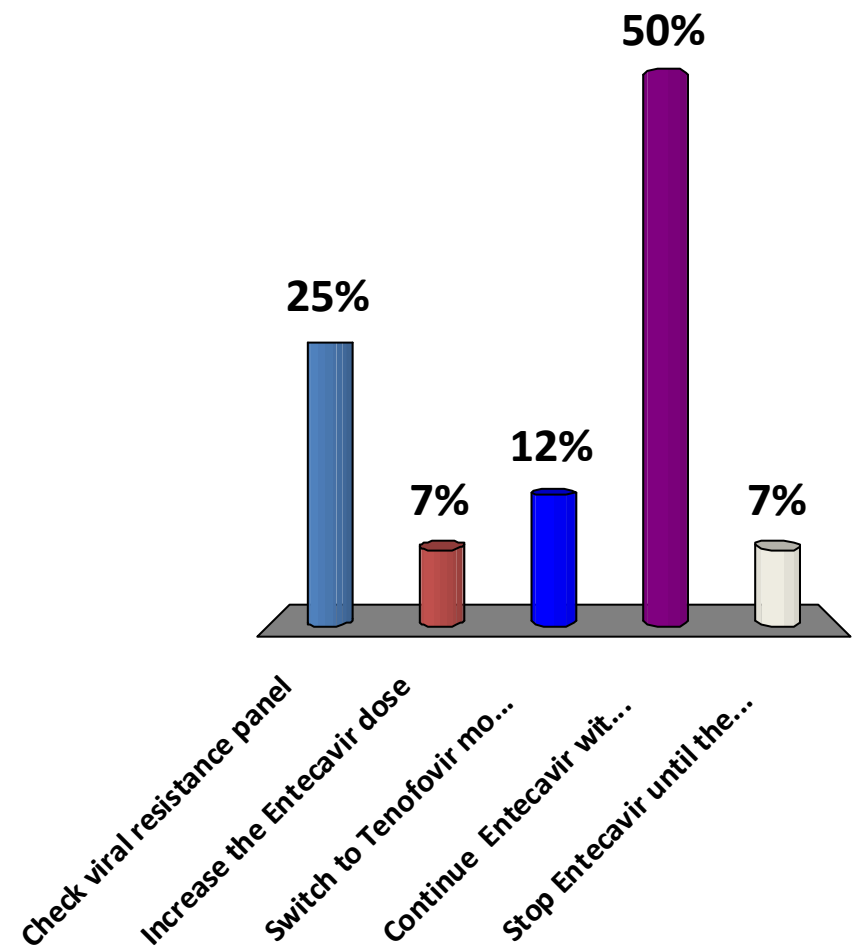
08/09/08 (5 months in treatment)

- ALT 224 IU/L, AST 180
- HBV DNA 2200 IU/mL.

What will you do next?

1. Check viral resistance panel
2. Increase the Entecavir dose
3. Switch to Tenofovir monotherapy
4. Continue Entecavir with more frequent monitoring of HBV DNA and ALT levels for 1-2 months
5. Stop Entecavir until the ALT returns to baseline values

- ALT 224 IU/L, AST 180
- HBV DNA 2200 IU/mL



- We Continued treatment with Entecavir while monitoring HBV DNA levels monthly and ALT levels every 2 weeks until ALT levels normal.

Rates of hepatic flare on therapy

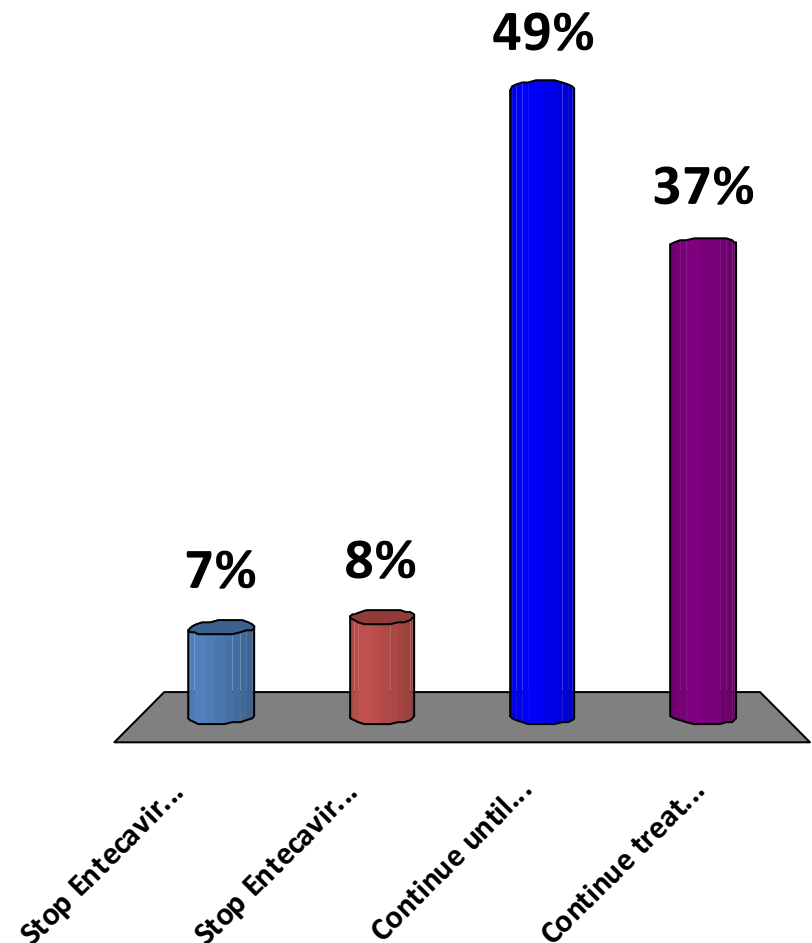
- Pegylated Interferon 8 %
- Entecavir 1 %
- Tenofovir 6 %
- Adefovir 2 %
- Lamuvidine 4 %

	03/07/08	06/11/08	08/09/08	08/22/08	09/11/08	02/24/09
ALT	84	30	224	370	110	22
AST	64	22	140	244	96	28
Bil	0.9	0.8	1.2	0.8	0.8	1.0
INR	1.1	1.2	1.1	1.2	1.0	1.0
HBV DNA	26,000,000 IU/mL	22,600	2000	undetectable	undetectable	undetectable
HBeAg	+	+	+	+	+	-
HBeAb	-	-	-	-	-	-

How long will you continue the Entecavir?

1. Stop Entecavir, check ALT and HBV DNA levels in 3 and 6 months .
2. Stop Entecavir after HBe Ab positive (anti-HBe seroconversion)
3. Continue until 6-12 months after anti-HBe seroconversion
4. Continue treatment until patient loses HBsAg antigen and acquires anti-HBs

HBV DNA –
HBeAg -



04/09/09 (12 months)

- HBeAg -/ anti-HBe Ab+

10/07/09 (18 months)

- HBV DNA levels undetectable, ALT normal range.
- Treatment stopped , HBV DNA and ALT every 3 months.

Case # 2

- 52-year-old Asian M with chronic hepatitis B. He was told to have HBsAg positive 10 years ago, after his mother developed hepatocellular carcinoma (HCC); 1 of his 3 siblings is also HBsAg positive.
- On physical examination no signs of chronic liver disease liver size is normal and spleen not palpable

Lab results 02/06/2004

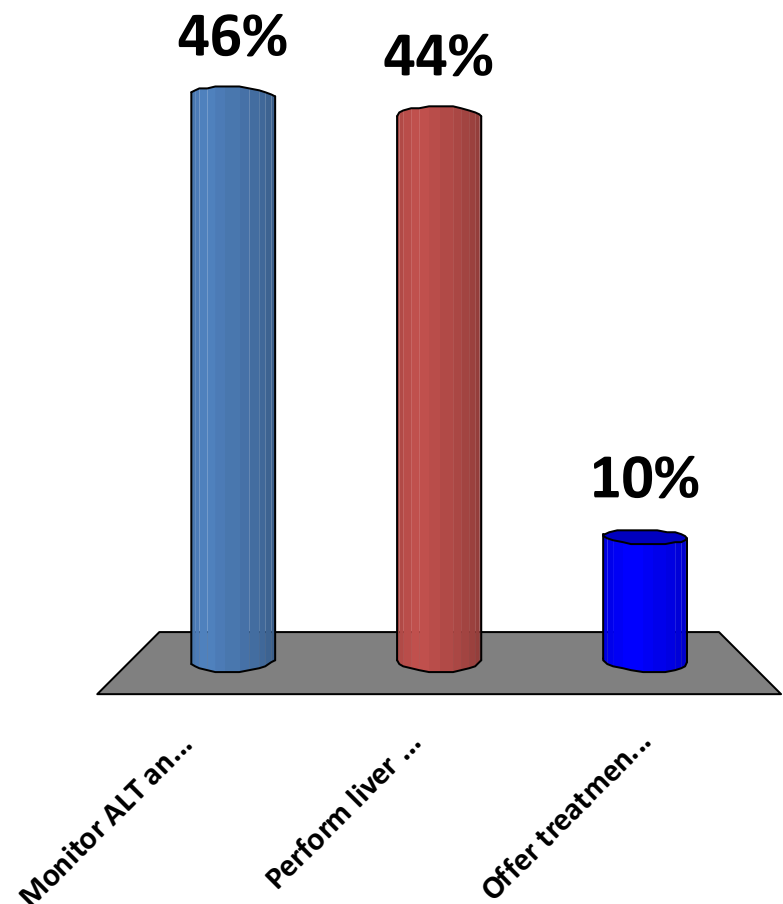
- ALT 34 U/L, AST 26 U/L
- Albumin, 3.7 g/dL
- Total protein, 7.5 g/dL
- Total bilirubin, 0.8 mg/dL
- White blood cell (WBC) count, 4.5 cells/mm³
- Hemoglobin, 14 g/dL
- Platelet count, 1.9 x 10⁵/mm³

- HBeAg negative, BCP mutation detected
- Anti-HBe positive
- HBV DNA level is 1740 IU/mL
- Genotype C
- AFP level is 6.5 ng/mL, creatinine and INR are normal.
- Ultrasound reveals heterogeneous liver architecture and no focal lesions.

What will you do?

1. Monitor ALT and HBV DNA every 6 months
2. Perform liver biopsy
3. Offer treatment

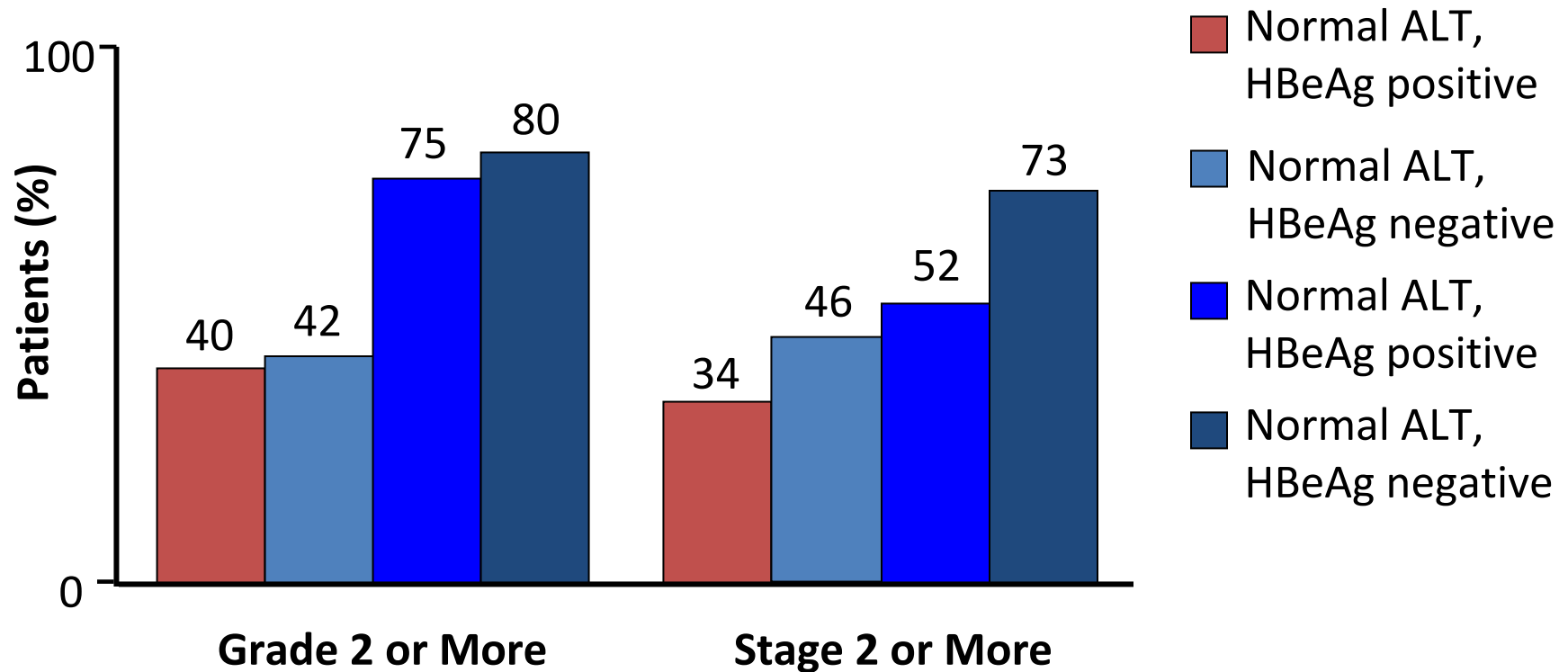
HBeAg-
HBV DNA 1740IU/MI
ALT 34



- Liver biopsy demonstrates grade 2 stage 4 disease

Chronic Hepatitis B Histopathology Occurs with Normal ALT

n= 452 Chinese Patients

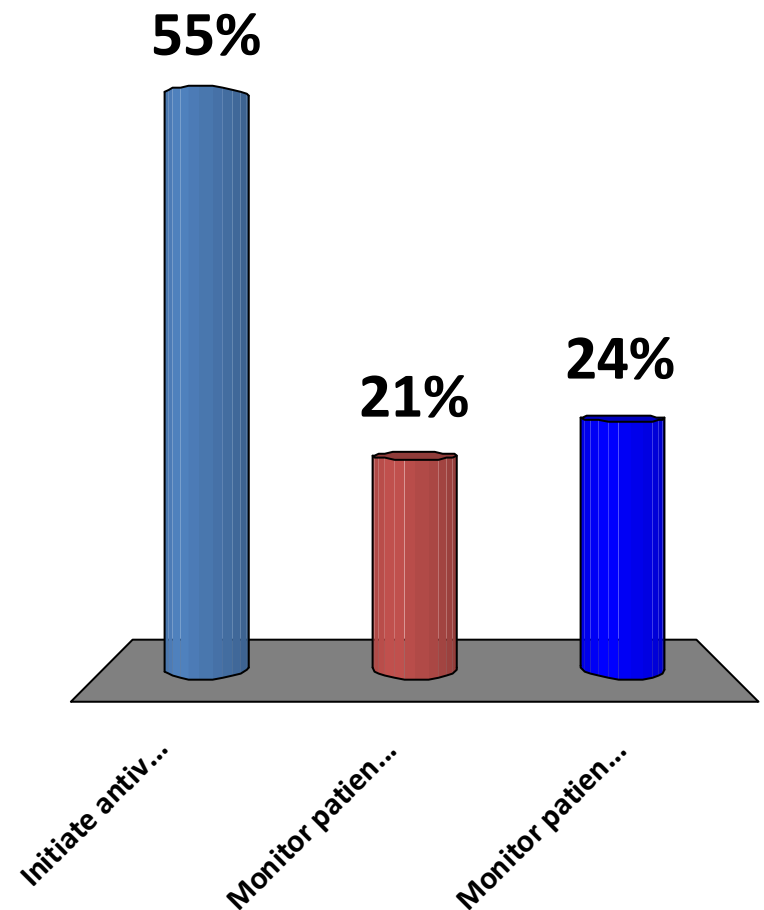


What would you recommend at this time?

1. Initiate antiviral therapy
2. Monitor patient every 3 months, antiviral therapy if HBV DNA levels increase to > 20,000 IU/MI
3. Monitor patient every 3 months, antiviral therapy if HBV DNA > 2000 IU/ML

NOTE: Liver biopsy demonstrates grade 2 stage 4 disease

52 M
HBsAg positive
HBeAg negative
HBV DNA 1740 IU/MI
ALT 34



Recommendations for Treatment Initiation in HBeAg-Negative Patients

	AASLD 2009 ¹	US Algorithm 2008 ²	EASL 2009 ³
HBV DNA, IU/mL	> 20,000 ¹	> 2,000	≥ 2,000
ALT, x ULN ²	1 to > 2	> 1	> 1
Liver biopsy, ³ grade/stage	Moderate/severe necroinflammation and/or significant fibrosis		
First-line therapy	ETV, TDF pegIFN	ETV, TDF, pegIFN	ETV, TDF, pegIFN

¹Consider liver biopsy if > 2,000 IU/mL and treat if significant disease found

²Persistent (> 3-6 months); specified 30 U/L for men and 19 U/L for women in AASLD and US Algorithm

³Biopsy recommended, but not required; best used selectively

Caveat: HBV DNA and ALT levels often intermittently elevated in HBeAg-negative disease.

¹Lok A, et al. *Hepatology*. 2009;50:661-662.

²Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.

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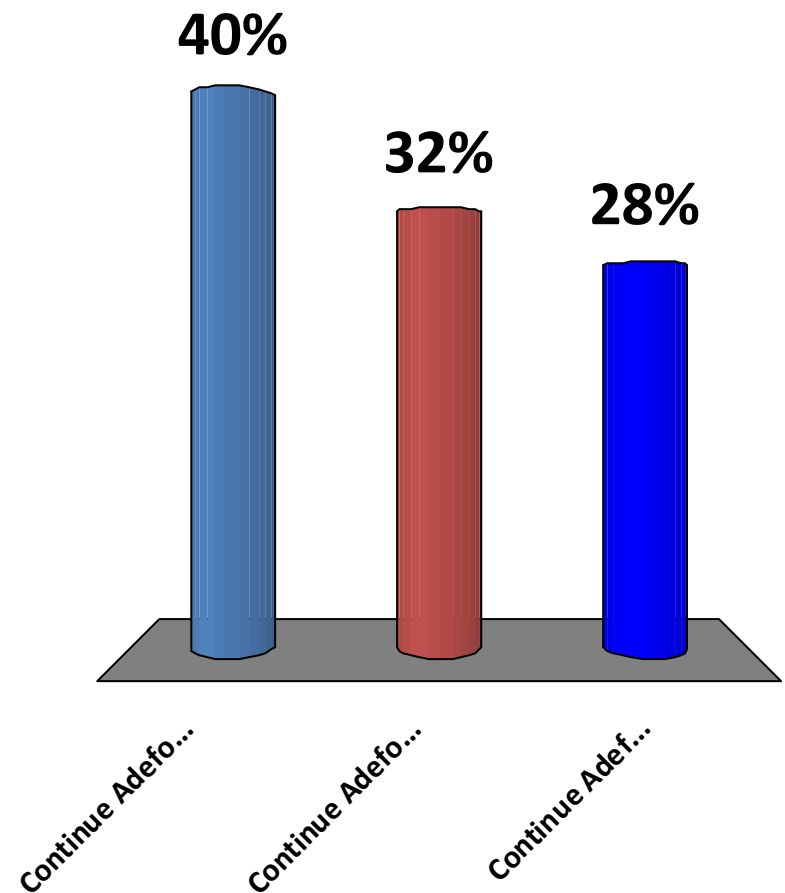
07/2004

- The patient is started on 10 mg of Adefovir
- After 12 weeks, his HBV DNA is undetectable
- ALT is 32 U/L, AST 38 U/L. Bilirubin, albumin, and creatinine levels are all normal.
- The patient continues on 10 mg without adverse effects.
- After 48 weeks of therapy, the patient remains negative for HBV DNA by PCR, and his ALT and AST levels remain normal.

How long will you continue Adefovir for this patient?

1. Continue Adefovir for 6 months after HBV DNA negative
2. Continue Adefovir for 1 year after HBV DNA negative
3. Continue Adefovir indefinitely and monitoring HBV DNA and ALT tests 6 months

48 Weeks of treatment
HBV DNA –
HBeAg -



How long to continue therapy?

- 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

- The patient continues on Adefovir 10 mg daily.
- He remains negative for HBV DNA by PCR after 2 years of treatment.
- ALT and AST levels are normal, HBeAg is negative, anti-HBe is positive, and HBsAg is positive and followed every 6 months

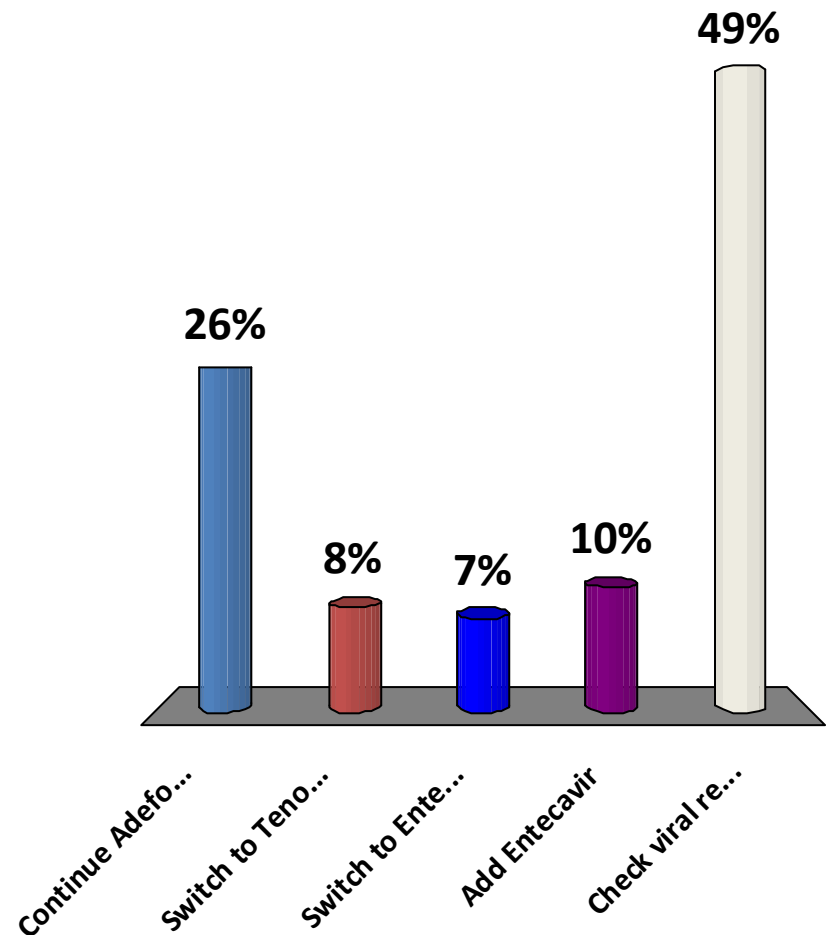
FU in clinic in 06/07/ 2009

- AST/ALT 46/68
- HBV DNA 12006 IU/ml
- Compliance ?

What will you do next?

1. Continue Adefovir and monitor HBV DNA
2. Switch to Tenofovir
3. Switch to Entecavir
4. Add Entecavir
5. Check viral resistance

AST/ALT 46/68
HBV DNA 12006 IU/ml
On Adefovir



- HBV Genotype: B



-
- Antiviral drugs Resistance Mutations



- Polymerase Inhibitors !!

- 3TC (lamivudine or Epivir) NO

- LDT (telbivudine or Tyzeka) NO

- FCV (famciclovir or Famvir) NO

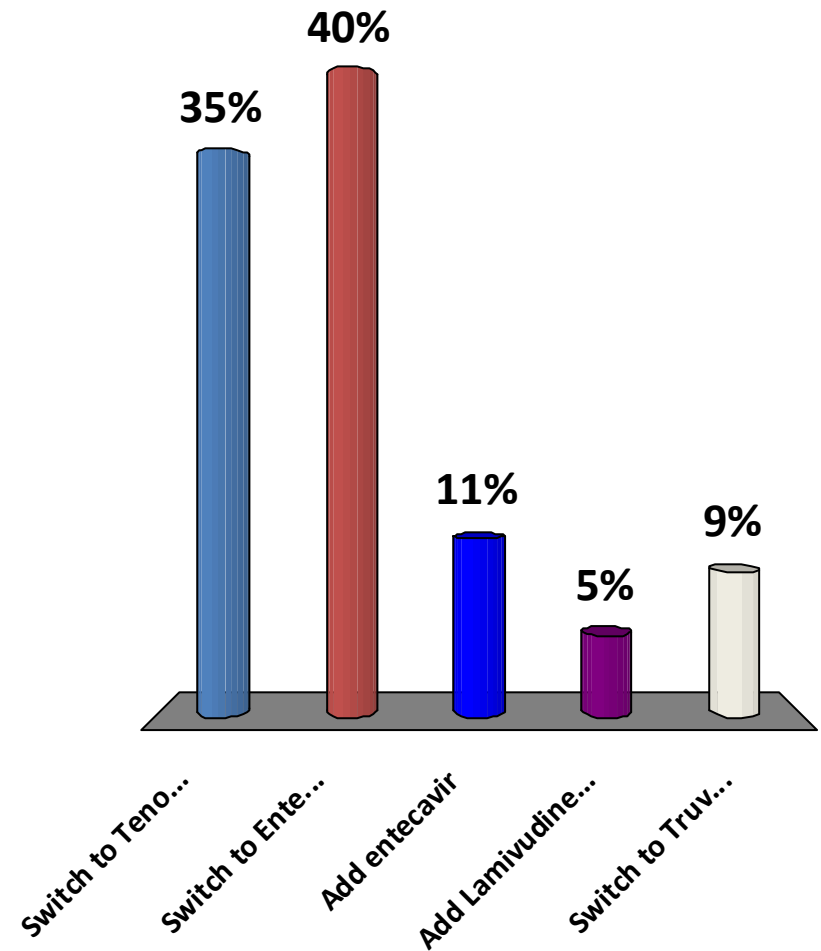
- **ADV (adefovir or Hepsera) YES A181A/V,N236T**

- ETV (entecavir or Baraclude) NO



What treatment do you consider now?

1. Switch to Tenofovir
2. Switch to Entecavir
3. Add entecavir
4. Add Lamivudine or Tebuvidine
5. Switch to Truvada



Tenofovir monotherapy for prior resistance to adefovir

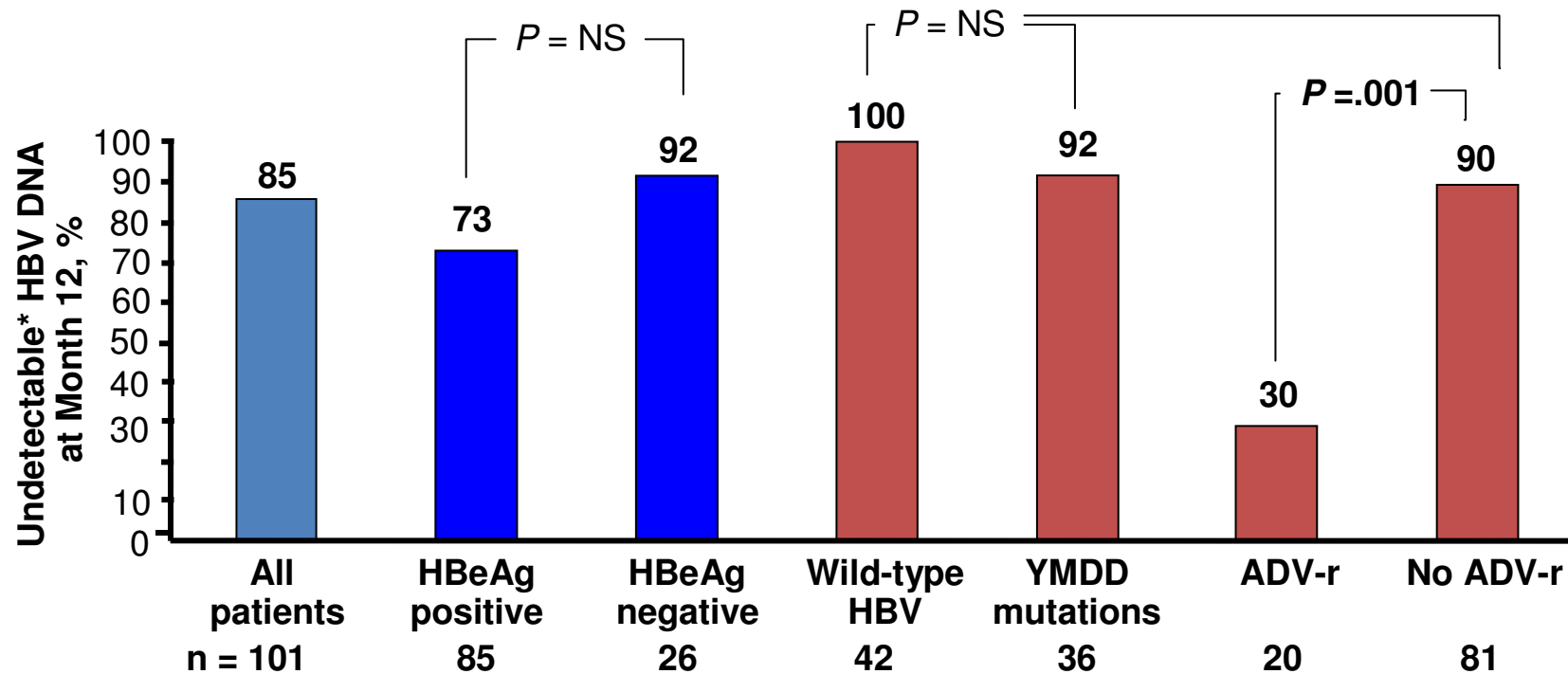
- Virologic response to tenofovir not affected by presence of lamivudine resistance mutations
- But significantly decreased when adefovir resistance mutations present
 - HBV DNA < 400 copies/mL for patients with vs without adefovir resistance

At Mo 12: 33% vs 90%

Overall: 52% vs 100%

TDF in Nucleoside-Experienced Patients

Undetectable* HBV DNA at Month 12



- Virologic breakthrough not observed during follow-up period, independent of presence of ADV resistance at start of TDF

* HBV DNA < 400 copies/mL (< 69 IU/mL)

Case # 3

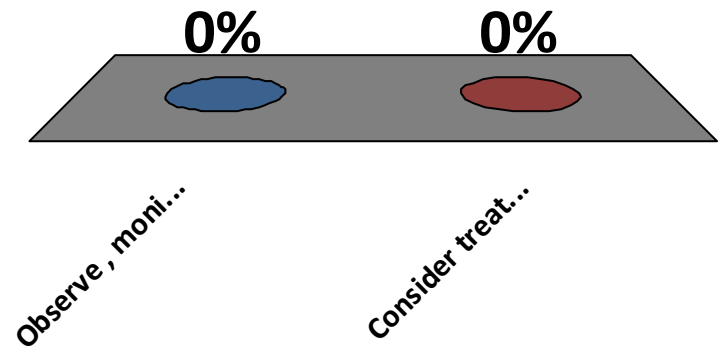
- YC is a 28-year-old Asian American, who is 8 weeks pregnant unremarkable medical history
- HBsAg positive during antenatal exam
- Current medications include daily prenatal vitamins.
- Exam no stigmata of chronic liver disease, and her abdomen appeared normal no hepatosplenomegaly

Laboratory results

- AST/ ALT 16 /19 U/L
- T bilirubin 1.0 mg/dL;
- Albumin, 4.5 g/dL
- Hb 12.3 g/dL PLT 250,000/mL
- HBsAg, positive, HBeAg, positive
- HBV DNA concentration, 2.5×10^6 IU/mL
- Liver US normal

What will you do next?

1. Observe , monitor ALT and HBV DNA
2. Consider treatment

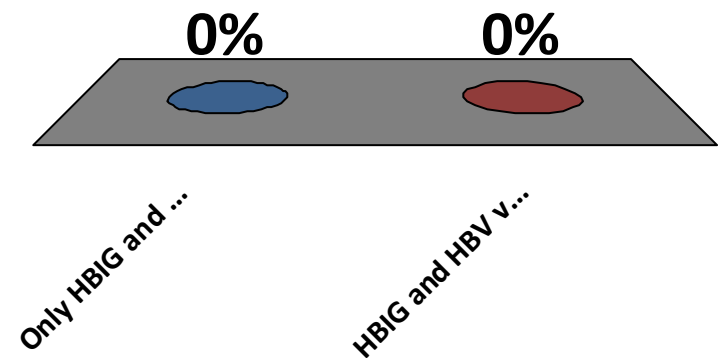


- Patient is monitored and now she is in third trimester of pregnancy. She is asymptomatic
- Laboratory results
 - AST/ ALT 24 /32 U/L
- T bilirubin 1.0 mg/dL;
- Albumin, 3.5 g/dL
- Hb 11.5 g/dL PLT 290,000/mL
- HBsAg, positive, HBeAg, positive
- HBV DNA concentration, 3.2×10^6 IU/mL

- Her obstetrician is concerned about risk of perinatal transmission in HBeAg positive with HBV DNA 3.2×10^6 IU/mL

What do you recommend now?

1. Only HBIG and HBV vaccination at time of birth
2. HBIG and HBV vaccination at time of birth and antiviral treatment now



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

Wedemeyer H, et al. Dtsch Med Wochenschr. 2007;132:1775-1782.
EASL Clinical Practice Guidelines.

Treatment Guidelines for Pregnant Women with Chronic Hepatitis B

- Drug Selection
 - FDA Category B: Telbivudine, Tenofovir
 - FDA Category C: Lamivudine, Entecavir, Adefovir
- Manufacturers maintain pregnancy registries and an international registry exists

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

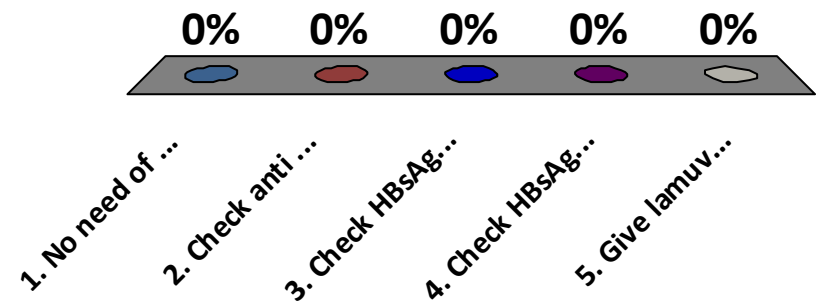
Drugs [package insert].

Case # 4

- 34-year-old Asian Vietnam in US > 30 years, received vaccination at age of 16 years married but no children , mother and one brother HBV
- Recently diagnosed breast cancer, underwent surgical lumpectomy
- Pathology: Tumor Estrogen-and progesterone-receptor negative and spread to regional lymph nodes. recommended treatment with radiation and chemotherapy.
- Prior to chemotherapy consulted for hepatitis B prophylaxis
- AST/ ALT 24 / 26 US Abdomen unremarkable

What will you do next?

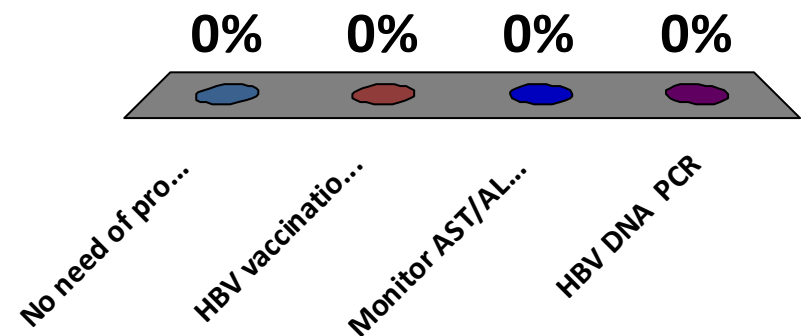
1. No need of prophylaxis
2. Check anti HBsAb level if low vaccinate
3. Check HBsAg
4. Check HBsAg, anti HBsAb , antiHBc ,
5. Give lamuvidine prior to chemotherapy



HBsAg negative and HBsAb negative
Anti Hbc positive

What do you want to do next?

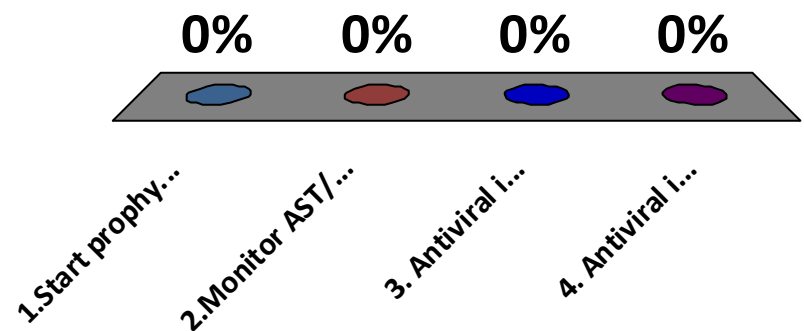
1. No need of prophylaxis
2. HBV vaccination booster/No need of prophylaxis
3. Monitor AST/ALT
4. HBV DNA PCR



- HBV DNA > 256 IU/ML (1286 copies/ml)

What will you do next?

1. Start prophylaxis
2. Monitor AST/ALT & HBV DNA
3. Antiviral if increase in HBV DNA >2000 IU/ML
4. Antiviral if increase in AST/ALT > 2 ULN and HBV DNA > 2000 IU/ML



Reactivation of HBV

Effect of Chemotherapy

- Reactivation of HBV reported in 20% to 50% of HBsAg+ patients and 3-5 % HBsAg - undergoing cytotoxic chemotherapy
- Clinical Features
 - May be asymptomatic
 - Icteric flares, hepatic decompensation and death have been reported
- Prophylactic antiviral therapy recommended
 - Initiate at time of chemotherapy induction
 - Maintain for 3-6 months post-chemotherapy

Risk of a chemotherapy-related hepatitis flare.

- The 2009 AASLD guidelines recommend prophylactic therapy for patients who have HBsAg-positive disease and are preparing to undergo chemotherapy.
- With the introduction of new nucleos(t)ide analogues that have received U.S. Food and Drug Administration (FDA) approval, clinicians now have several antiviral treatment options.

	Correct response	
Slide number 4	2	
Slide number 8	3/4	
Slide number 13	4	
Slide number 17	3	
Slide number 22	2	
Slide number 25	1	
Slide number 28	3	
Slide number 31	5	
Slide number 33	3/5	
Slide number 38	For discussion	
Slide number 40	For discussion	
Slide number 45	4	
Slide number 47	4	
Slide number 48	1	