Chronische Hepatitis B

Wie, wanneer en met wat behandelen ?

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Patient 1

- Caucasian heterosexual Male, 45 years, has been on and off living and working in Thailand. He presents with jaundice 4 weeks after a 4-weeks holiday in Thailand.

- Family physician and Public Health service:
- HBsAg (+) AST 200 IU/l ALT 350 IU/l
- Bilirubin 65 umol/l; INR ratio 1,1

Patient 1 Question

- Is this HBV infection acquired during his recent holiday in Thailand ?

- Yes ---- green
- No ----- red

Staging and grading

- IgM anti HBc negative
- HBeAg positive; HBV DNA 10^e8 IU/ml

- Anti-Delta: negative; anti-HCV: negative
- Anti-HIV: negative
- Lues serology: negative
- IgG HAV:positive; IgM/IgG HEV:negative

Staging and grading

- Liver ultrasound: irregular surface, features of cirrhosis
- Fibroscan: F3-F4 fibrosis
- Indication for a liver biopsy ?

Treatment - indication ?

- timing ?

- contraindications

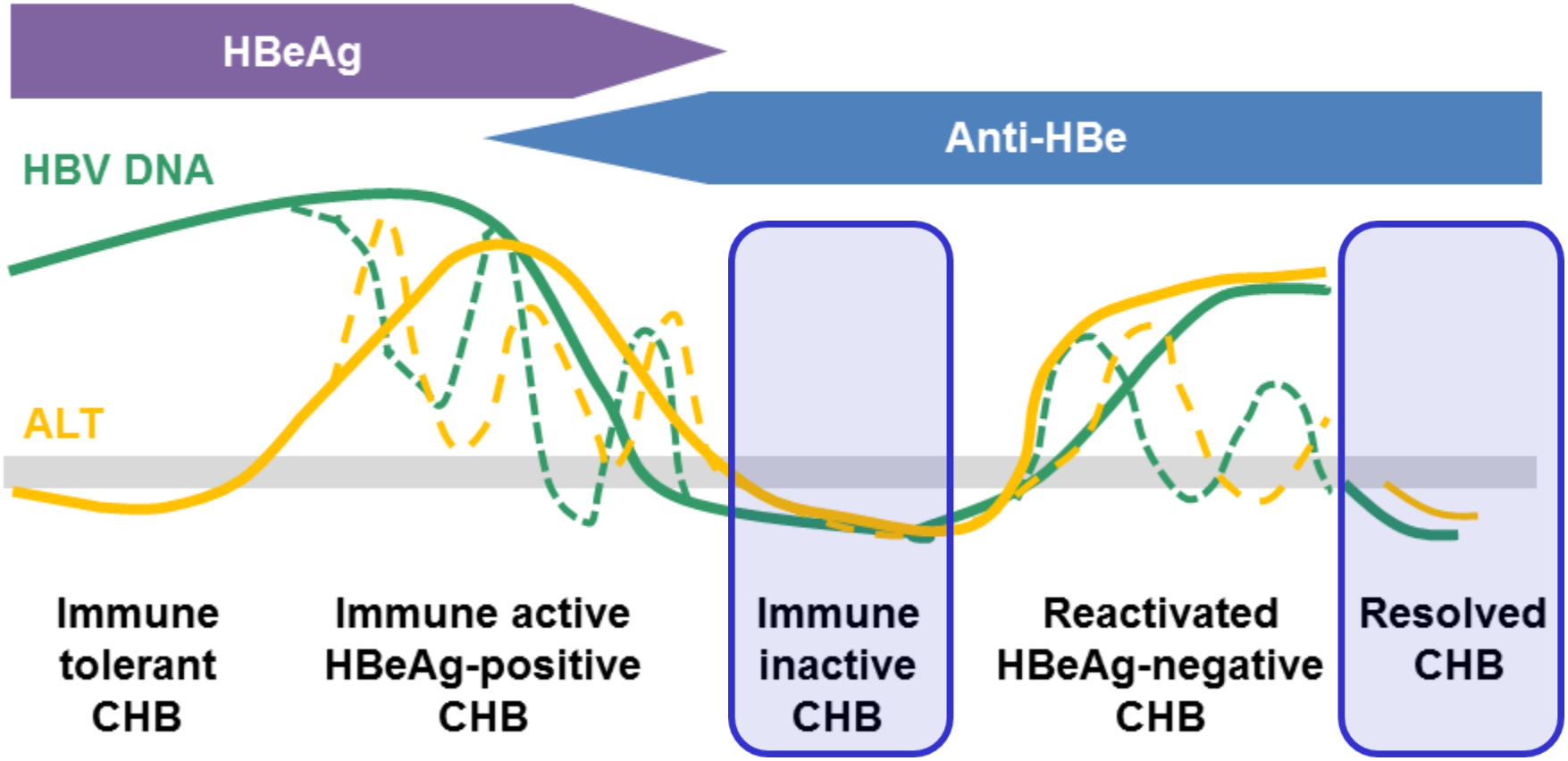
Staging and grading

- Liver biopsy chronic HBV, signs of recent exacerbation with liver tissue collapse.
- Fibrosis F3-F4
- No other aetiology suspected

- HBV viral genotype G

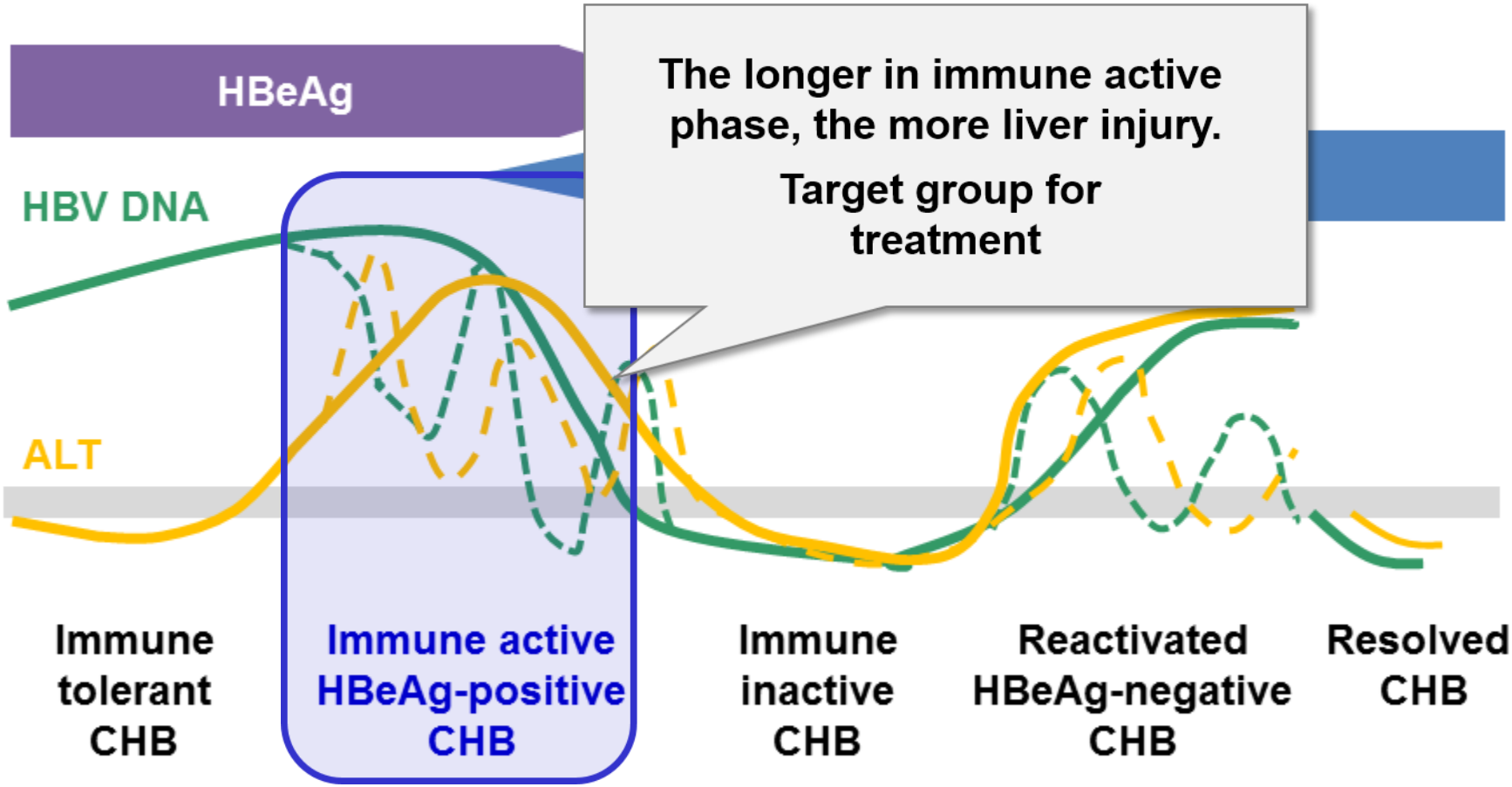
Phases of Chronic Hepatitis B (CHB)

Inactive or Resolved Disease is What is Desired



Lok AS, et al. *Arch Intern Med.* 2006;166:9.

HBeAg-Positive "Active" Chronic Hepatitis B (CHB)



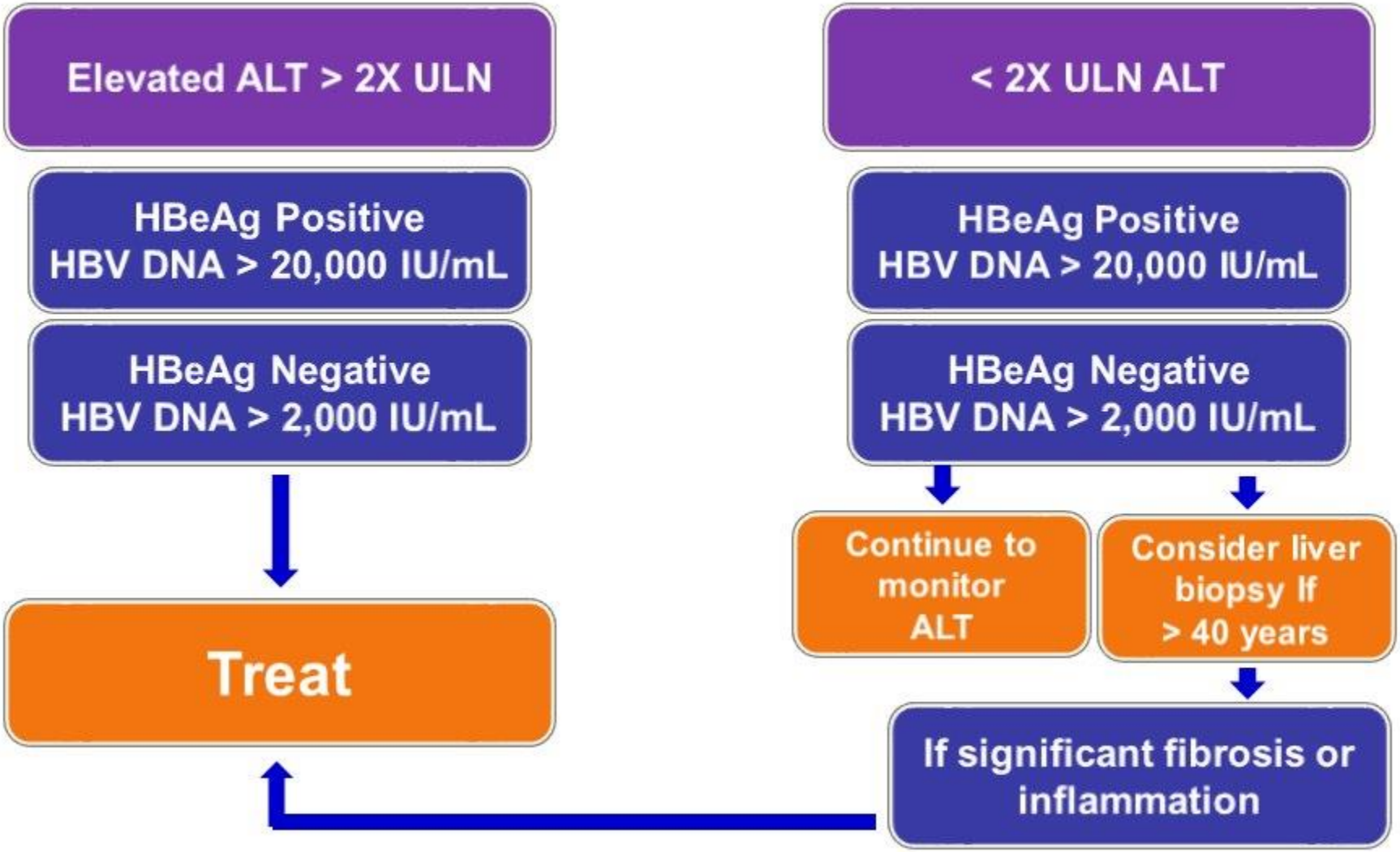
Lok AS, et al. *Arch Intern Med.* 2006;166:9.

Treatment goals HBV

1. **Sustained suppression of HBV replication**
   - *Decrease in serum HBV DNA to < 2.10^5 IU/ml*
   - *HBeAg to anti-HBe seroconversion*
   - *HBsAg to anti-HBs seroconversion*
2. **Remission of liver disease**
   - *Normalization of serum ALT levels*
   - *Decreased necroinflammation in liver*
3. **Improvement in clinical outcome**
   - *Decreased risks of developing cirrhosis*
   - *Regression of cirrhosis*
   - *Decreased risk of liver failure and HCC*
   - *Increased survival*

Identifying Treatment Candidates

Algorithm to Identify Treatment Candidates



ULN= upper limit of normal

Adapted from AASLD Practice Guidelines.

What is "Significant Fibrosis and Inflammation"?

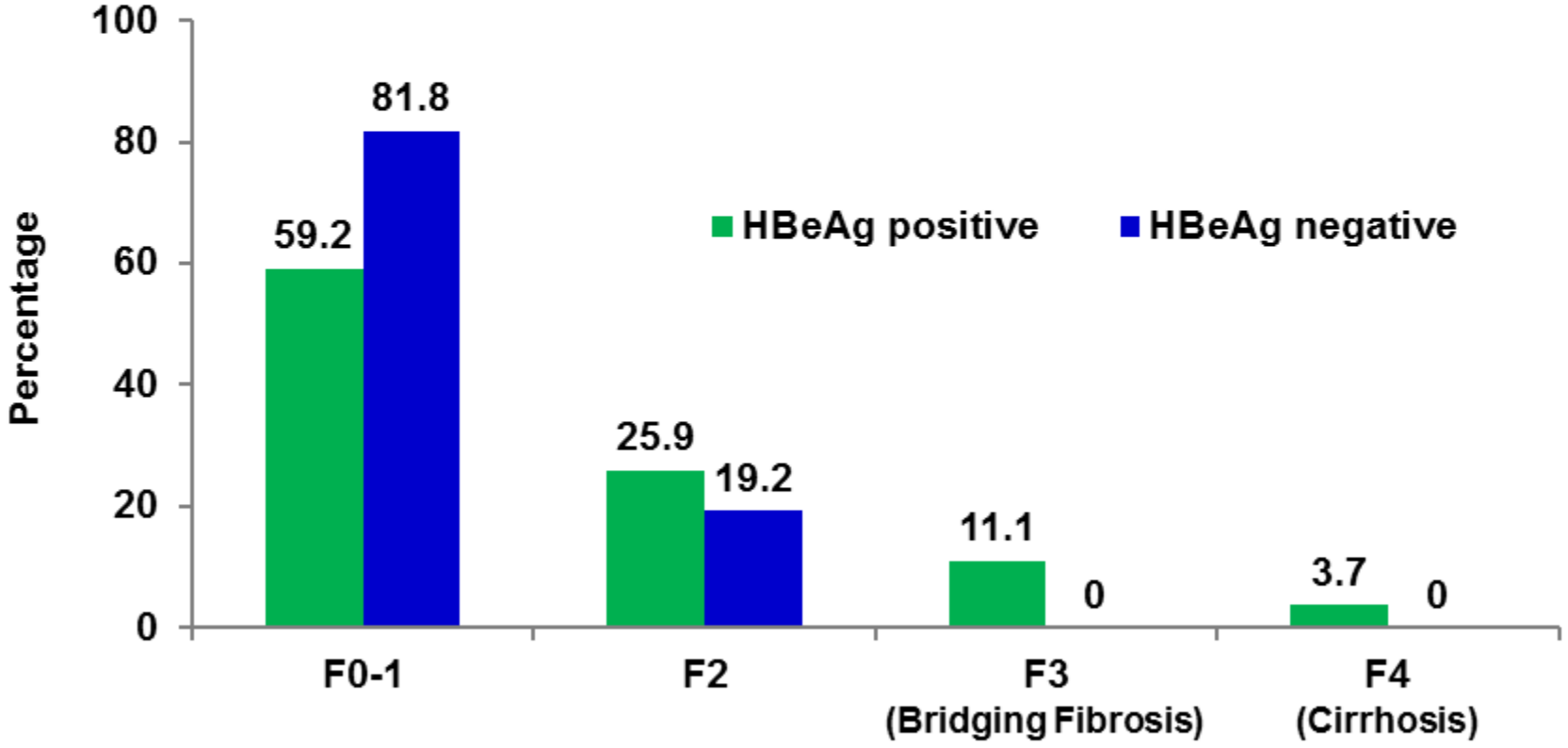
- Significant fibrosis = score of 2 or higher (scale of 4)
  - Fibrosis stage can be determined by liver biopsy or noninvasive assessment (serological tests, liver stiffness measurements)
  - Noninvasive tests (eg, APRI) have best accuracy for minimal (F0) and advanced fibrosis (F3-4)

- Significant necroinflammatory activity = moderate to severe = score of 2 or higher (scale of 4)
  - Necroinflammatory activity can only be determined by liver biopsy

AASLD Practice Guidelines.

Patients With Normal ALT May Have Significant Fibrosis

- 189 HBsAg positive patients with **persistently normal** ALT ≥ 1-yr f/u*



*≥ 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.

Importance of Identifying Patients With HBV Cirrhosis

- **Warrant surveillance for complications of cirrhosis**
  - Varices
  - Hepatocellular carcinoma
- **Treatment guidelines differ**
  - Urgency of treatment
  - Duration of therapy
  - Use of peg-interferon versus nucleoside analogues

Interferon or Nucleos/tide Analogues?

Treatment	Interferon	Nucleos/tide Analogues
Route	Subcutaneous injection	Oral
Duration of treatment	Finite duration, ~ 12 months	Long duration, years to life
Antiviral activity	Modest, additional immunomodulatory effects	Stronger antiviral activity
HBsAg loss	1-3% after 1 year	Rare, 0-1% after 1 year
Resistance mutations	None	0-25% after 1 year
Side effects	Frequent	Rare

Lok ASF, McMahon BJ. *Hepatology*. 2007; 45: 507–539.
Lok ASF, McMahon BJ. *Hepatology*. 2009; 50: 661–662.

Safety and Efficacy of Nucleos/tide Analogues

	LMV	ADV	ETV	TBV	TDF
Antiviral activity	++	+	+++	+++	+++
Safety	+++	++	+++	++	++
Rate of antiviral resistance	High	Intermediate	Low*	High	Low

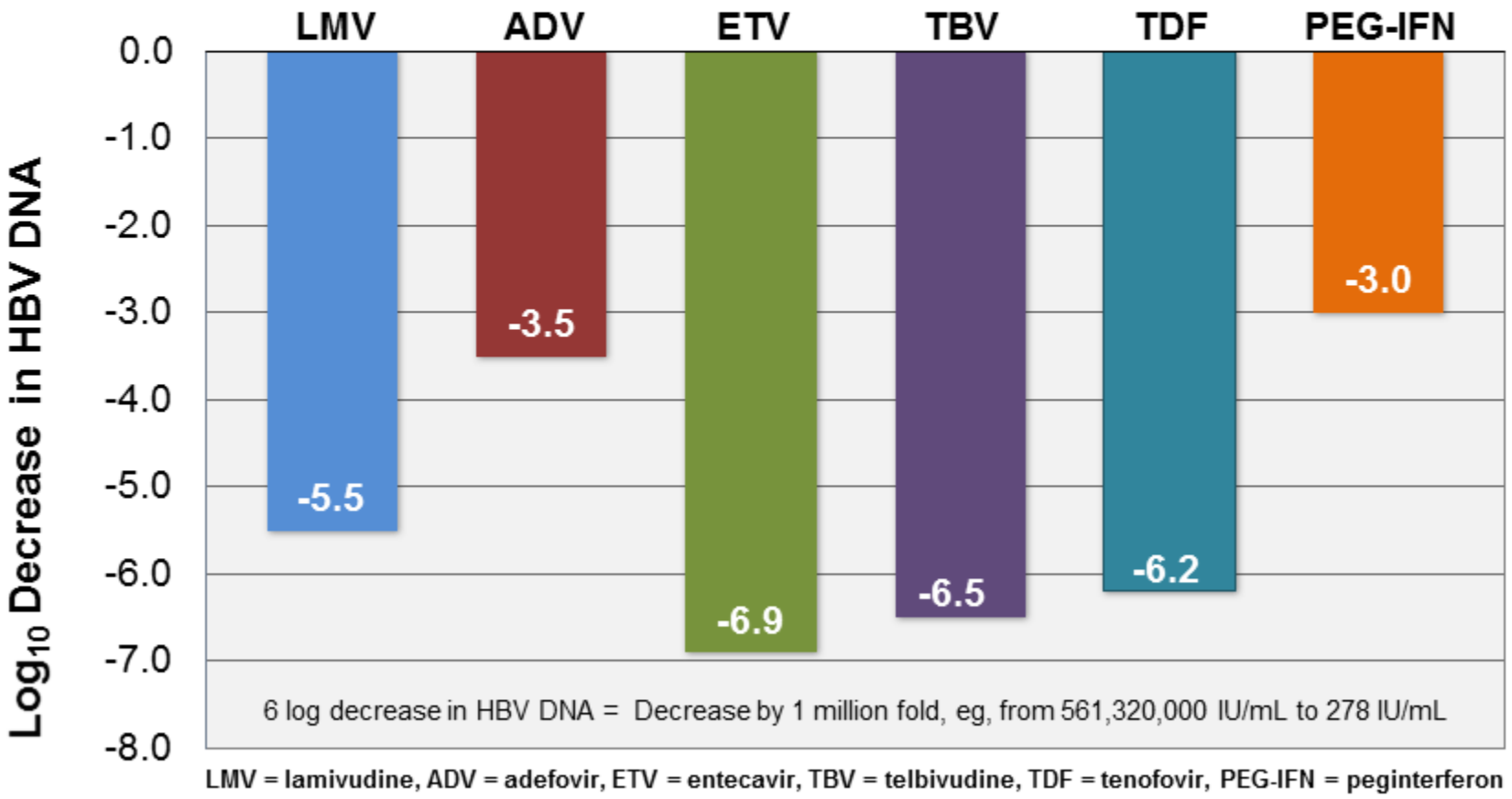
LMV = lamivudine, ADV = adefovir, ETV = entecavir, TBV= telbivudine, TDF = tenofovir

*Rate of resistance higher in patients who have prior lamivudine resistance

Antiviral activity and safety graded + to +++ with +++ indicating more potent antiviral activity / better safety profile

Scaglione SJ, Lok AS. *Gastro.* 2012; 142: 1360-1368.

Decrease in Serum HBV DNA After 1-Year of Treatment in HBeAg+ or HBeAg- Patients With Chronic Hepatitis B



LMV = lamivudine, ADV = adefovir, ETV = entecavir, TBV = telbivudine, TDF = tenofovir, PEG-IFN = peginterferon

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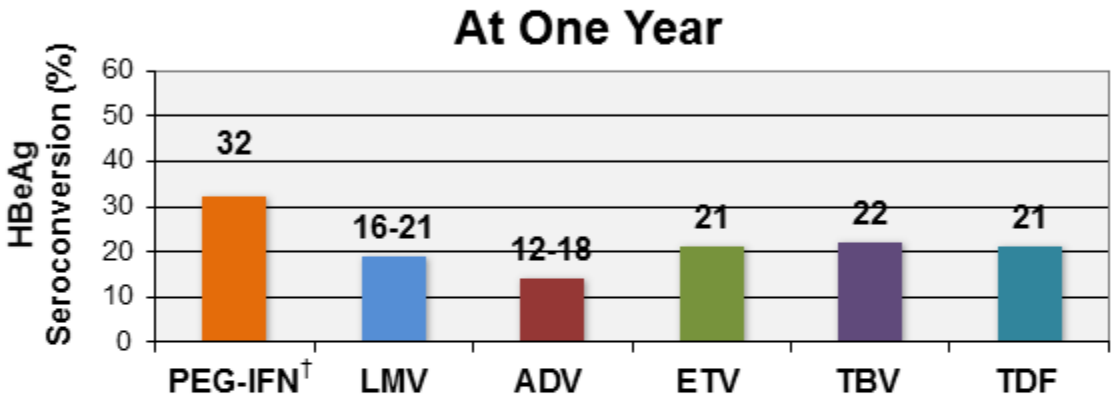
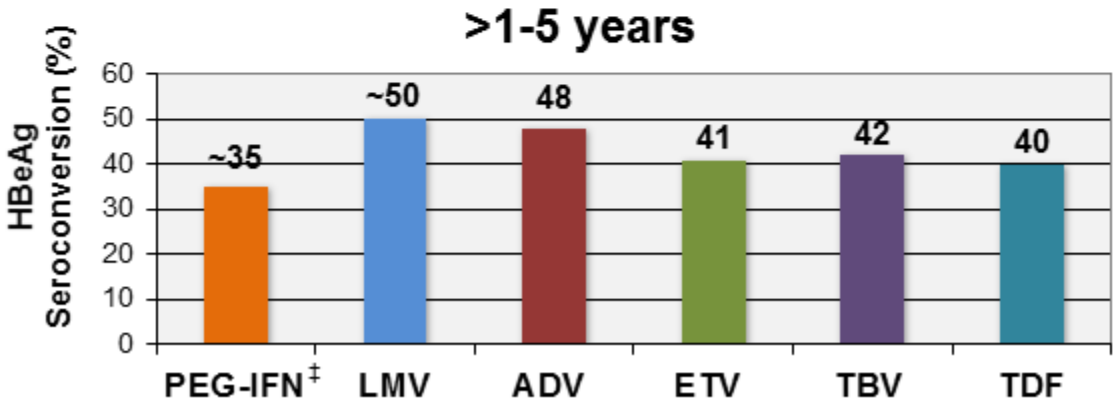
HBeAg Seroconversion After 1 to 5 Years of Treatment





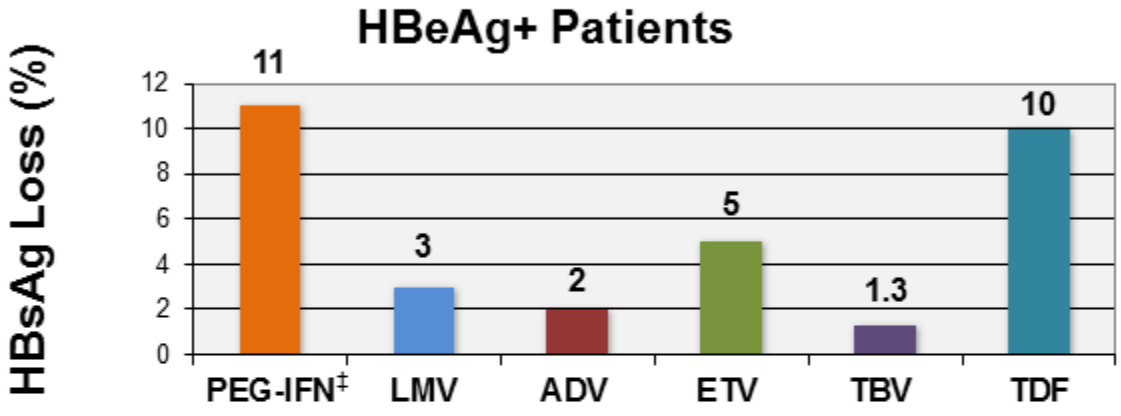
PEG-IFN = peginterferon
LMV = lamivudine
ADV = adefovir
ETV = entecavir
TBV = telbivudine
TDF = tenofovir

Response of Peg-IFN assessed after treatment
† = 6 months off Rx
‡ = 3 years off Rx

Response of nucleos/tide analogue assessed on treatment

Scaglione SJ, Lok AS. *Gastro.* 2012; 142: 1360-1368.

HBsAg Loss After 2 to 5 Years of Treatment



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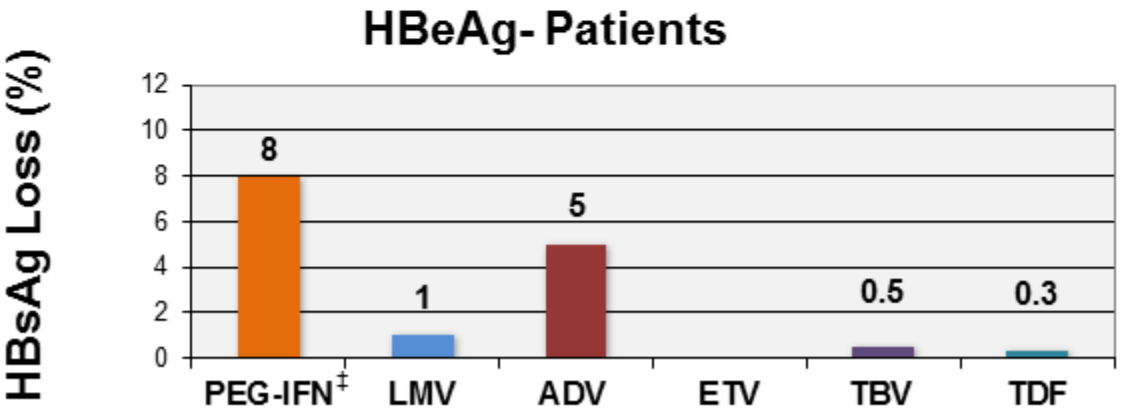


Response of IFN assessed after treatment
‡ = 3 years off Rx

Response of nucleos/tide analogue assessed on treatment

Scaglione SJ, Lok AS. *Gastro.* 2012; 142: 1360-1368.

How Efficacious Are Currently Available HBV Therapies?

- Potent viral suppression but not eradication
- Low rate of HBsAg loss
- Reverse hepatic fibrosis and even cirrhosis
- Prevent progression to liver failure and to a smaller extent HCC

Current treatment controls but does NOT cure HBV

Treatment of Hepatitis D (HDV)

- **Whom to treat?**
  - Patients with chronic hepatitis D and moderate or severe inflammation or fibrosis

- **Which drugs?**
  - Peginterferon
  - None of the nucleos/tide analogues has been shown to be effective
  - Addition of nucleos/tide analogues to interferon does not improve response

Rizzetto M. *Hepatology*. 2009; 50: 1043–105.

Patient 2

- Chinese heterosexual male, 35 years, works as a cook. He presents because of a source and contact tracing. No complaints, large familiy; two family members died of HCC.

- Family physician and Public Health service:
- HBsAg (+) AST 20 IU/l ALT 30 IU/l
- Bilirubin 15 umol/l

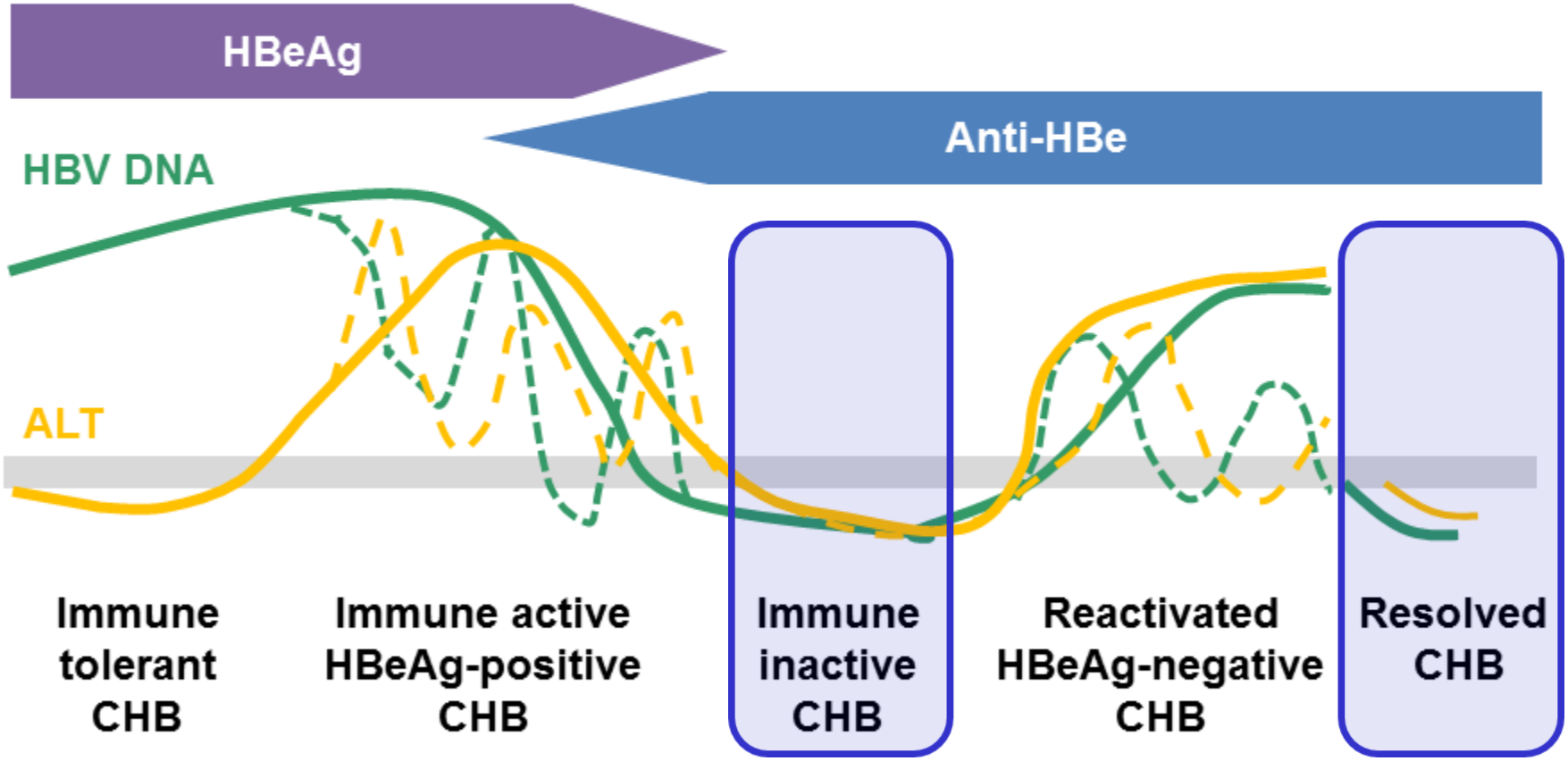
Patient 2

- Virology HBsAg positive, HBeAg (+), HBV DNA $10^{e}9$ IU/ml, genotype A, anti-HDV negative

- Ultrasound normal.
- Fibroscan F0

Phases of Chronic Hepatitis B (CHB)

Inactive or Resolved Disease is What is Desired



Lok AS, et al. *Arch Intern Med.* 2006;166:9.

Should we treat patient 2 ?

- Green: yes, treat him with antiviral therapy

- Red: no indication for treatment with antiviral therapy

Should Patients in Immune Tolerant Phase be Treated?

NO except in

- Pregnant women to reduce mother-to-child transmission
- Patients who need to be on immunosuppressive therapy
- Patients who are >40 years old
- Patients with family history of HCC

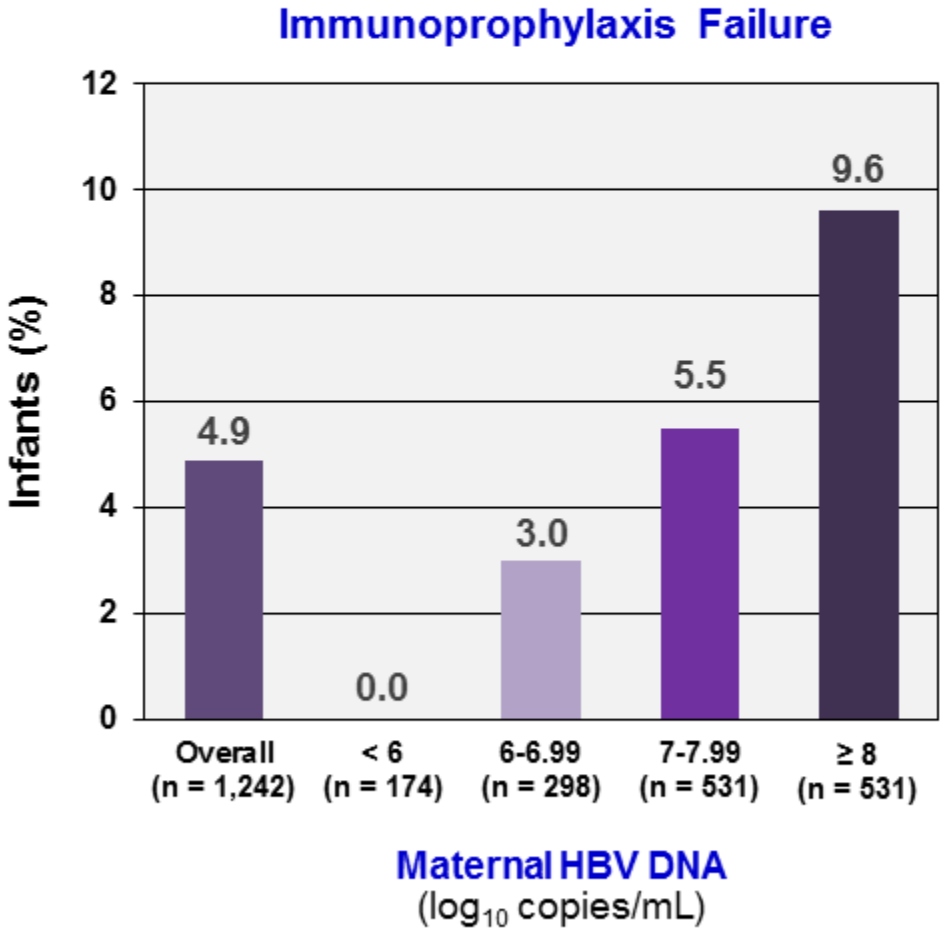
Management of the Pregnant Patient with HBV

- All pregnant women should be tested for HBsAg
- Infants born to mothers who are HBsAg-positive should receive both HBIG and hepatitis B vaccine < 12 hours after birth, with subsequent vaccination at 1 and 3 or 6 months
  - > 90% of children will then be immune to HBV
  - HBIG may need to be ordered ahead of time
- Vaccine failure associated with:
  - Inadequate therapy
  - Infants of mothers with high HBV DNA (>1 million IU/mL)

Lok, 2007.
van Zonneveld, 2003
Han World J Gastro 2011; Zhang Hep 2014 in press

Maternal HBV Viral Levels Correlate Directly with Immunoprophylaxis Failure in Infants

- N = 1,242 pregnant women
- Immunoprophylaxis failure rate
  - Overall: 4.9%
- Independent risk factor for vertical transmission of HBeAg positive mothers
  - Maternal HBV DNA levels



Han G, et al. *Hepatology*. 2011;54(suppl):444A. Abstract 170.

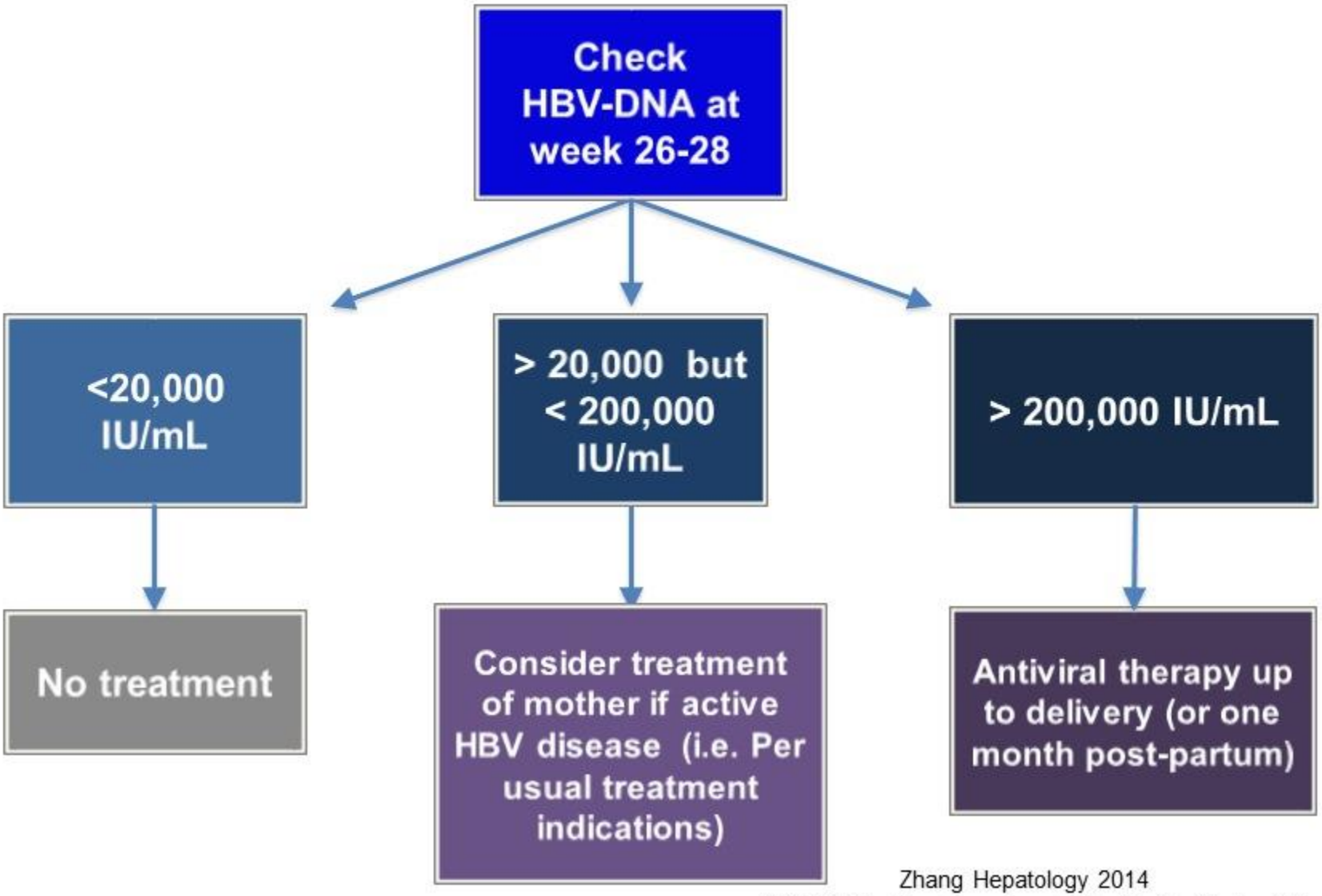
Safety and Efficacy of HBV Antivirals Used in Third Trimester to Prevent Mother-to-Child Transmission of HBV

Antiviral	Pregnancy class	Drug resistance	Risk of birth defects	Median infection rate, treatment vs. controls
Lamivudine	C	+++	Not increase APR, n>4000	11 studies, n=1693 3% vs. 16%
Telbivudine	B	++	Not increase APR, N<50 Observational studies, n>800	4 studies, n=813 0% vs. 8%
Tenofovir	B	None reported	Not increase APR, n>2000 Minimal effects on bone growth	4 studies, n=125 0% vs. 5%

APR = antiretroviral pregnancy registry

Adapted from Sarkar M, Hepatology 2014; 60: 448

Treatment of HBV in Pregnancy



Zhang Hepatology 2014

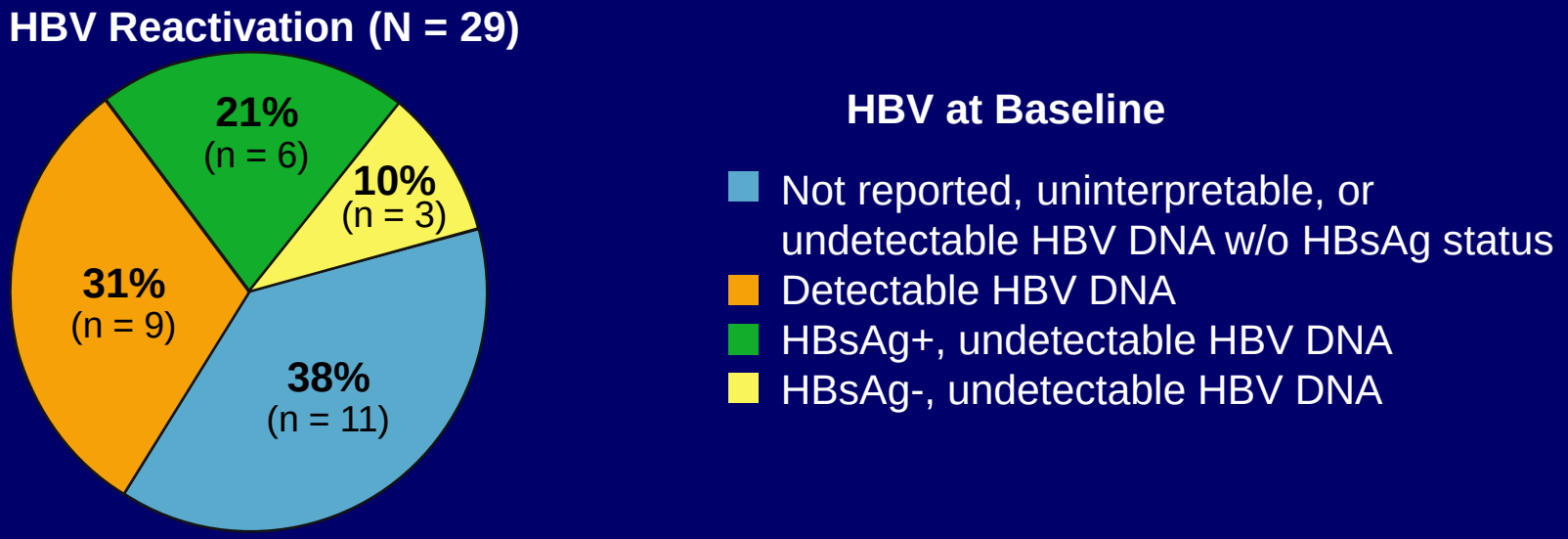
HBV Prophylaxis for Patients Receiving Immunosuppressive Therapy

- Candidates
  - HBsAg+[1-6]
  - HBsAg-/anti-HBc+ ***if***
    - Receiving therapy associated with high HBV reactivation risk (AGA,[5] ASCO[6]*)
    - Detectable HBV DNA (EASL,[2] APASL[3], AASLD[4])
- Timing of initiation[1-6]
  - At or before onset of immunosuppressive therapy

1. Weinbaum CM, et al. MMWR Recomm Rep. 2008:57:1-20. 2. EASL. J Hepatol. 2012;57:167-185. 3. Sarin SK, et al. Hepatol Int. 2016;10:1-98. 4. Lok AS, et al. Hepatology. 2009;50:1-36. 5. Reddy KR, et al. Gastroenterology. 2015;148:215-219. 6. Hwang JP, et al. J Clin Oncol. 2015;33:2212-2220.

HBV Reactivation in Pts Receiving DAAs: Postmarketing Cases Reported to FDA

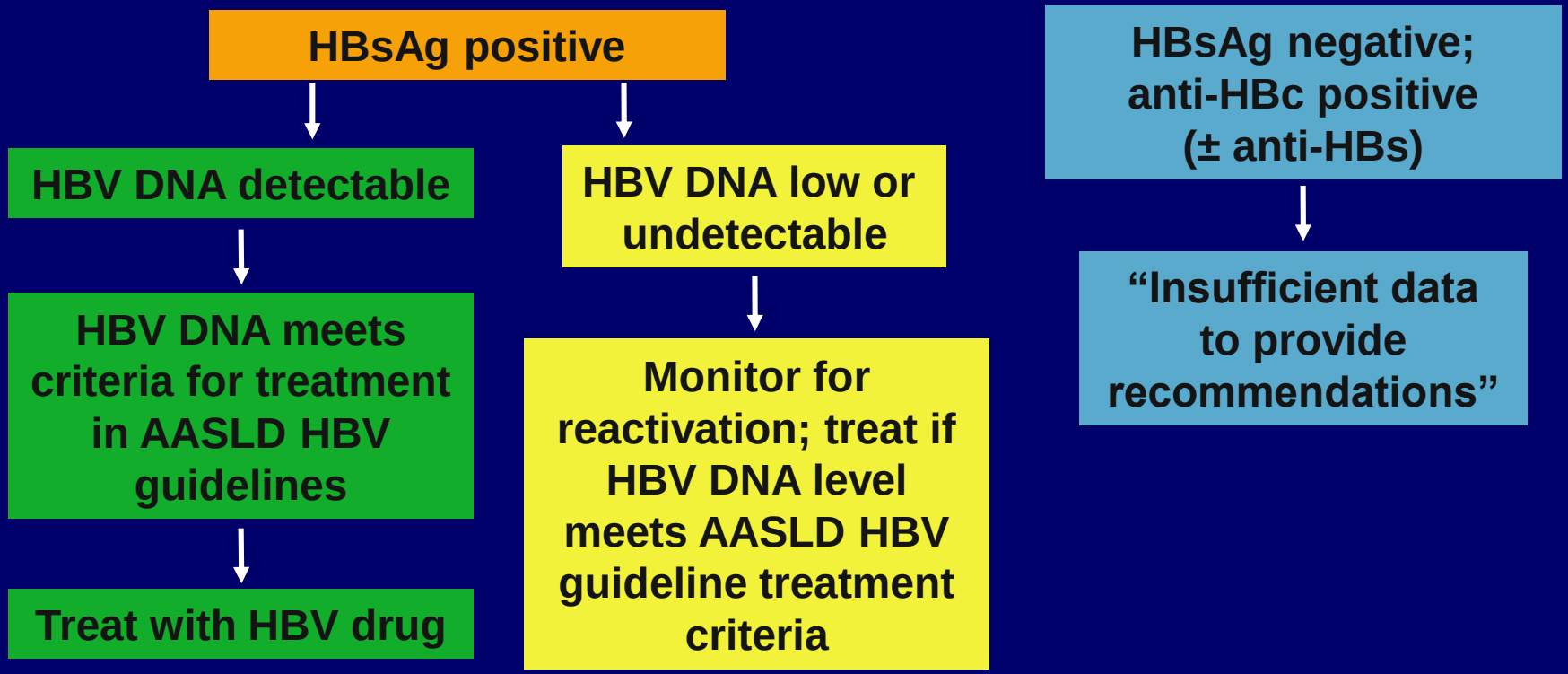
- 29 confirmed cases in ~ 3 yrs (november 2013 to october 2016)
  - pts from japan (n = 19), us (n = 5), other (n = 5)
  - most cases occurred within 4-8 wks of initiation
  - 2 deaths, 1 transplant, 6 hospitalizations, 10 daa discontinuations



Bersoff-Matcha SJ, et al. AASLD 2016. Abstract LB17.

HBV Testing and Monitoring During HCV DAA Therapy: AASLD/IDSA Guidance

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - No HBV markers: VACCINATE (this is not new)
  - HBV markers present:



AASLD/IDSA. HCV guidance. September 2016.

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HBV Guidelines

- EASL App iLiver (Android and Apple)

J Hepatol 2012;57:167-85.

- AASLD Practive Guideline HBV
  www.AASLD.org

Hepatology 2016;63;1:261-283.

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