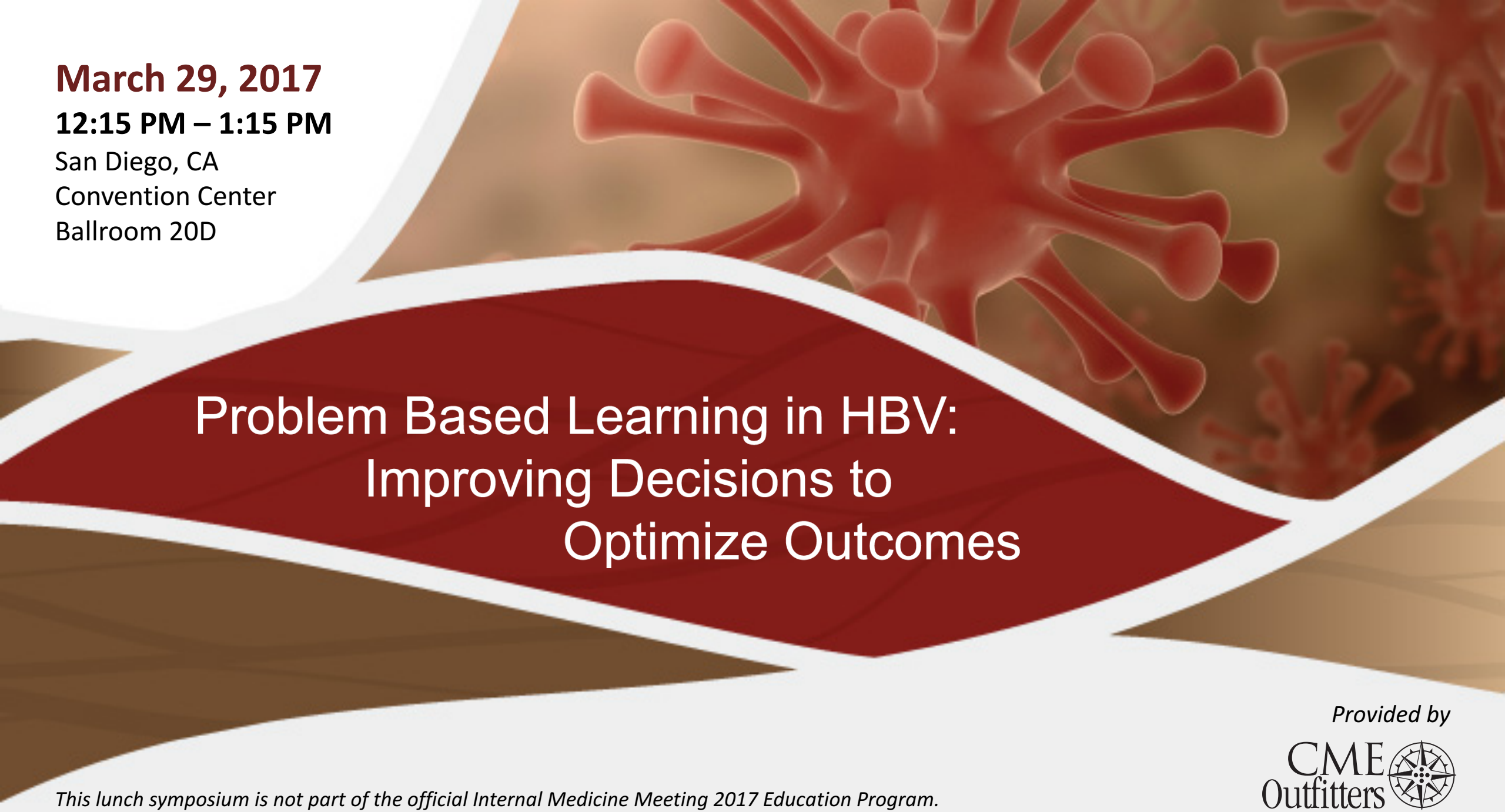
March 29, 2017

12:15 PM – 1:15 PM

San Diego, CA
Convention Center
Ballroom 20D

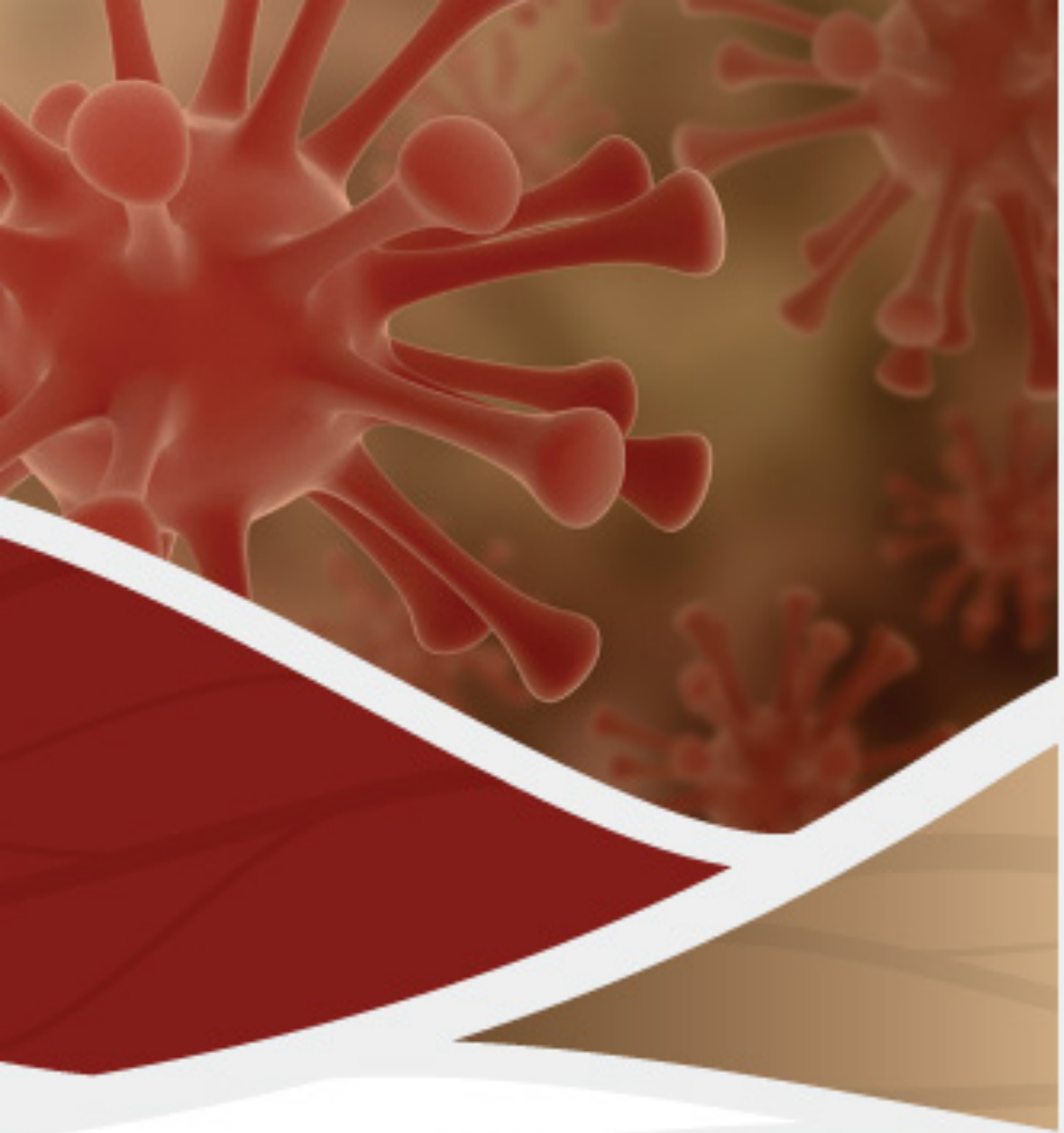


Problem Based Learning in HBV: Improving Decisions to Optimize Outcomes

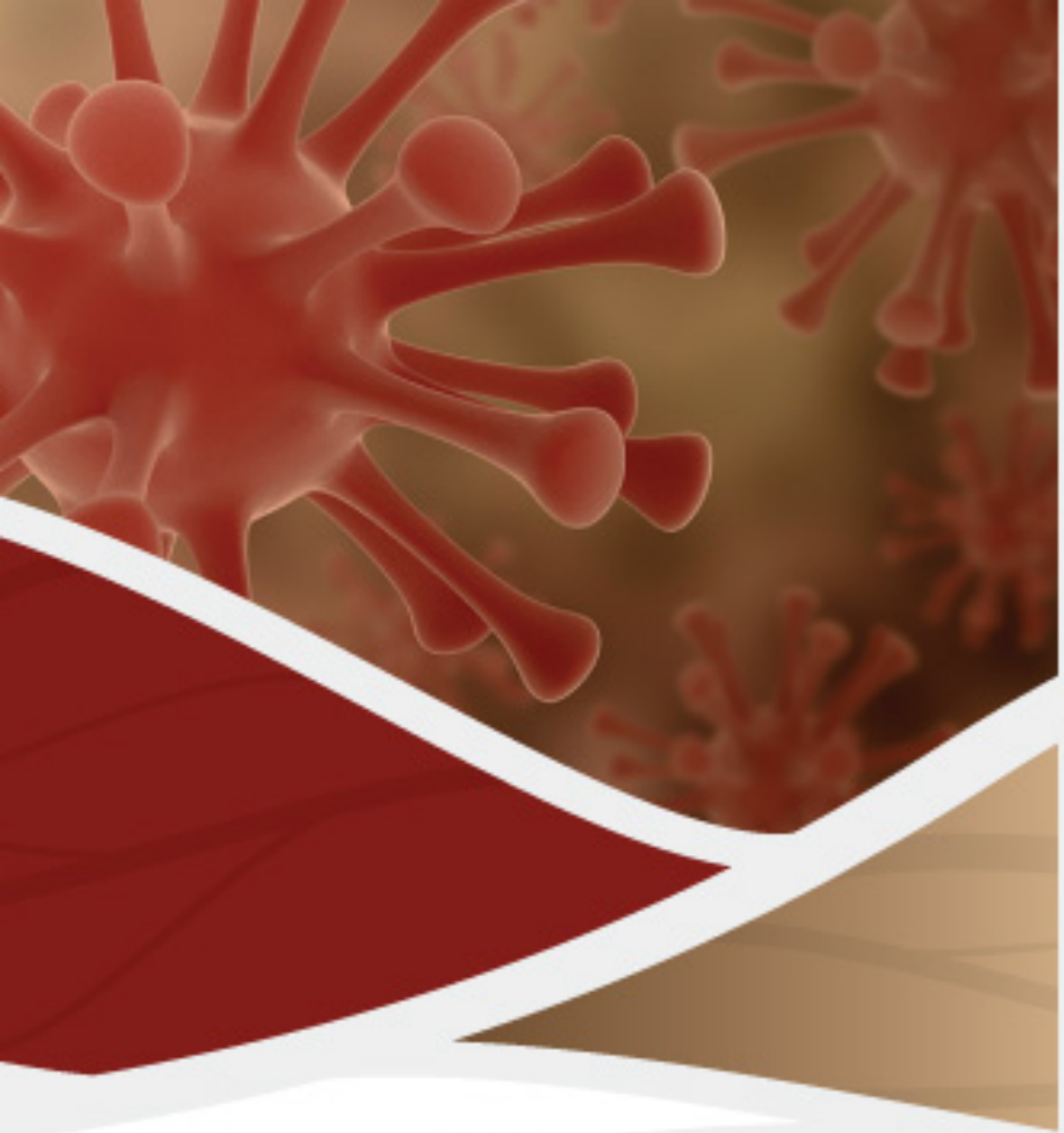
Provided by

CME Outfitters

This lunch symposium is not part of the official Internal Medicine Meeting 2017 Education Program.

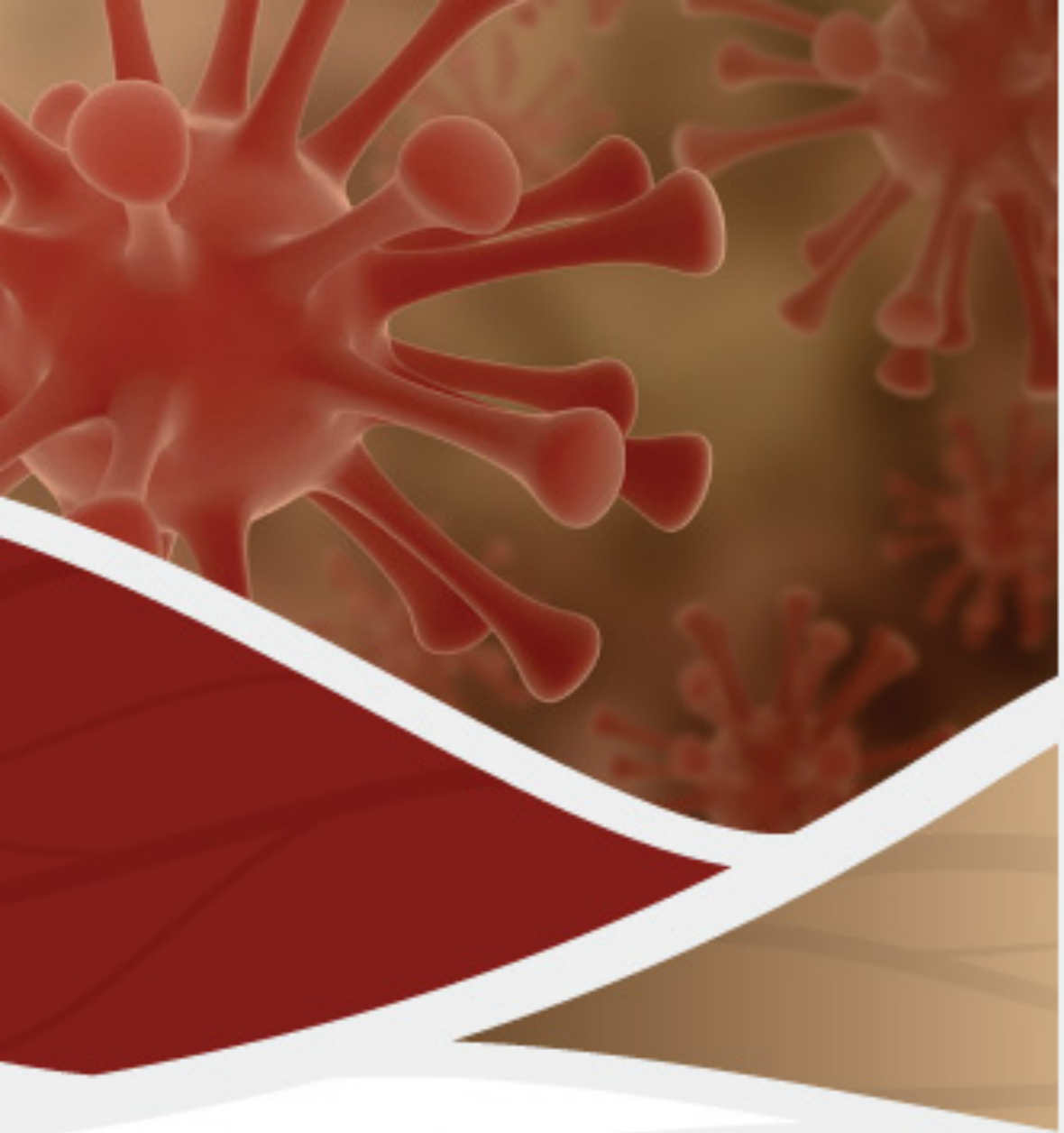


Supported by an educational grant from Gilead Sciences



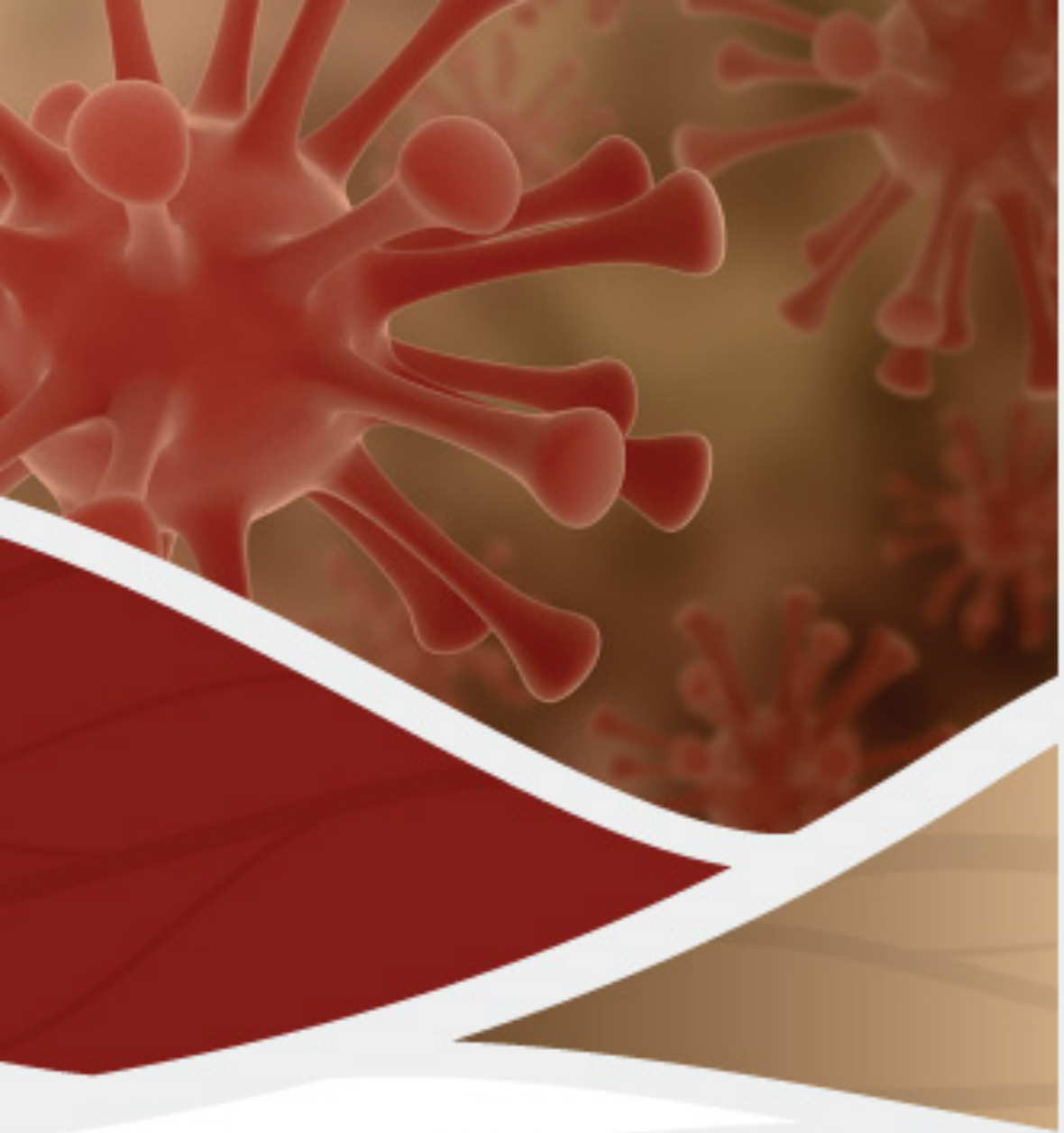
Kris V. Kowdley, MD FACP

Director, Liver Care Network
and Organ Care Research
Swedish Medical Center
Seattle, WA



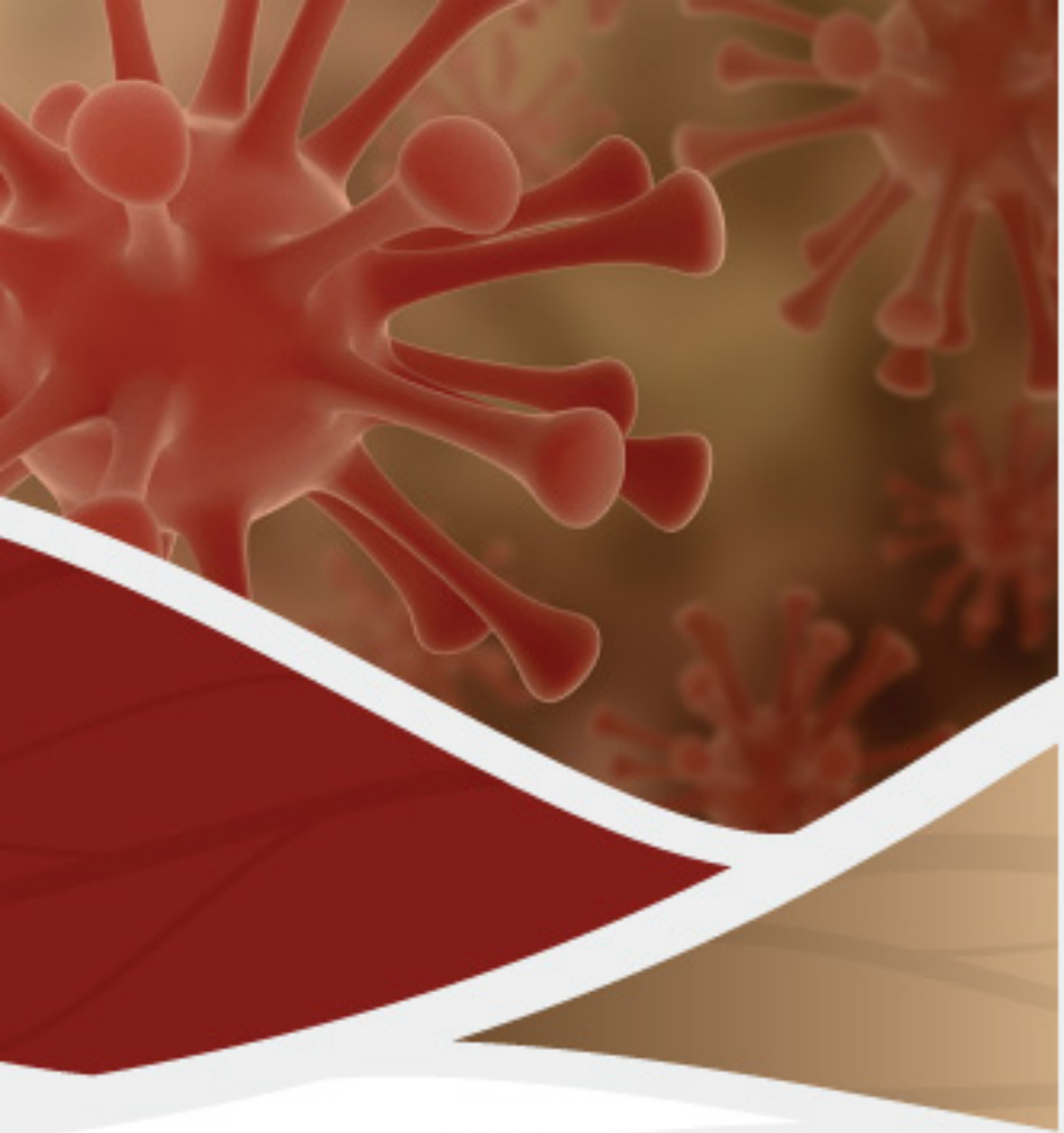
Su Wang, MD, MPH

Internist
Medical Director
Center for Asian Health
Saint Barnabas Medical Center
Livingston, NJ



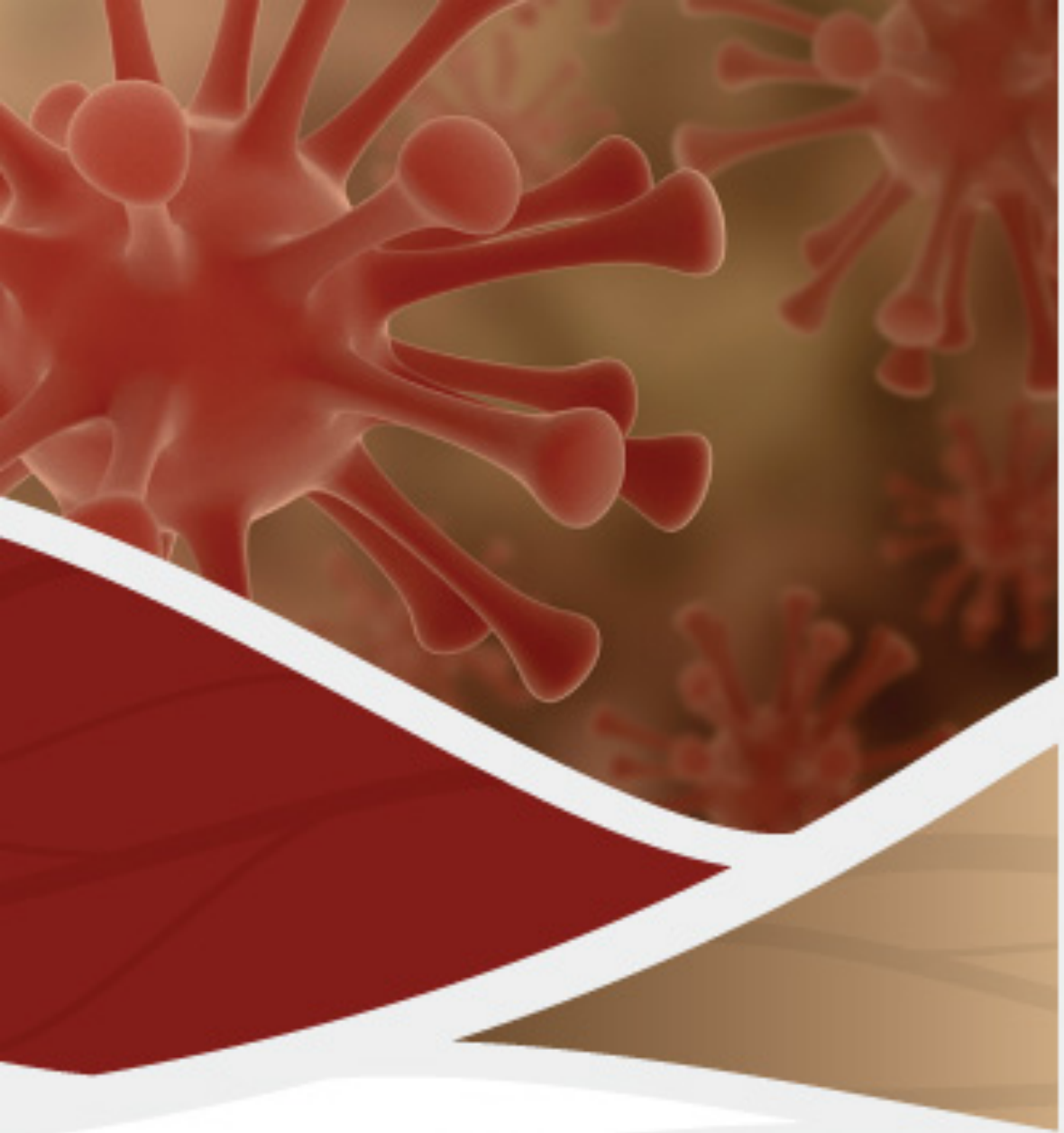
Learning Objective 1

Increase the rate at which clinicians appropriately screen at-risk patients for HBV.



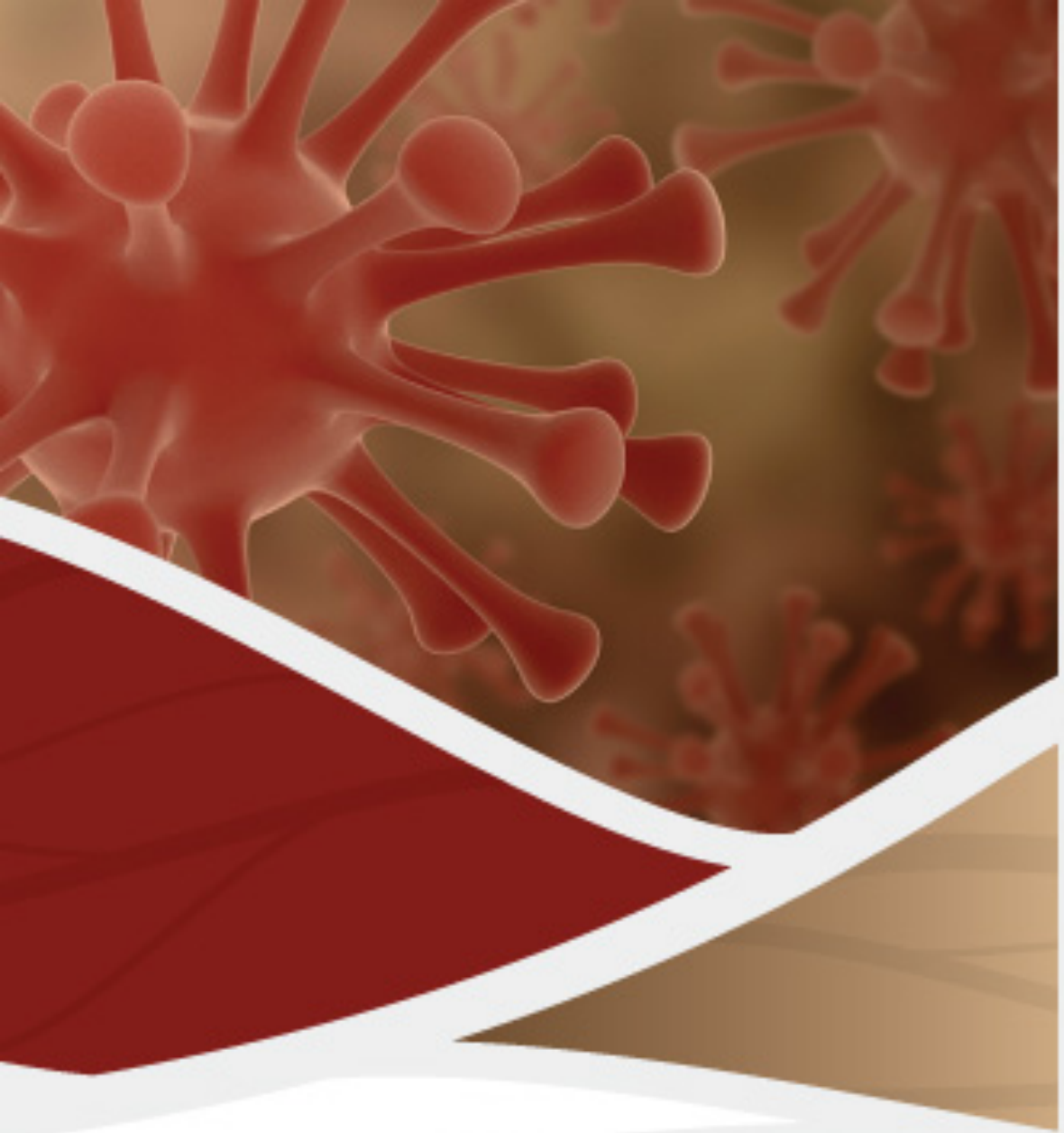
Learning Objective 2

Develop a treatment strategy for patients who test positive for HBV to ensure they are referred and monitored for optimal care.



Learning Objective 3

Integrate a team-based care model for patients who test positive for HBV to monitor adherence to therapy.

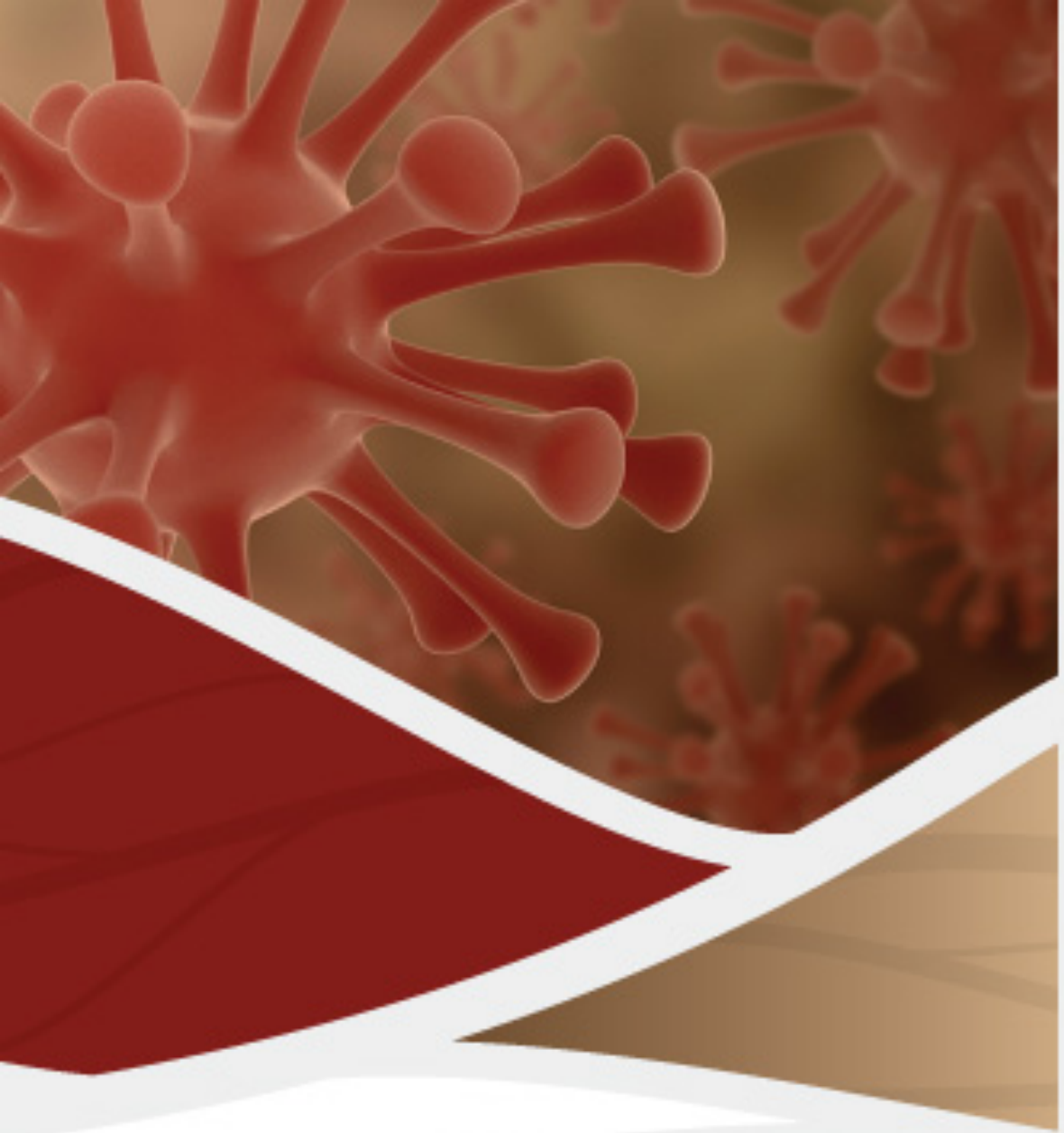


Medical Simulation Segment #1

- Problem-based learning
- Interactive case
- Real-time feedback

Mr. Osei

- 45 years old
- Father from Ghana, mother from US
- Type II Diabetes
- Comes to establish care and annual check-up



Screening & Next Steps After Diagnosis

Recent Hepatitis B Screening Changes

U.S. Preventive Services TASK FORCE

- 2015 USPSTF upgrades HBV screening to grade B (Grade B)
  - Recommends HBV screening for at-risk populations
  - Must be covered by insurance plans as a preventative service

CMS.gov
Centers for Medicare & Medicaid Services

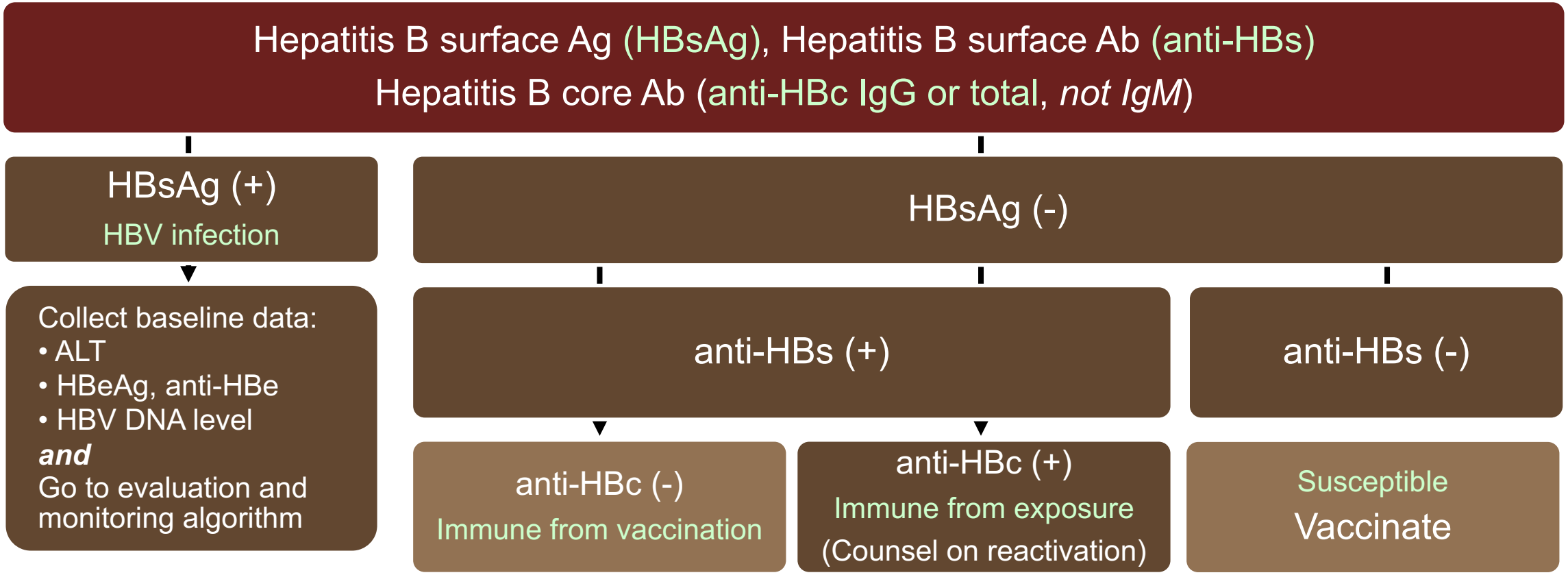
- October 2016, Medicare begins covering HBV screening under part A & part B

At-Risk Groups Include

- ✓ Persons born in HBV endemic regions of the world: Asia, Africa, Pacific Islands, Middle East, Eastern Europe, Mexico, Central America, and the Caribbean
- ✓ Injection drug users
- ✓ Men who have sex with men
- ✓ Persons with condition that may require immune-modifying therapy
- ✓ Persons with elevated ALT/AST of unknown etiology
- ✓ Blood or tissue donors
- ✓ Pregnant women
- ✓ Infants born to HBV-infected mothers
- ✓ Hemodialysis patients
- ✓ Household and sexual contacts of HBV-infected individuals
- ✓ HIV-positive individuals

McMahon BJ. *Medical Clinics of North America*. 2014:98(1);39-54.; McHugh JA, et al. *J Fam Pract,* 2011;60(9):E1-E8.

HBV Screening Algorithm



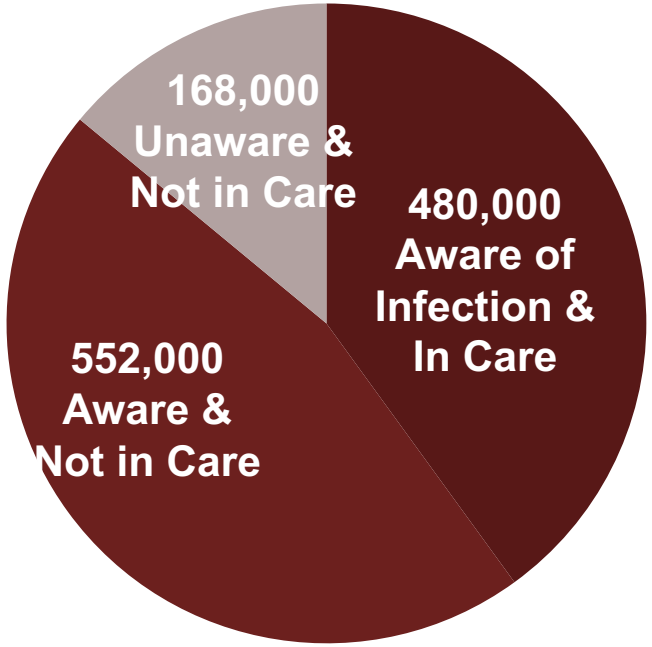
HBsAg = hepatitis B surface antigen; Anti-HBs = antibody to hepatitis B surface antigen; Anti-HBc = antibody to hepatitis B core antigen; HBeAg = hepatitis B e antigen

McMahon BJ. *Medical Clinics of North America*. 2014:98(1);39-54.; McHugh JA, et al. *J Fam Pract,* 2011;60(9):E1-E8.

Impact of National Screening Strategies
HIV vs HBV Care Cascade

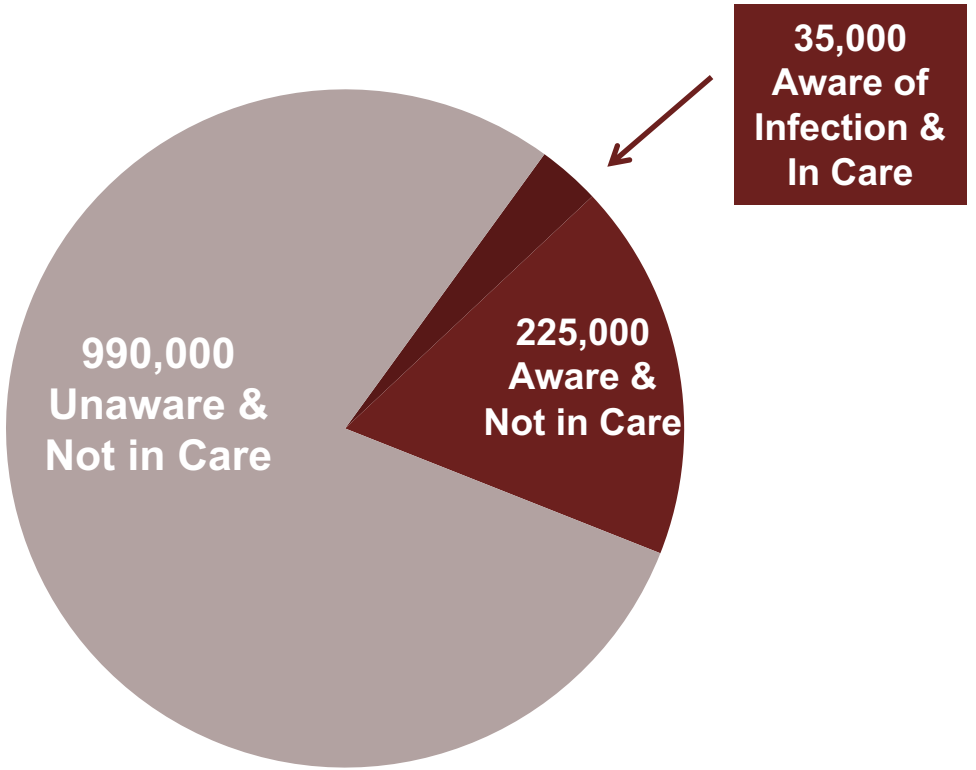
1,200,000
in US with **HIV**

Routine Screening
One time for all adults, as of 2006

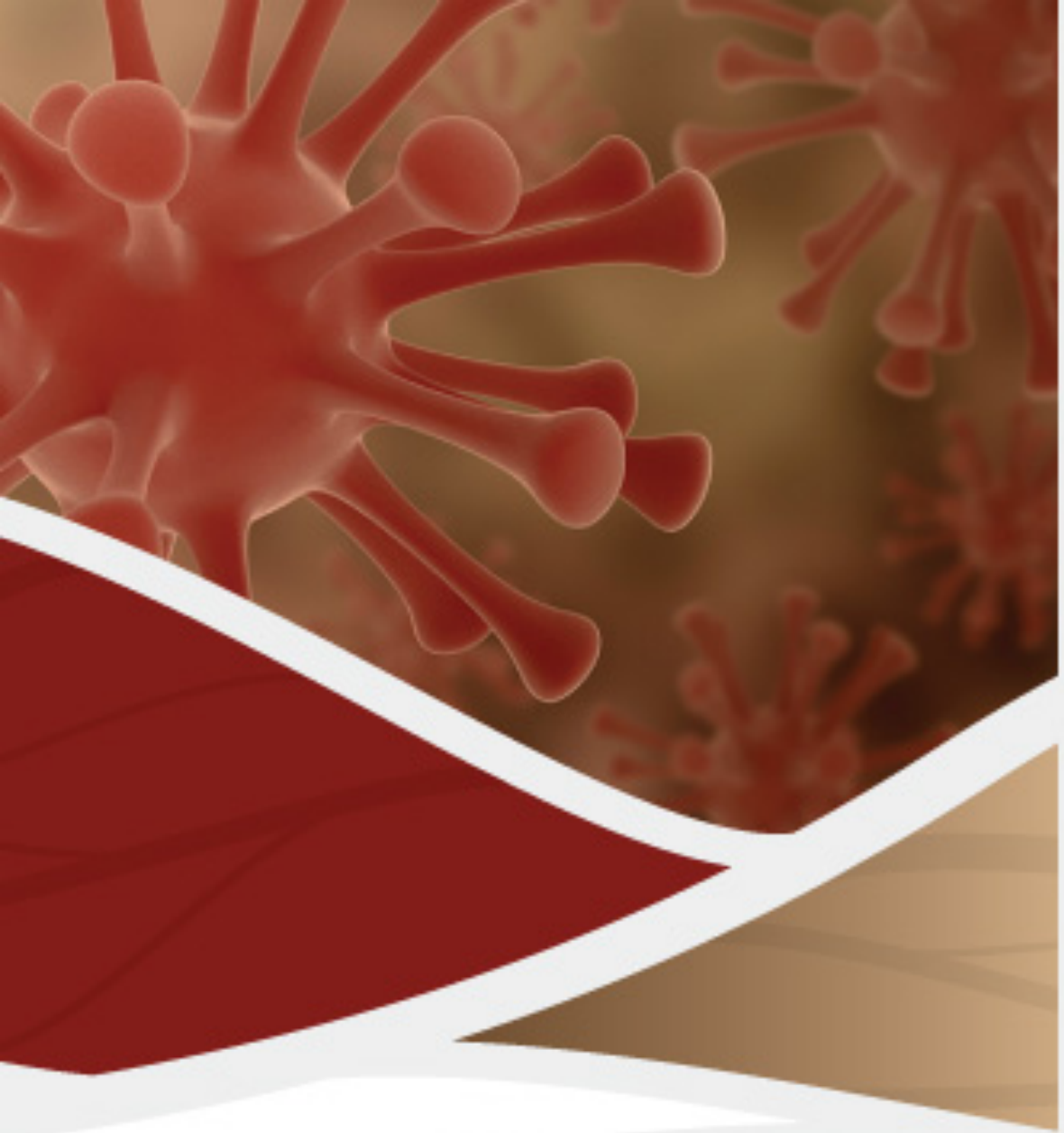


1,250,000
in US with Chronic **HBV**

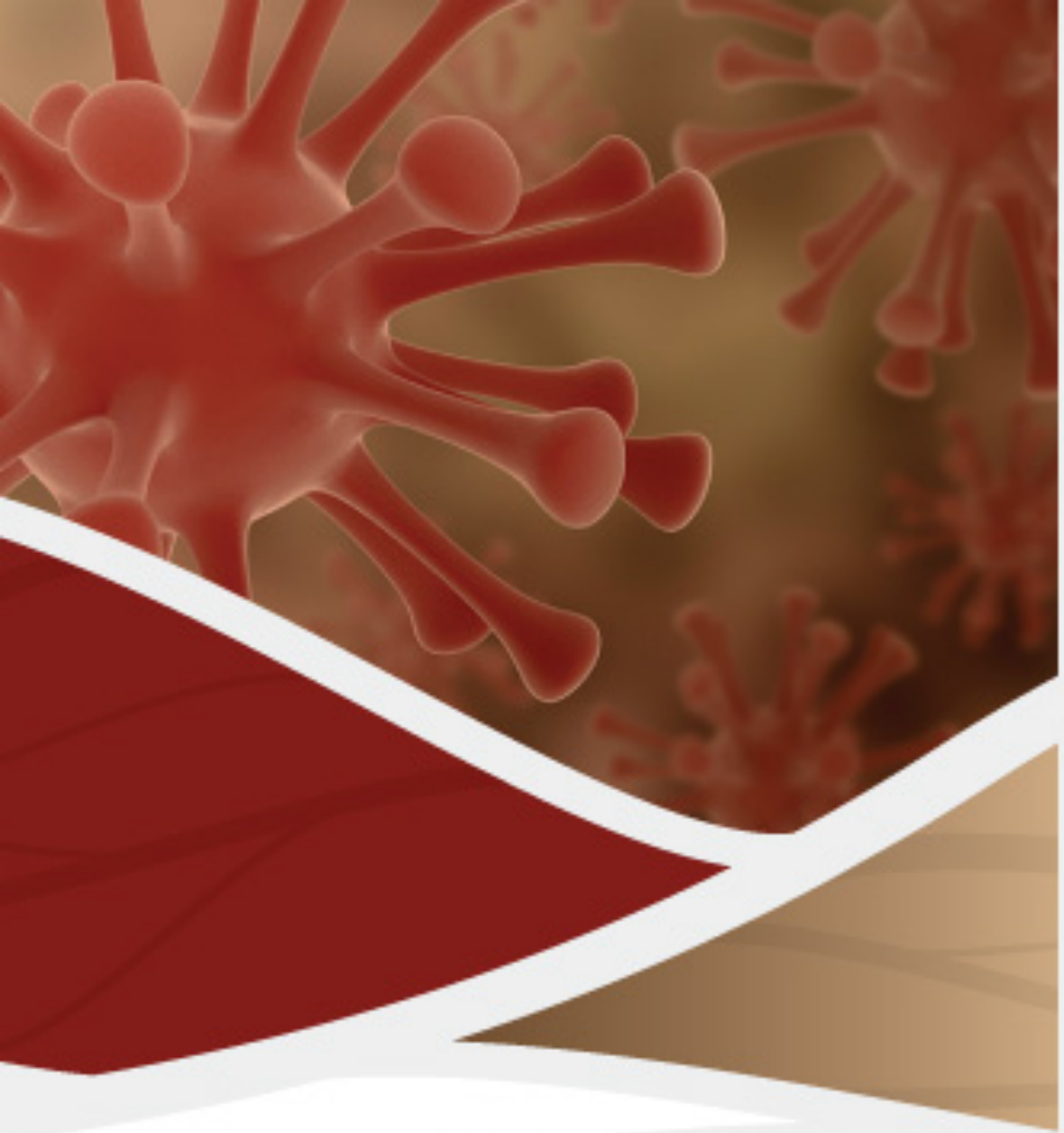
Risk-Based Screening



HIV –CDC HIV Surveillance System & Monitoring Project, 2011 https://www.cdc.gov/vitalsigns/hiv-aids-medical-care/
HBV - Cohen C. *J Vir Hepat*. 2011;18:377–383.



Results from Simulation #1



Medical Simulation Segment #2

- Lab results
- Next steps

Hepatitis B Medical Care

- Chronic hepatitis B (CHB) often a lifelong infection
  - Asymptomatic even with ongoing inflammation
  - Increased risk of HCC and cirrhosis
- All HBsAg+ need routine monitoring
  - Every 3-12 months
  - HBV viral load and LFTs
  - Liver cancer screening – ultrasound or CT and alpha-fetoprotein (AFP)
    - Unlike HCV, HCC in HBV+ occurs in non-cirrhotics
- Hepatitis B “carrier” is overused
  - False sense of security that condition is benign
  - HBV can fluctuate between “active” and “inactive”
  - “Carrier state” should only apply to HBeAg -, HBV DNA <2000 IU/ml & normal ALT (<19 women, <30 men)

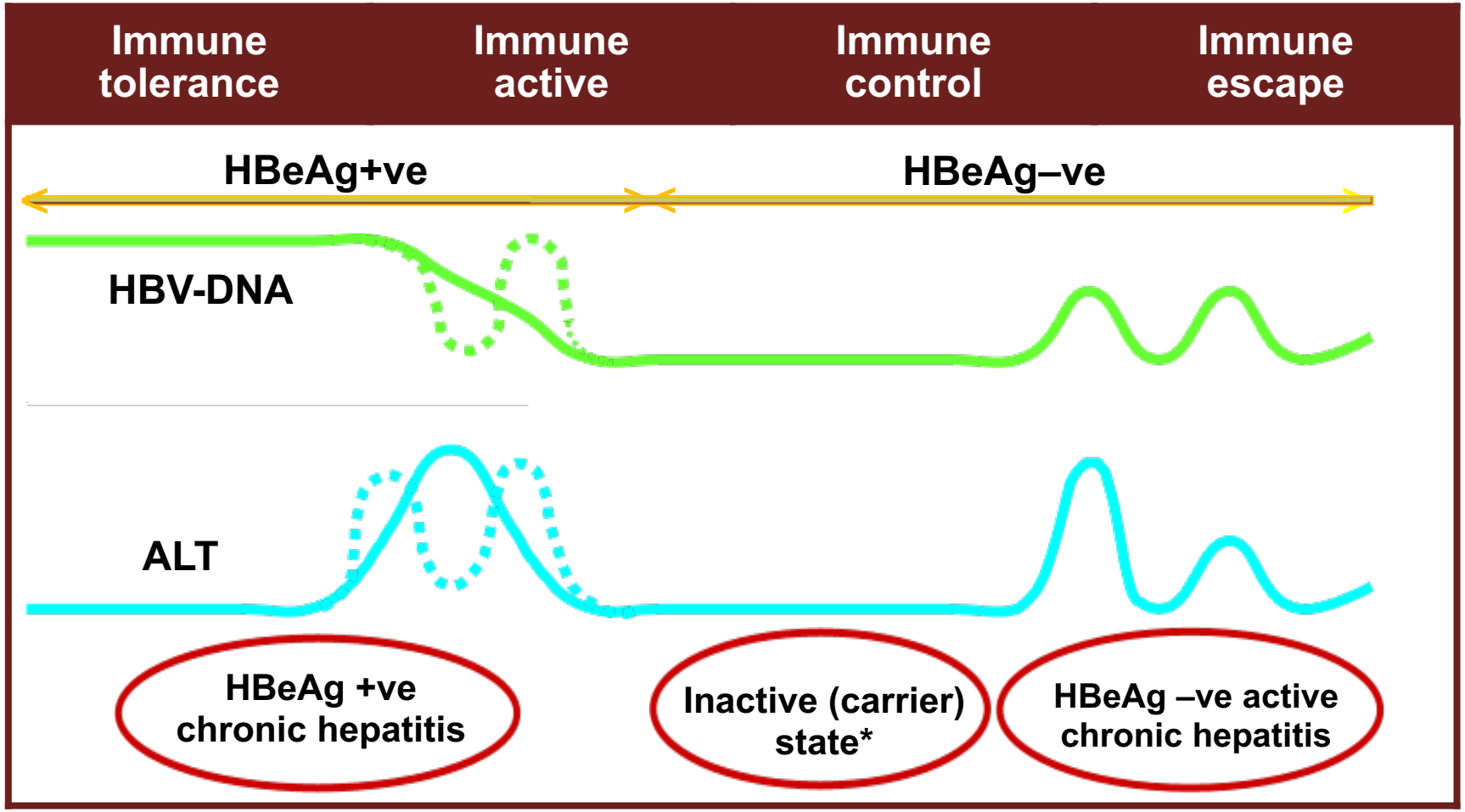
CDC website. Available at https://www.cdc.gov/hepatitis/hbv/bfaq.htm. Accessed March 21, 2017 Terrault, N Hepatology 2016; ; El-Serag HB. Gastroenterology. 2012;142(6):1264-1273,

Initial Evaluation of HBV+ Patients

- History and physical examination
  - Family history of Hep B, liver cancer or other liver disease
  - Examine for stigmata of liver disease (late finding)
- HBV counseling
  - Symptoms of hepatitis flares, importance of regular visits
  - Partners and household contact testing
  - Transmission risks
    - Avoid sharing toothbrush, razors, cover wounds, etc
  - Protecting the liver
    - Limit ETOH and herbal use
    - Hep A vaccine
- Laboratory tests
  - HBeAg / anti-HBe
  - HBV DNA quantification
    - Viral load
  - CBC with platelets
    - Low platelets?
  - Liver panel (AST/ALT, total bilirubin (TB) / direct bilirubin (DB)
  - Prothrombin time / international normalized ration (INR)
  - Alpha fetoprotein
  - Anti-HAV
  - Anti-HCV
  - Hepatitis Delta (pt origin, IVDU)

Modified from Terrault, N et al (2016), AASLD guidelines for treatment of chronic hepatitis B. Hepatology, 63: 261–283. Lok AS, et al. *Hepatology*. 2001;34:1225-124,

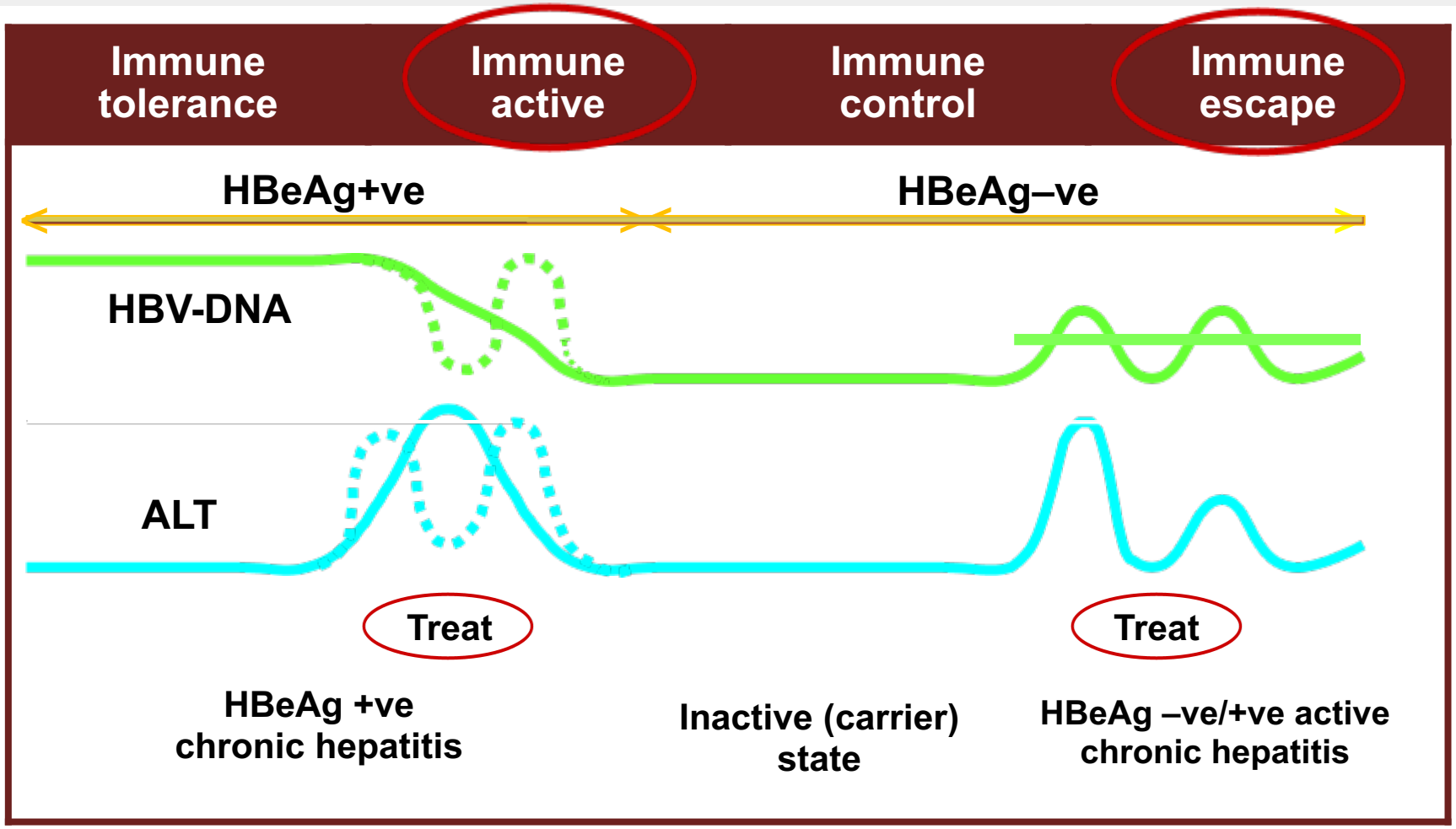
The Phases of Chronic Hepatitis B



*Previously considered to be 'healthy carriers'

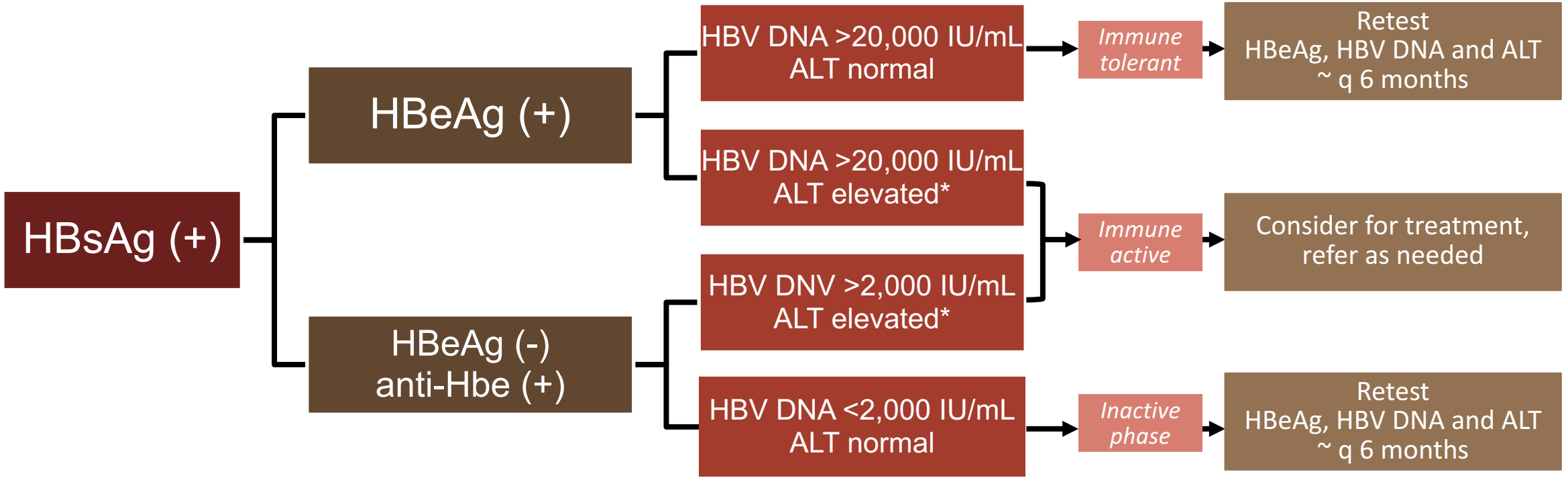
World Gastroenterology Organisation Practice Guideline. Available at http://www.worldgastroenterology.org/guidelines/global-guidelines/hepatitis-b/hepatitis-b-english#Ref27. Accessed March 22, 2017.

Who Should Be Considered for Treatment



World Gastroenterology Organisation Practice Guideline. Available at http://www.worldgastroenterology.org/guidelines/global-guidelines/hepatitis-b/hepatitis-b-english#Ref27. Accessed March 22, 2017.

Primary Care HBV Evaluation/Monitoring Algorithm

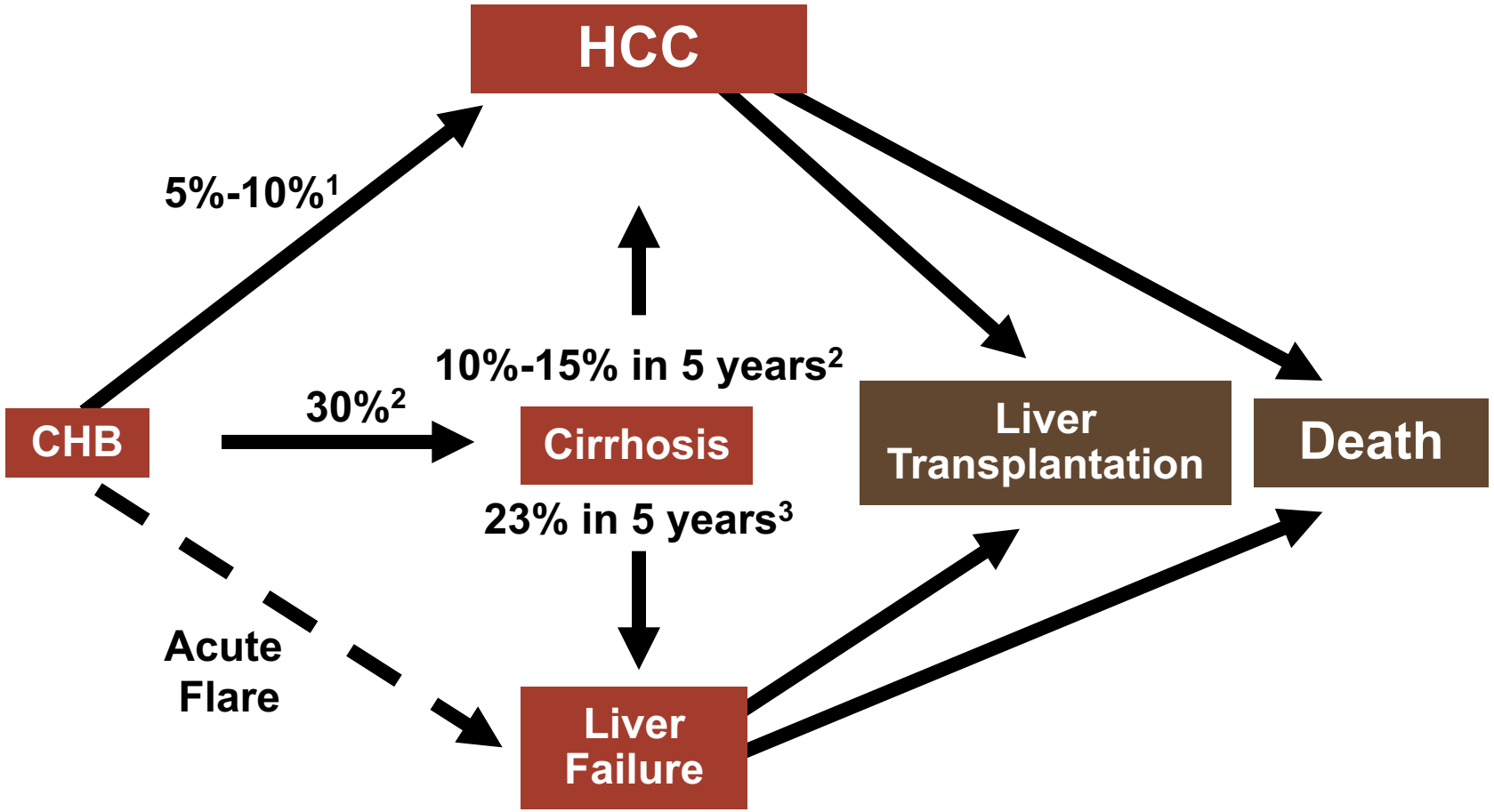


*New norms establish elevated ALT as ≥19 IU/L for women and ≥30 IU/L for men

Terrault, N et al (2016), AASLD guidelines for treatment of chronic hepatitis B. Hepatology, 63: 261–283.

McMahon BJ. *Medical Clinics of North America*. 2014:98(1);39-54.
McHugh JA, et al. *J Fam Pract*. 2011;60(9):E1-E8.

Natural History of HBV Infection



[1] Torresi J, et al. *Gastroenterology.* 2000;118:S83-S103.; [2] Fattovich G, et al. *Gastroenterology.* 2004;127:S35-S50.;
[3] Fattovich G, et al. *Hepatology.* 1995;21:77-82.

HCC Surveillance: Radiology +/- AFP q 6 Months

AASLD Indications for Screening

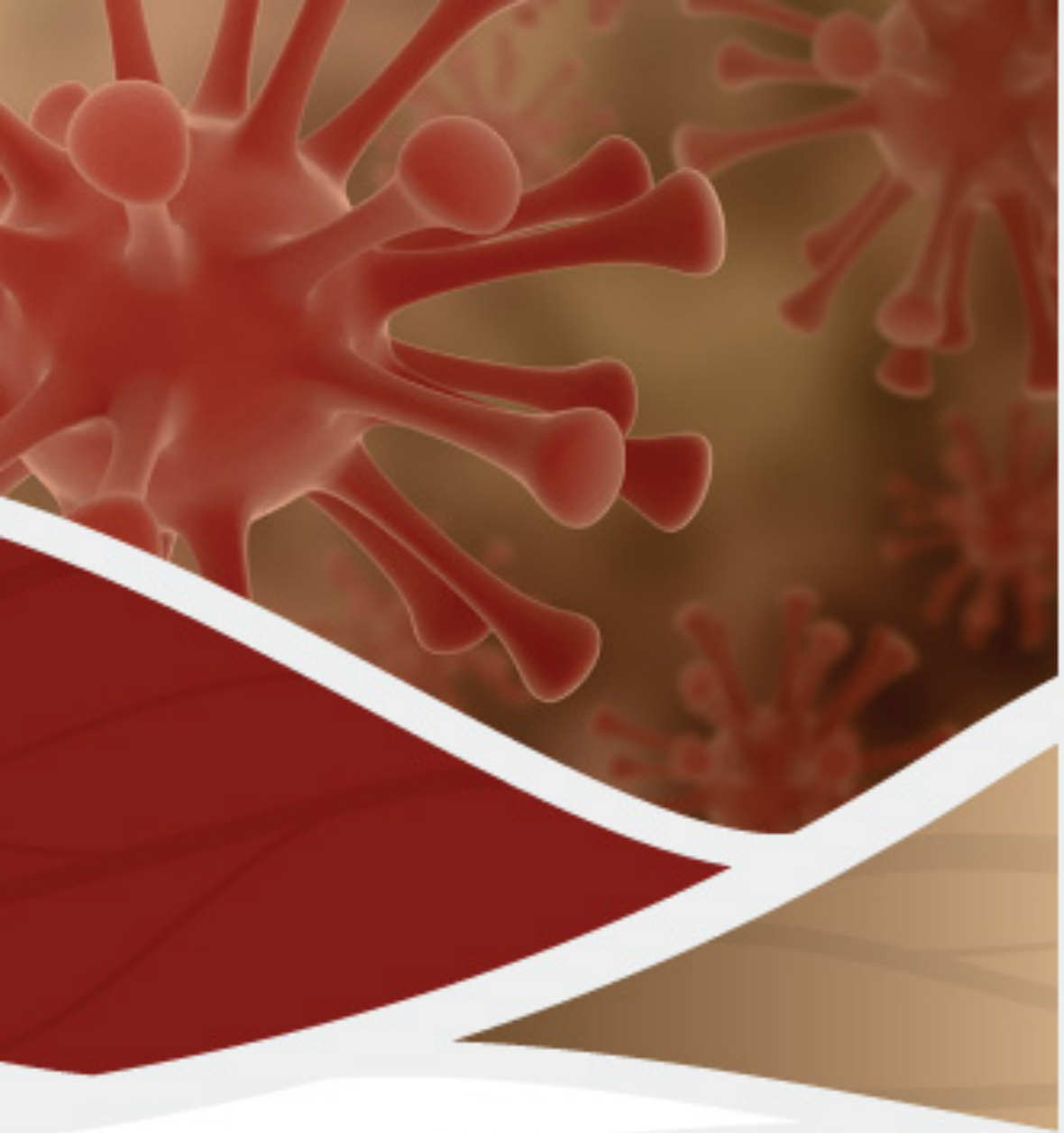
- Males ≥ 40 years old
- Females ≥ 50 years old
- All cirrhotics
- Family history of HCC
- Africans ≥ 20 years old
- Noncirrhotic, younger hepatitis B carriers may require HCC surveillance→

Additional Risk Factors

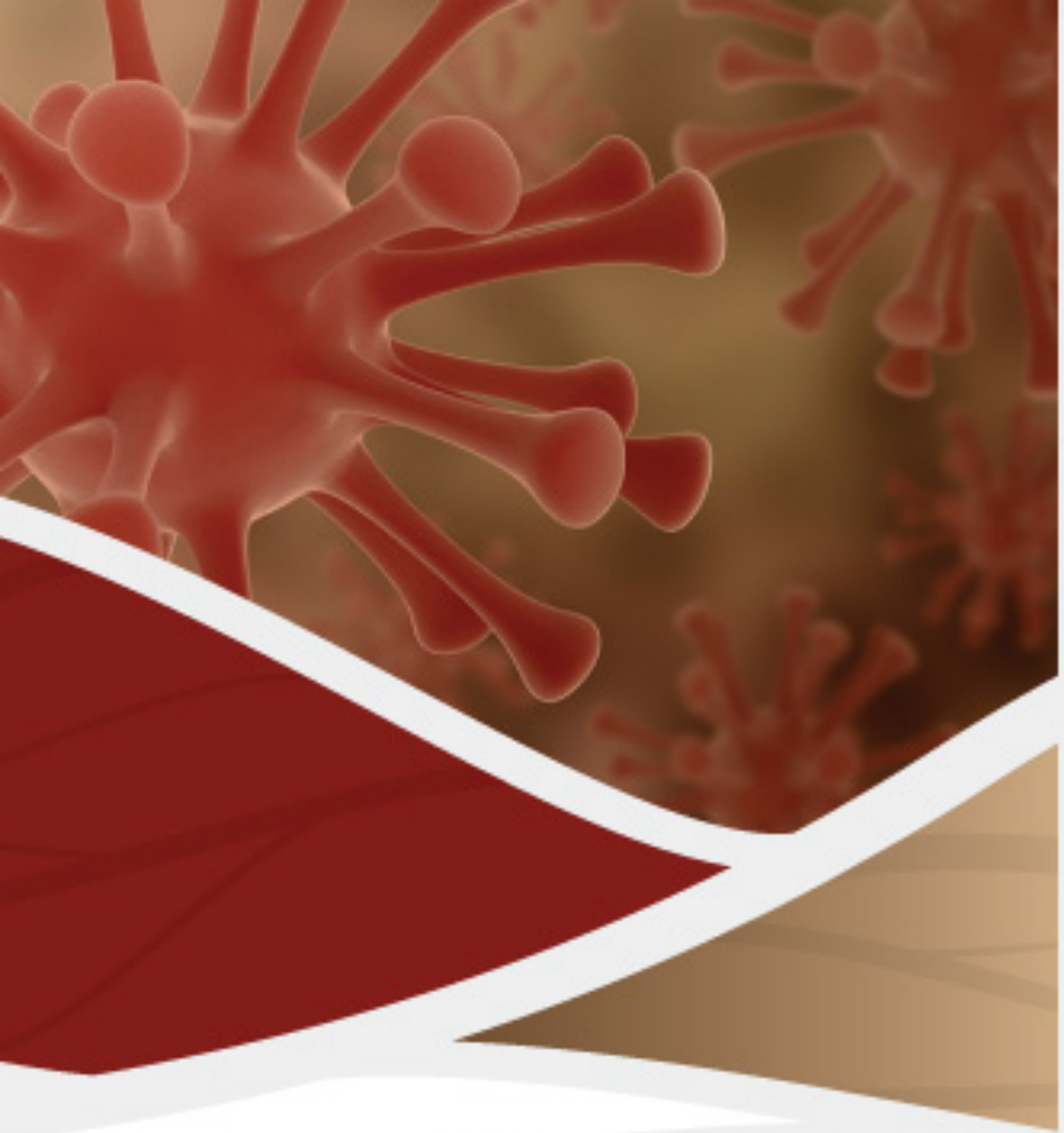
- Basal core promoter (BCP) or precore mutations
- Genotype C
- Coinfection with HCV, HIV, HDV
- Persistently high HBV DNA
- Late HBeAg loss (40+ years)
- Persistent elevation of LFTs (>1.5 ULN*)
- ETOH, smoking
- Cirrhosis

*Abnormal ALT is: male ≥30 U/L or female ≥19 U/L

Bruix J, et al. *Hepatology*. 2005;42:1208-1236.; Chan HL, et al. *Gut*. 2004;53(10):1494-1498.



Results from Simulation #2



Goals of Treatment

Updated AASLD Guidelines: When to Treat

HBeAg Positive			HBeAg Negative		
HBV DNA, IU/mL	ALT	Histologic Disease	HBV DNA, IU/mL	ALT	Histologic Disease
Any	> 2 x ULN	N/A	Any	> 2 x ULN	N/A
> 20,000	Any	Any	> 2000	Any	Any
Any	Any	Cirrhosis	Any	Any	Cirrhosis

Do not stop treatment in HBeAg-negative pts with cirrhosis

Changes to guidance:

- Lower threshold for treating HBeAg-negative pts
- Treat all pts with cirrhosis regardless of HBV DNA

Terrault NA, et al. *Hepatology*. 2016;63:261-283.

Goals and Benefits of Hepatitis B Treatment

- Achieve sustained suppression of HBV replication and remission of hepatic disease
- Prevention of long-term negative clinical outcomes (e.g., cirrhosis, HCC, death) by durable suppression of HBV DNA
- Primary endpoint
  - Sustained decrease in serum HBV DNA level to undetectable
- Secondary endpoints
  - Decrease or normalize serum ALT
  - Improve liver histology
  - Seroconversion from HBeAg+ to HBeAb+
  - Loss of HBsAg

Terrault NA, et al. *Hepatology*. 2016;63:261-283; Martin P, et al. *Clin Gastroenterol Hepatol*. 2015;13:2071-2087; Lok AS, et al. *Hepatology.* 2009;50(3):661-662.

AASLD Guidelines: Initial Treatment

Treatment	Preferred	Notes
Entecavir	Yes (unless previous history of lamivudine resistance)	High potency, high genetic barrier to resistance
Tenofovir	Yes	High potency, high genetic barrier to resistance
PegIFN	Yes	Less safe in pts with cirrhosis
Adefovir	No	Low genetic barrier to resistance
Lamivudine	No	Low genetic barrier to resistance
Telbivudine	No	Low genetic barrier to resistance

- Treatment with antivirals does not eliminate the risk of HCC, and surveillance for HCC should continue in persons who are at risk

Lok ASF, McMahon BJ. *Hepatology*. 2001;34:1225-1241.

Treatment Recommendations: First-Line Therapy in Patients Without Cirrhosis

HBeAg Positive or Negative Chronic HBV

Preferred	Not Preferred
Tenofovir DF*	Adefovir
Entecavir	Lamivudine
Peg-IFN alfa-2a	Telbivudine

***Guidelines developed prior to the approval of tenofovir AF**.
Tenofovir DF, entecavir, and pegIFN alfa-2a are preferred primarily because of lack of resistance with long-term use. Before initiating treatment, all patients should have a baseline assessment of liver fibrosis for evaluating histologic response to therapy.

Terrault NA, et al. *Hepatology*. 2016;63:261-283.; Martin P, et al. *Clin Gastroenterol Hepatol*. 2015;13:2071-2087.

Treatment Recommendations: Chronic HBV Patients With Cirrhosis

Compensated Cirrhosis

Preferred	Alternative	Not Preferred
Tenofovir DF*	PegIFN alfa-2a†	Lamivudine
Entecavir		Telbivudine

Decompensated Cirrhosis

Preferred	Not Preferred
Tenofovir DF*	PegIFN alfa-2a and alfa-2b‡
Entecavir	

***Guidelines developed prior to the approval of tenofovir AF.**

All HBeAg-positive or HBeAg-negative patients with cirrhosis (compensated or decompensated) and any level of detectable HBV DNA should receive treatment for chronic HBV.

†Well-compensated cirrhosis only.
‡Contraindicated due to safety concerns.

Terrault NA, et al. *Hepatology*. 2016;63:261-283.; Martin P, et al. *Clin Gastroenterol Hepatol*. 2015;13:2071-2087.

AASLD Summary of Tenofovir DF: Assessed 2-3 Years After Continuous Therapy

	HBeAg-Positive	HBeAg-Negative
HBV DNA suppression (%) <60 IU/mL	76	93
HBeAg loss (%)	--	--
HBeAg seroconversion (%)	21	--
ALT normalization*	68	76
HBsAg loss (%) 1 year post-treatment 3 years post-treatment	 3 8	 0 --

*ALT normalization defined by laboratory normal at time of studies.

Terrault NA, et al. *Hepatology.* 2016;63:261-283.

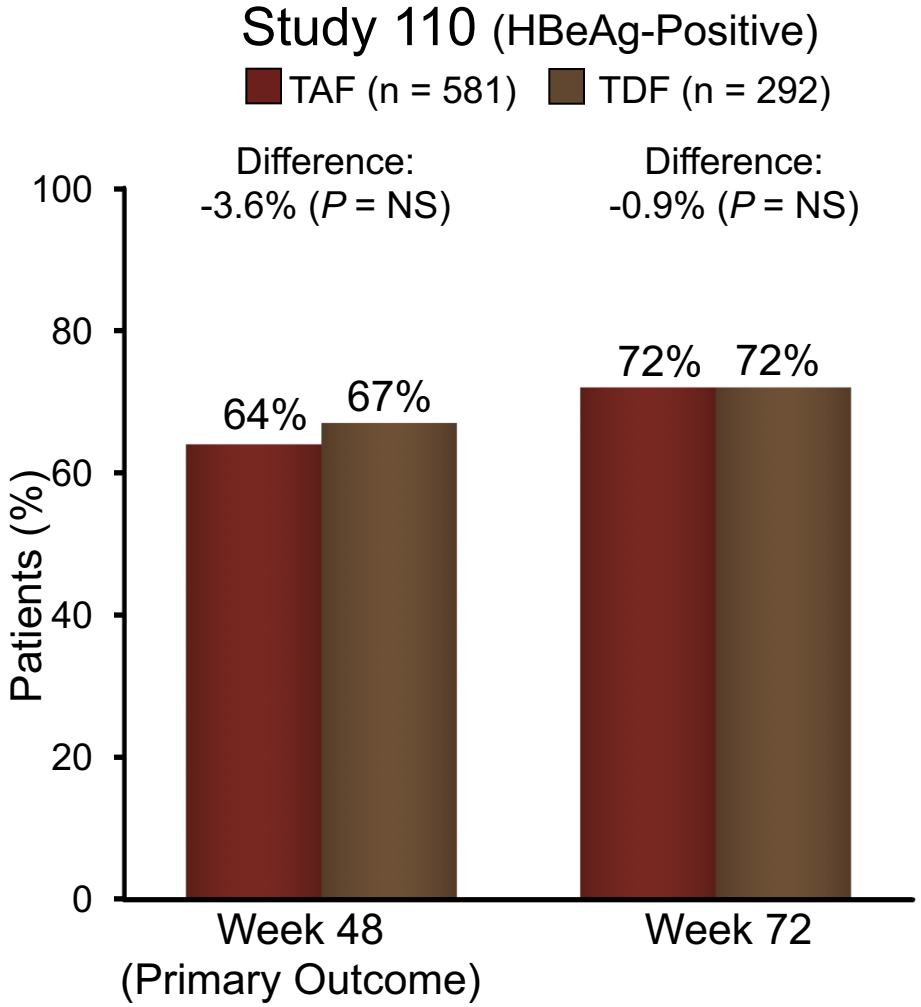
AASLD Summary of Entecavir: Assessed 2-3 Years After Continuous Therapy

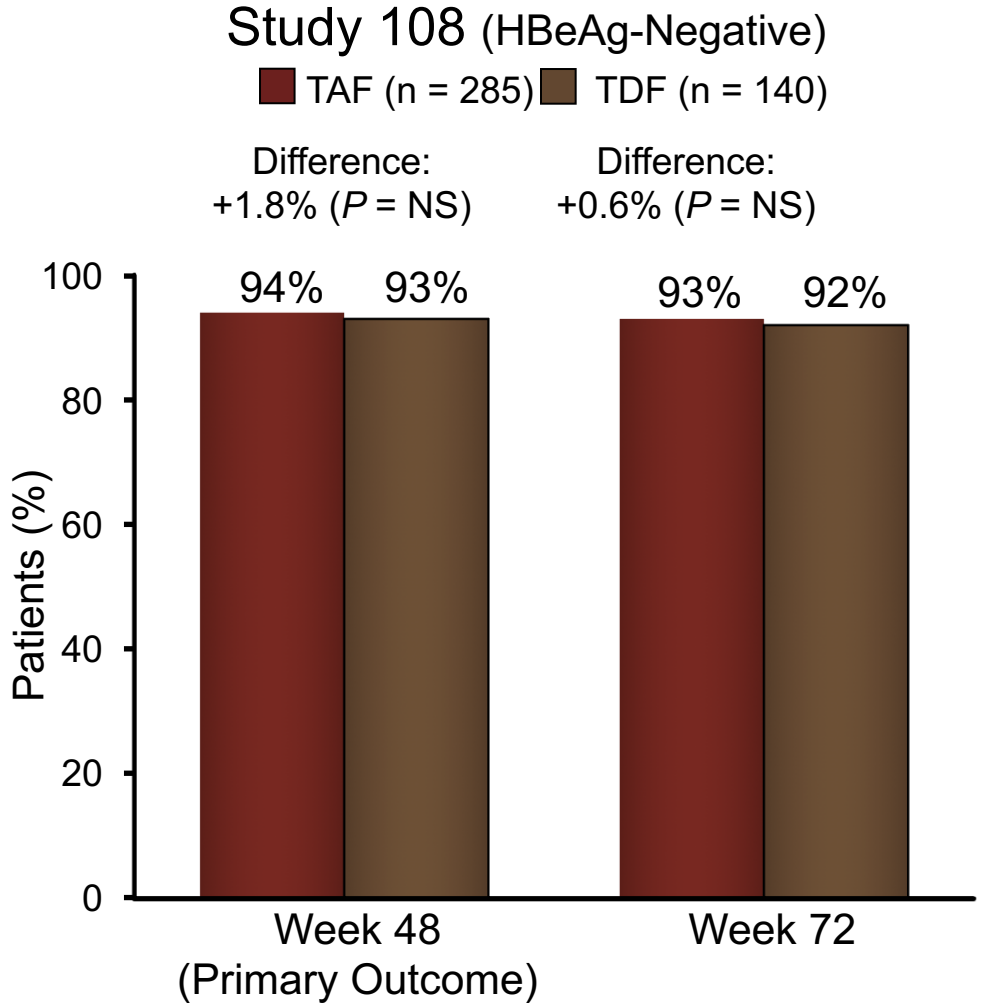
	HBeAg-Positive	HBeAg-Negative
HBV DNA suppression (%) <50-60 IU/mL <60 IU/mL	 61 --	 -- 90-91
HBeAg loss (%)	22-25	--
HBeAg seroconversion (%)	21-22	--
ALT normalization*	68-81	78-88
HBsAg loss (%) 1 year post-treatment 2 years post-treatment	 2-3 4-5	 0-1 --

*ALT normalization defined by laboratory normal at time of studies.
Additional considerations in adults: Dose: 0.5 mg daily for most patients. 1.0 mg daily if lamivudine- or telbivudine-experienced, or decompensated cirrhosis. Dose adjustment required for patients with creatinine clearance <50 mL/min. Pregnancy category C. Potential adverse events (per PI): lactic acidosis. Monitoring on treatment: Lactic acid levels if clinical concerns.

Terrault NA, et al. *Hepatology*. 2016;63:261-283.

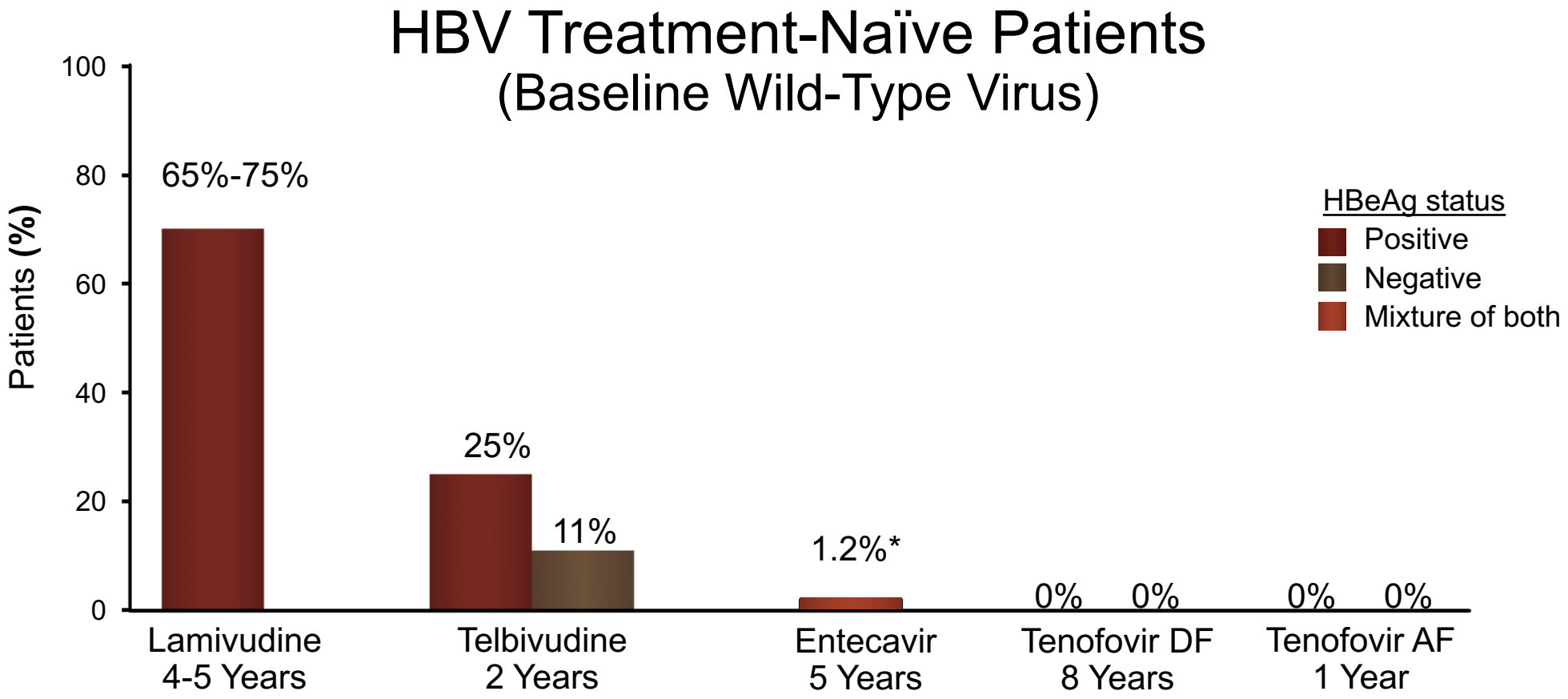
Studies 110 and 108: HBV DNA <29 IU/mL With Tenofovir AF vs. DF





Seto W-K, et al. *Hepatology.* 2016;64(suppl S1):35A. Abstract 67. Buti M, et al. *Lancet Gastroenterol Hepatol.* 2016;1:196-206.
Chan HL, et al. *Lancet Gastroenterol Hepatol.* 2016;1:185-195.

Cumulative Incidence of Drug Resistance During HBV Therapy



*Absence of prior lamivudine resistance.

Martin P, et al. *Clin Gastroenterol Hepatol.* 2015;13:2071-2087.; Buti M, et al. *Lancet Gastroenterol Hepatol.* 2016;1:196-206.; Chan HL, et al. *Lancet Gastroenterol Hepatol.* 2016;1:185-195.

Long-Term Follow-Up and Management

- Multidisciplinary approaches for monitoring adherence
- Periodic Surveillance for Hepatocellular Carcinoma: AASLD Guidelines
  - Hepatitis B carriers at high risk
    - All cirrhotic hepatitis B carriers
    - Family history of hepatocellular carcinoma
    - Asian males ≥40 years of age
    - Asian females ≥50 years of age
    - Africans ≥20 years of age
    - High HBV DNA levels and ongoing hepatic inflammatory activity
    - Platelet count <170,000/μL
  - Liver ultrasound surveillance
    - HBV guidelines: every 6 to 12 months

Bruix J, et al. *Hepatology.* 2011;53:1020-1022.

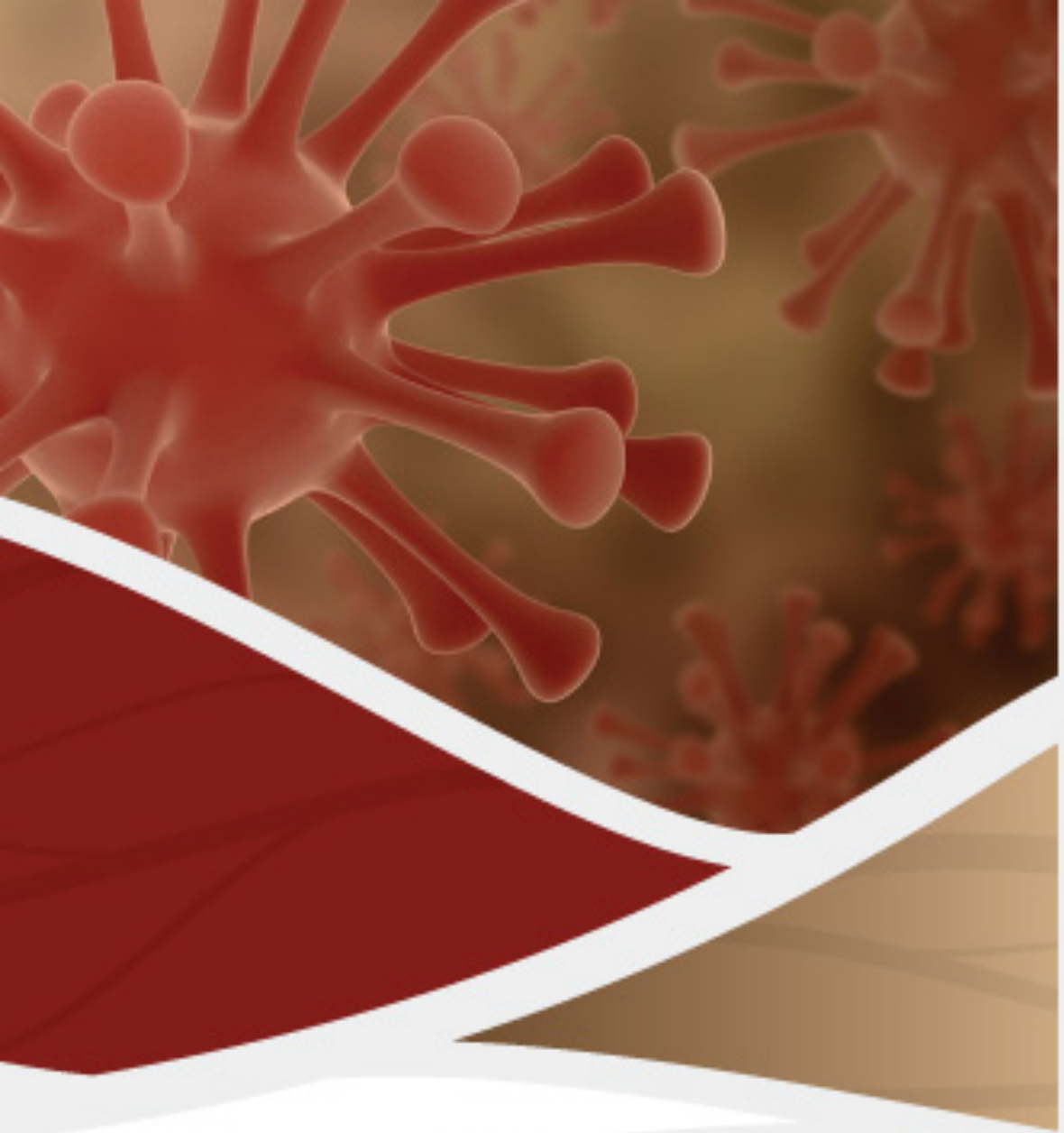
Treatment Duration and Cessation

- Factors to consider:
  - Risks of virologic relapse, hepatic decompensation, liver cancer, and death
  - Burden of continued antiviral therapy, financial concerns associated with medication costs and long-term monitoring, adherence, and potential for drug resistance with treatment interruptions
  - Patient and provider preferences

Terrault NA, et al. *Hepatology*. 2016;63:261-283.

You Are the Crucial Link to HBV Screening and Care

- Internists are at the forefront of HBV screening (Just 3 tests- HBsAg, HBcAb, HBsAb IgG)
- Vaccinate those susceptible (HBsAb negative)
- Internists can evaluate HBV+ individuals
  - HBV DNA, HBeAg/HBeAb, liver studies
  - Household screening, HBV education
  - Periodic follow-up/ monitoring, liver cancer screening
- Treat those with signs of liver inflammation
- For complex cases, collaborate with hepatology or infectious disease (can initiate tx and IM follows)



Questions & Answers