Hepatitis B virus screening and treatment to prevent hepatocellular cancer

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Hepatitis B virus (HBV) prevalence in US

National Health and Nutrition Examination Survey[1,2]

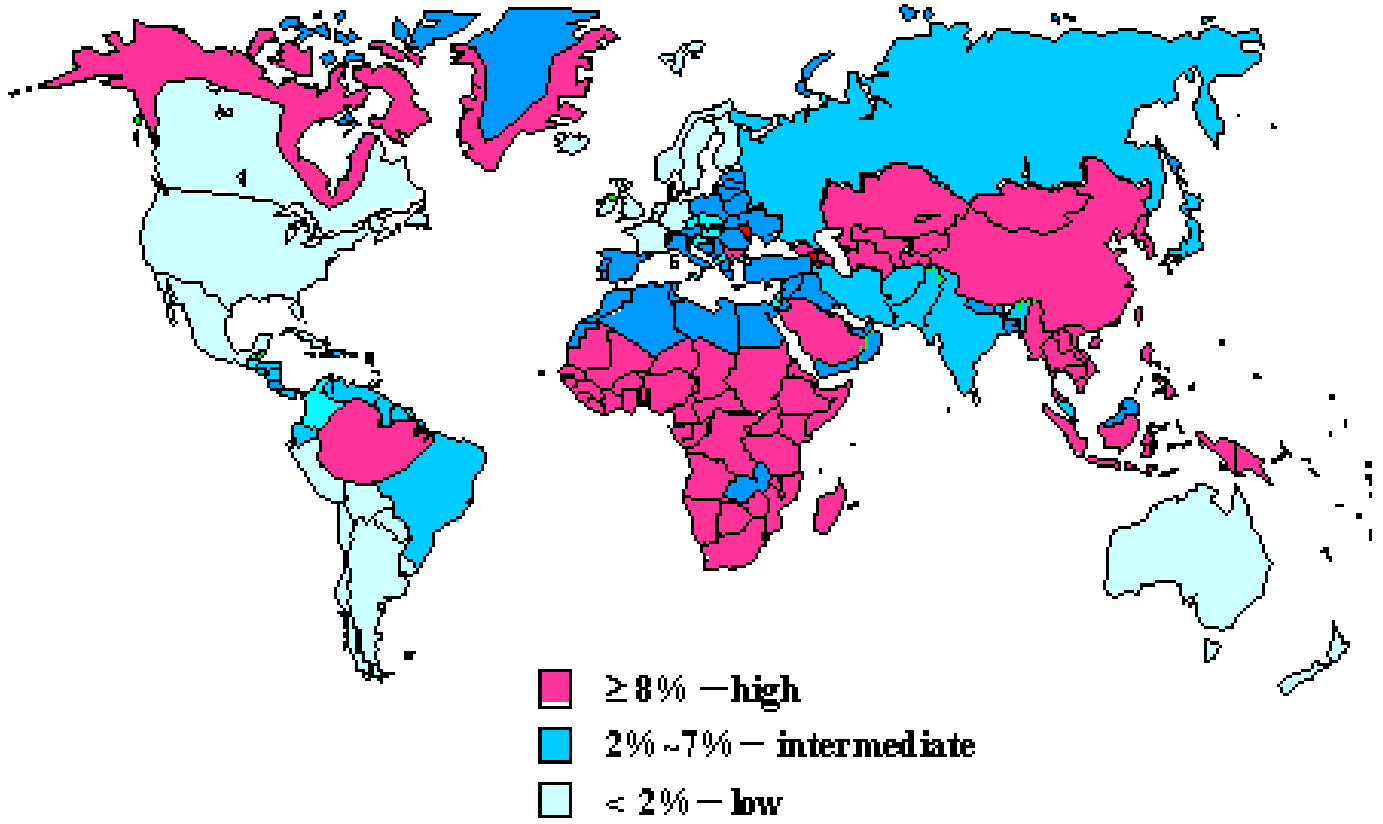
- Overall chronic HBV prevalence – 0.3%
  - US born – 0.2%
  - Non-US born – 1.3%
- 862,000 HBsAg+ persons
- Under representation of high-risk groups

Meta-analysis of 1372 articles[3]

- Country-specific HBV prevalence applied to number of non-US born persons using Census population estimates
  - Non-US born (average) – 3.5%
- 2.2 million HBsAg+ persons

[1]Patel, Clin Infect Dis, 2019. [2]Le, Hepatology 2020. [3]Kowdley, Hepatology, 2012.

Global prevalence of chronic HBV



Hou, Int J Med Sci, 2005. Mast, MMWR, 2005.

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Chronic HBV and hepatocellular cancer (HCC)

Worldwide, chronic HBV is the main cause of HCC

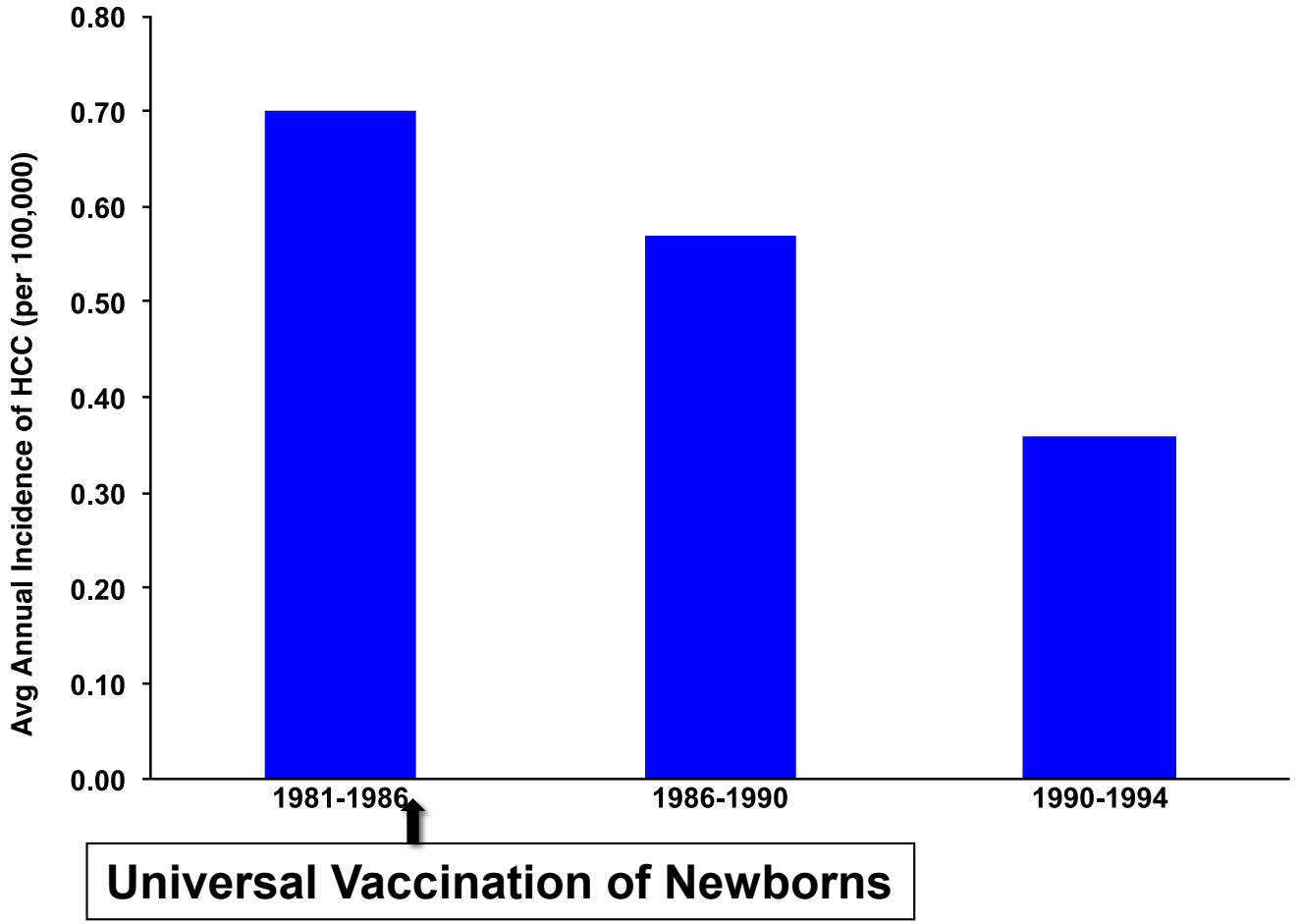
- Direct oncogenic effect regardless of degree of fibrosis or presence of cirrhosis[1,2]

WHO strategy to eliminate viral hepatitis by 2030

- Reduce chronic HBV incidence by 90%, mortality by 65%[3]
- Requires coordinated cascade of care plan
  - Vaccination
  - Screening
  - Treatment

[1]El-Serag, N Engl J Med, 2011. [2]Levrero, J Hepatol, 2016. [3]World Health Organization, Combating Hepatitis B and C to Reach Elimination by 2030, 2016.

HBV vaccination programs have led to reduced HCC incidence in Asia



Chang, N Engl J Med, 1997

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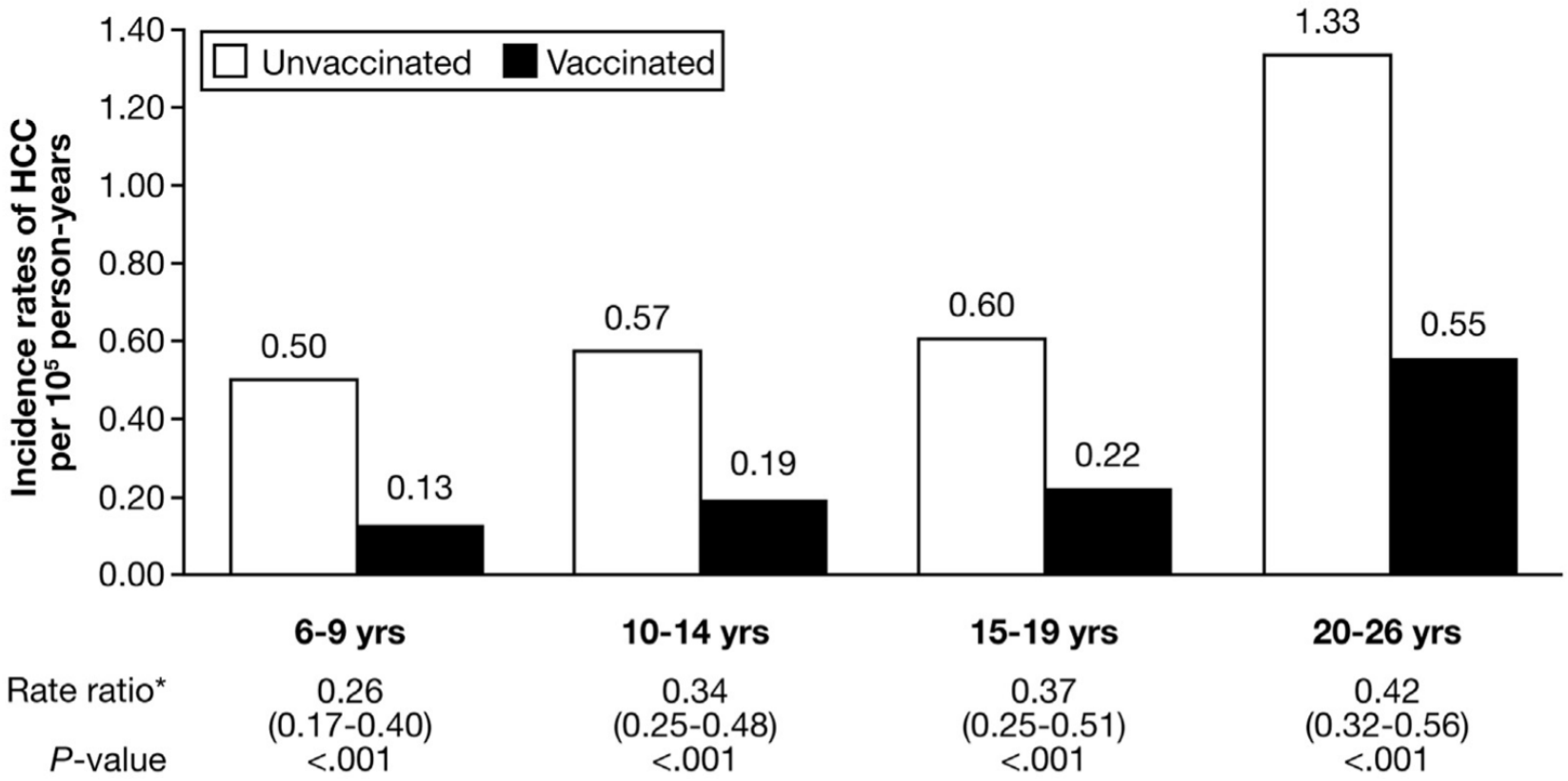
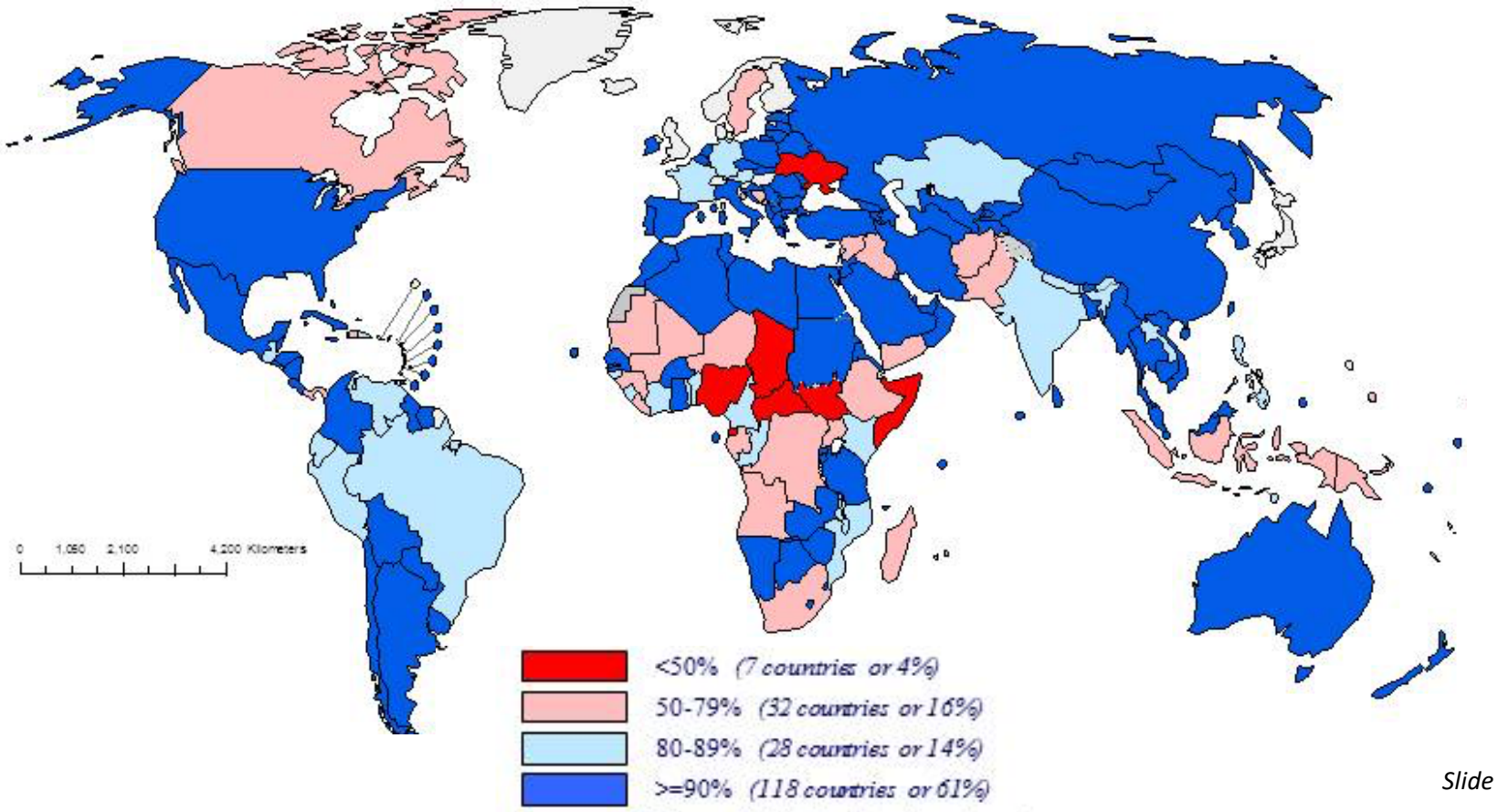
Success of HBV vaccination programs



Chang, Gastroenterology, 2016

Slide courtesy of Amit Singal, MD

HBV vaccination uptake remains low in many countries



WHO | UNICEF

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HBV vaccination - US

Key part of US strategy to eliminate HBV[1,2]

- Universal vaccination of all infants at birth
- Vaccination of adolescents and high-risk adults

3 doses results in protective antibody response at 1, 2, 6 months

- Recombivax, Engerix, Twinrix

2 doses approved in 2017, given 1 month apart

- Heplisav-B

Rise in acute HBV prevalence along with opioid crisis

- Immunity may be decreasing in young adults[3]
- Anti-HBc+ prevalence among injection drug use 20%[4]

[1]National Viral Hepatitis Action Plan, 2017-2020. [2]US Preventative Services Task Force Hepatitis B Virus Infection: Screening, 2014. [3]Yeo, Hepatology, 2019. [4]Shing, Clin Infect Dis, 2020.

HBV screening

Screening is essential and beneficial to

- Patients – linkage to care for HBsAg+ persons
- Society – through reduction of transmission by vaccination

3 HBV tests

- HBsAg, anti-HBc, and anti-HBs
- Chronic HBV: HBsAg+ (and anti-HBc+)

Only 32% of chronic HBV patients are aware of their infection[1]

- Most HBsAg+ persons are asymptomatic

[1]Zhou, Clin Gastroenterol Hepatol, 2020

Risk-based HBV screening in the US

Screening is recommended for high risk groups[1,2,3]

- Born in country with HBV prevalence >2%
- US born, not vaccinated, parents from a country with HBV prevalence >8%
- Household contacts and sex partners of HBsAg+ person
- Past or current user of injected drugs and needle sharing contacts
- Men who have sex with men
- Persons with HIV
- Chronic liver disease
- Cancer or conditions requiring immunosuppressive therapy

[1]Weinbaum, MMWR Recomm Rep, 2008. [2]US Preventative Services Task Force Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults: Screening, 2020. [3]Terrault, Hepatology, 2018.

Risk-based HBV testing in Europe was inaccurate and inefficient

51 primary care clinics in North Rhine Westphalia, Germany, 21k patients[1]

- Testing only if born in a country ≥2% prevalence
  - Missed 60% (65/93) HBsAg+ adults
- Testing only if any HBV risk factor present
  - Missed 33% (31/93) HBsAg+ adults

10 centers in Paris, 4000 patients[2]

- Testing only if any CDC HBV risk factor present
  - HBsAg: 100% sensitivity, 37% specificity
  - 70% of study population reported at least 1 risk factor and would need testing

[1]Wolfram, J Hepatol, 2015. [2]Bottero, PlosOne, 2014.

HBV testing recommendations for US pregnant mothers is not risk-based

2 large US studies focused on pregnant mothers

- >5000 mothers, Jackson FL, 1985[1]
- >4000 mothers, Cleveland OH, 1983-84[2]

Testing only if HBV risk factor present

- Missed 50% of HBsAg+ mothers[1,2]

Led to universal HBV screening for pregnant mothers in 2009[3]

[1]Jonas, Ann Intern Med, 1987. [2]Kumar, Ann Intern Med, 1987. [3]US Preventative Services Task Force Hepatitis B Virus Infection in Pregnant Women: Screening, 2019.

US study in cancer patients may be applicable to a broader population

Patients with HBV and cancer are at risk for HBV reactivation

- Accurate screening is required to prevent serious adverse liver outcomes after systemic anticancer therapy

Internally validated CDC survey among cancer patients[1]

- 2124 patients with cancer screened for hepatitis and completed 19 question hepatitis risk factors survey
- Using bootstrapping methods, models of up to 6 risk factors developed
- Over 90% of cancer patients who complete HBV survey would need to have HBV testing done
- Risk based screening is impractical

[1]Hwang, J Clin Oncol, 2018.

Risk-based testing for cancer patients may miss HBV patients

	19 question study survey	Our 6 question model	Our 5 question model
HBV risk factors	CDC survey[1] and 1 race/ethnicity question	Age ≥50 years Asian or Black race Birthplace outside US Household HBV exposure Male Injection drug	Age ≥50 years Asian or Black race Birthplace outside US Household HBV exposure Male
Sensitivity	100%	100%	99.3%
Specificity	8.4%	10.8%	10.8%
False negative rate	0%	0%	0.7%
Missed HBV patients	0	0	1
% cancer patients would need HBV serologic test[2]	92% (1956/2124)	89.9% (1910/2124)	89.8% (1908/2124)

[1]https://www.cdc.gov/hepatitis/riskassessment/. [2]Percent with ≥1 affirmative answer to any question in HBV risk survey indicating need for blood testing. Hwang, J Clin Oncol, 2018.

Risk-based testing for cancer patients is inefficient

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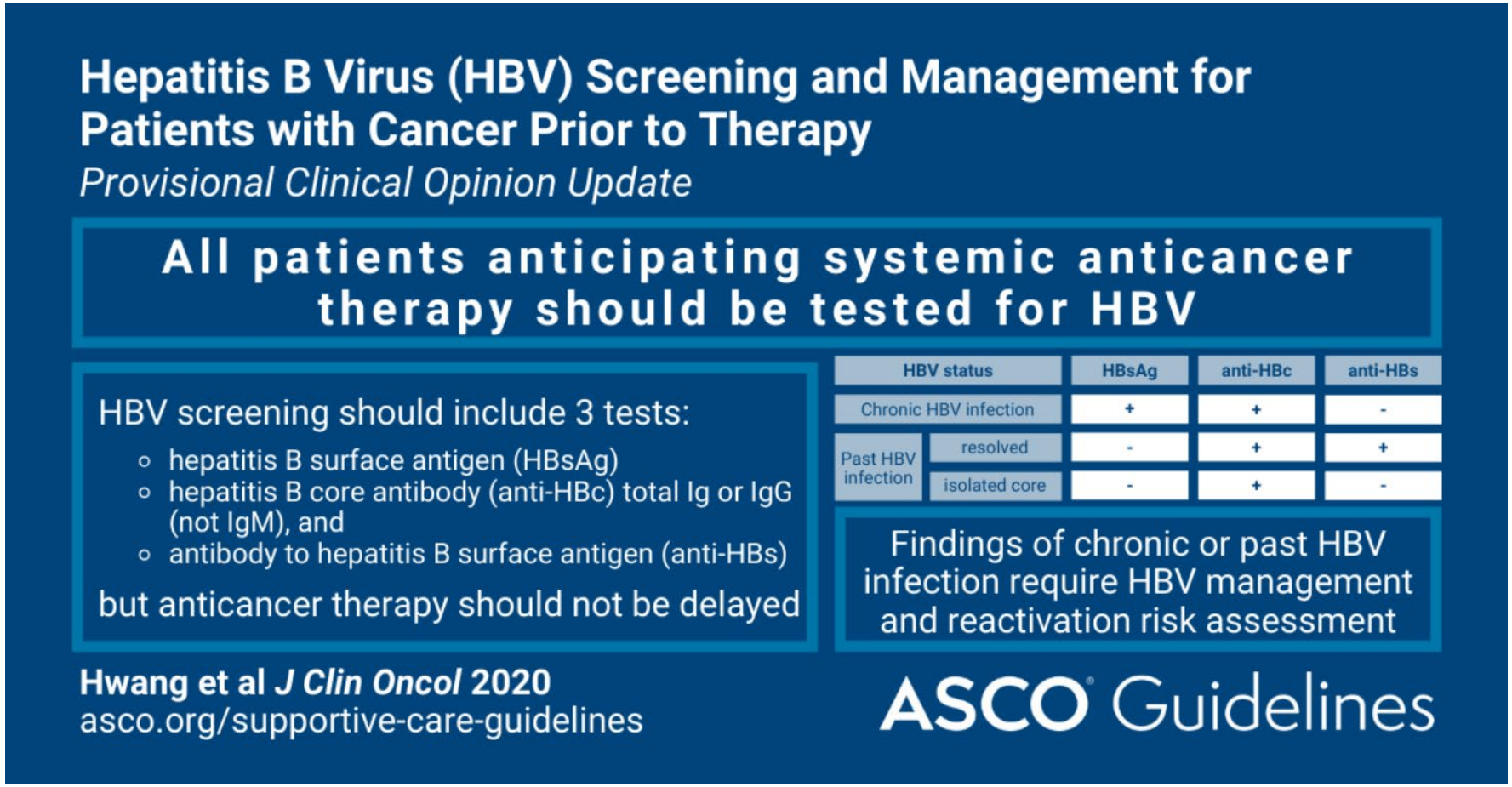
ASCO recommends universal HBV testing



Optimal HBV screening strategies in US primary care setting

Results from oncology are likely applicable to the general population

Externally validate risk survey in our CPRIT Collaborative Action Program to Reduce Liver Cancer Mortality in Texas project

- CPRIT Award RP190513: Patient-Centered Liver Cancer Prevention in the Houston Community

Determine whether risk-based or universal HBV screening is more appropriate at HOPE Clinic, a federally qualified health center in Houston

Once completed, our CPRIT study could provide data to clarify optimal HBV testing strategies

HBV Treatment

Decision to start and stop antivirals for HBsAg+ patients depends on ALT and HBV DNA levels

Currently available antiviral therapies are not curative, require long duration of therapy to suppress virus

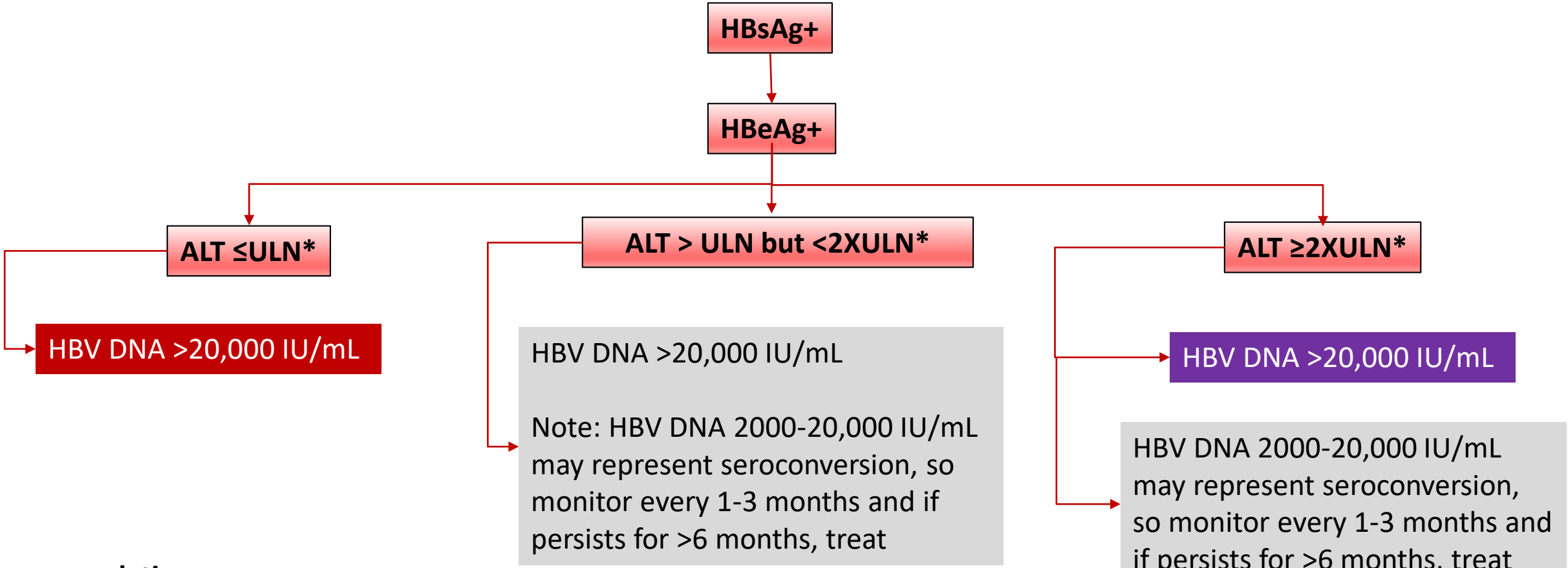
Preferred oral, antiviral therapy
- Tenofovir disoproxil fumarate
- Tenofovir alafenamide
- Entecavir

Non preferred oral, antiviral therapy
- Telbivudine
- Adefovir
- Lamivudine

HBV Therapy Generic	Brand Name	Dose	Approved	Comments
First Line				
Entecavir (ETV)	**Baraclude**	**0.5mg/1.0 mg po qd**	2005	Generic
Tenofovir (TDF)	**Viread**	**300 mg po qd**	2008	Generic in US 2018
Tenofovir alafenamide (TAF)	**Vemlidy**	**25 mg po qd**	2016	Less bone, renal toxicity
Peginterferon alfa-2a	**Pegasys**	**180 ug SQ q week**	2005	Finite tx, 48 weeks
Second Line				
Adefovir (ADV)	**Hepsera**	**10 mg po qd**	2002	Low potency, high rate of resistance
Telbivudine (LDT)	**Tyzeka**	**600 mg po qd**	2006	High potency, high rate of resistance
Third Line				
Lamivudine (LAM)	**Epivir**	**100 mg po qd**	1998	Low potency, high rate of resistance

US Food and Drug Administration, FDA-Approved Drugs, accessdata.fda.gov/scripts/cder/drugsatfda/

Slide courtesy of Su Wang, MD



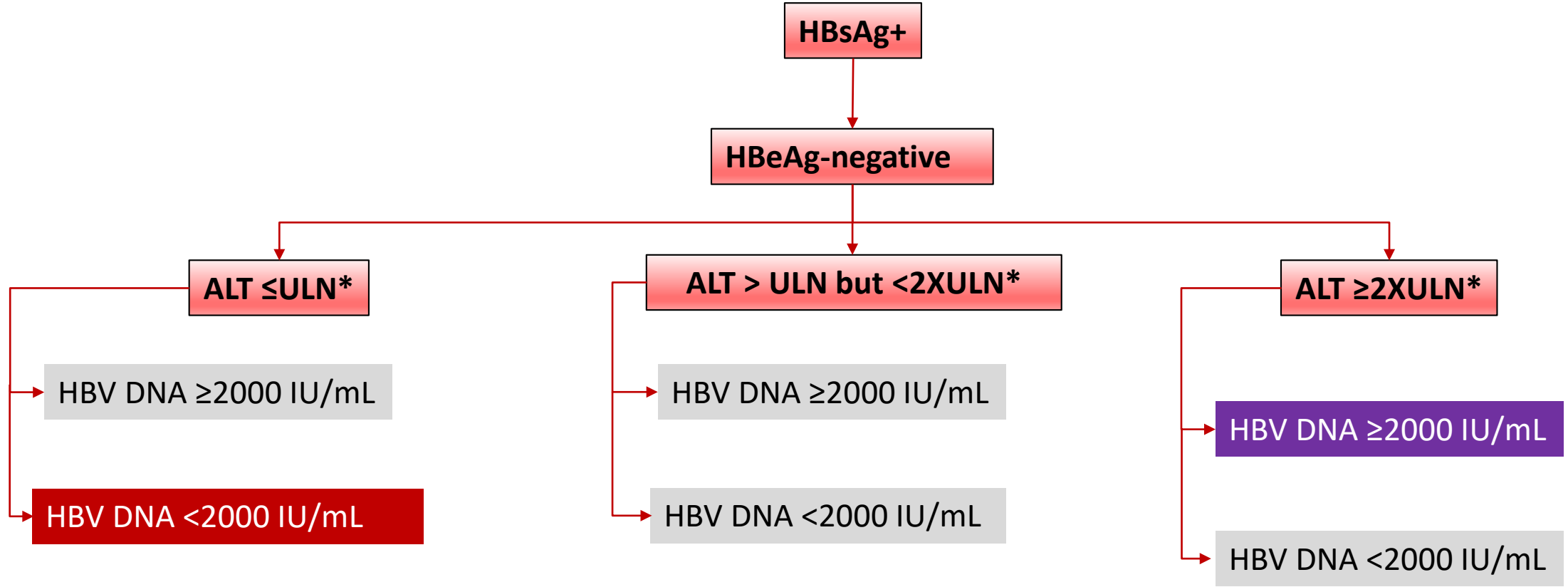
Recommendations:

Treat

Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBeAg every 6-12 months.

Assess disease severity using non-invasive tests and/or liver biopsy; consider other causes of liver disease if elevated ALT. If staging indicates ≥F2 or ≥A3, treat. If other causes of ALT elevation excluded and elevation persistent, treat, especially if age >40.

Terrault, Hepatology, 2018.



Recommendations:

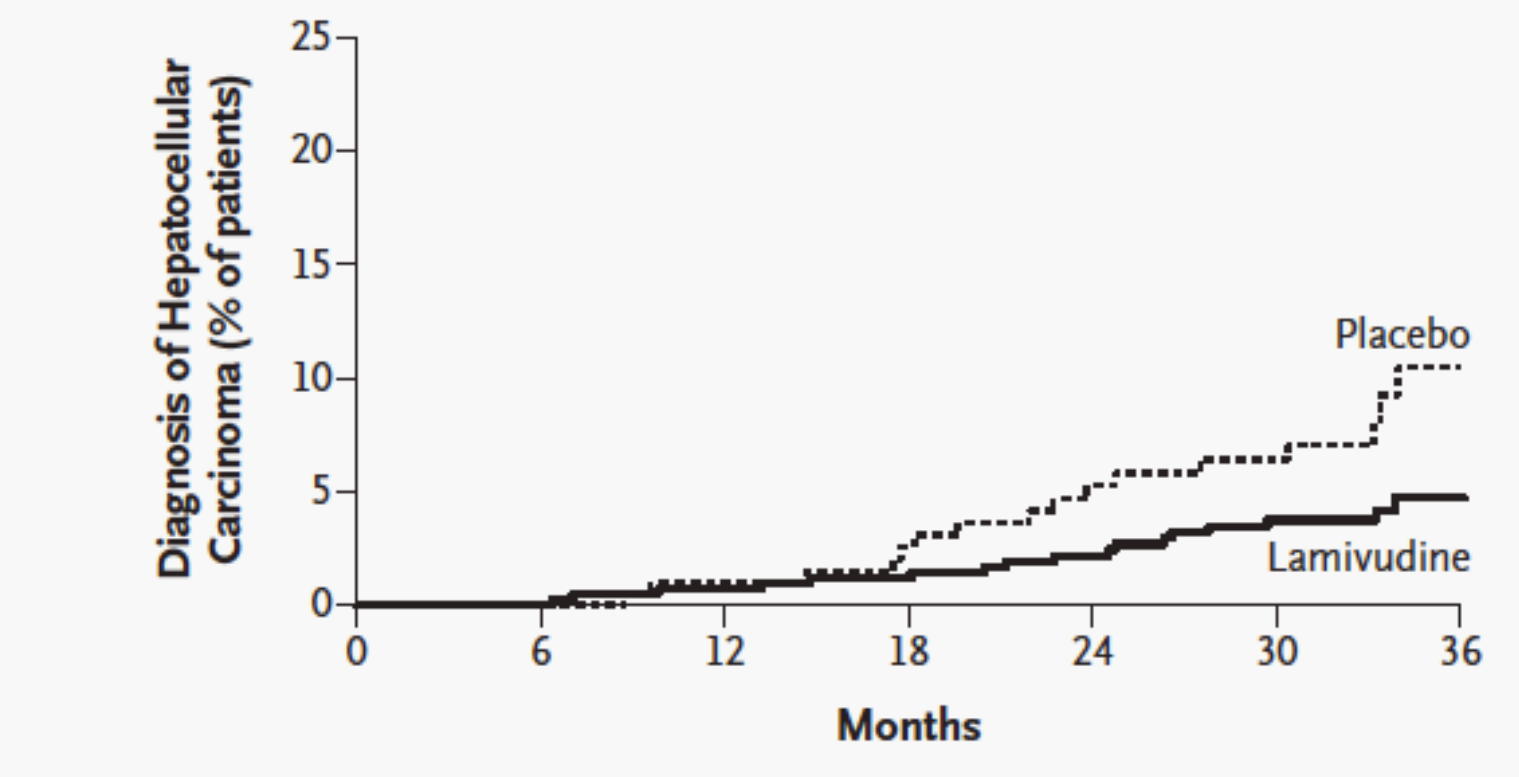
Treat

Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBsAg annually.

If ALT ≤ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months.
If ALT >ULN, exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy.
If staging indicates ≥F2 or ≥A3, treat. If persistent ALT >ULN with HBV DNA ≥2000 IU/mL, treat, especially if age >40.

Terrault, Hepatology, 2018.

Antiviral treatment reduces HCC incidence in persons with chronic HBV - RCT



Liaw, N Engl J Med, 2004

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Antiviral treatment reduces HCC incidence in persons with chronic HBV – US cohorts

Two US cohort studies found that antiviral therapy associated with decreased risk of HCC in HBsAg+ patients

2600 HBsAg+ patients in Chronic Hepatitis Cohort Study (CHeCS)[1]

- 1992-2011, median follow up 5.2 yrs, propensity-score matching
- 820 patients had antiviral therapy; 1851 patients did not
- adjusted HR 0.39 (95% CI 0.27-0.56)

3665 patients in US and Taiwanese REVEAL-HBV cohort[2]

- 1991-2014 N. California; 1992-92 Taiwan; median follow up 8.9 yrs
- 548 patients had antiviral therapy; 3117 patients did not
- adjusted HR, 0.24 (95% CI 0.15-0.58)

[1]Gordon, Clin Gastroenterol Hepatol, 2014. [2]Hoang, Medicine, 2016.

Summary

HBV vaccine prevents HCC and reduces mortality

Accurate and efficient screening of HBsAg+ persons is critical

- Linking patients to care
- Reducing transmission

Risk-based HBV screening has limitations

- Broader screening recommendations may be warranted

Antiviral therapy is effective in preventing HCC