Hepatitis C Virus Webinar 3: Hepatitis C Post Treatment: Key topics for consideration

Michigan Opioid Collaborative

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Disclosures

- Funding from Michigan Department of Health and Human Services to Michigan Opioid Collaborative

Objectives of Webinar

1. Discuss post treatment considerations
2. Discuss HCV in Pregnancy
3. Describe the clinical management of HCV and HBV coinfection.

Post Treatment Considerations

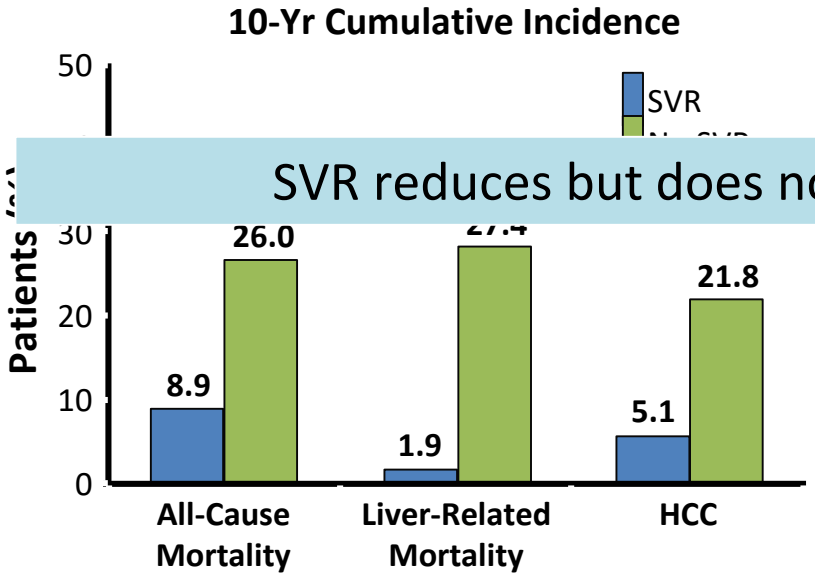
- Consequences of liver disease
  - Cirrhosis (fibrosis assessment pretreatment!)
    - HCC risk
    - Liver function
- Reinfection risk if ongoing exposures
  - HCV RNA testing every 6-12 months
- No ongoing exposures
  - Annual ALT, promote liver health
- HCV antibody positive life long

HCC Screening

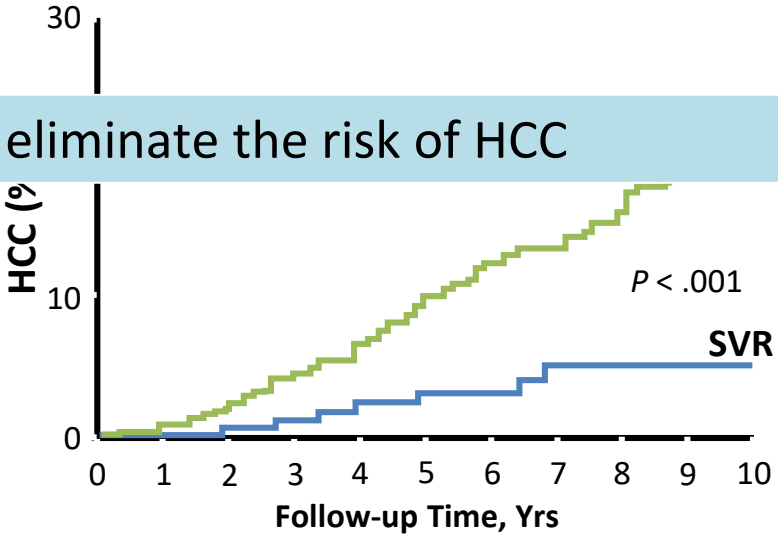
- All patients with F3 and F4 pre treatment
  - Lifelong
  - US +/- AFP every 6 months
  - Can be done by non specialists
  - Many will refer to periodically see specialists to monitor for liver decompensation
- Some patients may have fibrosis improvement post treatment
  - >60% will have histological changes that persist post cure
  - Current tools are not great at assessing regression of fibrosis post SVR to determine who can safely stop HCC screening

Hepatocellular Carcinoma (HCC) After Interferon-Based Treatment

Long-term follow-up of 530 patients with F3/F4, treated for HCV



SVR reduces but does not eliminate the risk of HCC

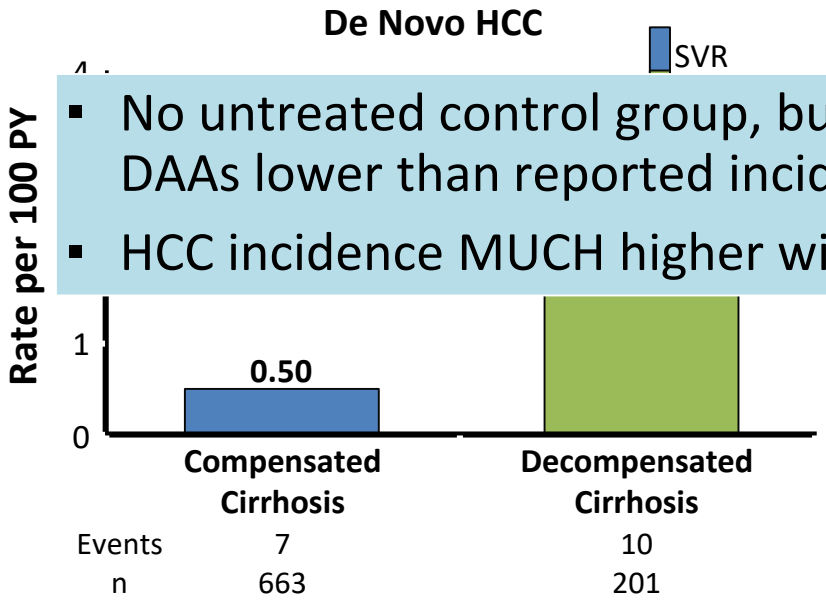


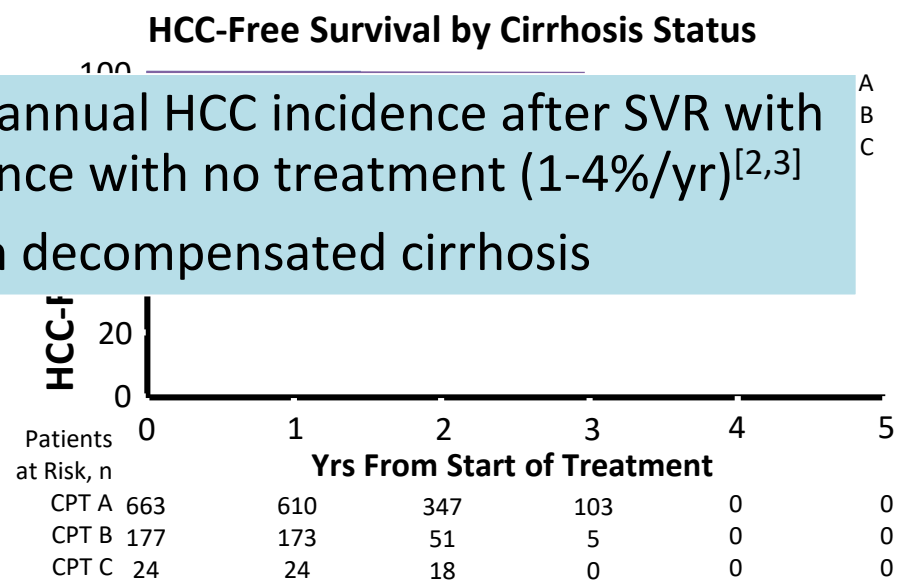
van der Meer. JAMA. 2012;308:2584.

Slide credit: clinicaloptions.com

And With DAAs?

Patients with cirrhosis followed after SOF-based SVR; median follow-up: 85 wks



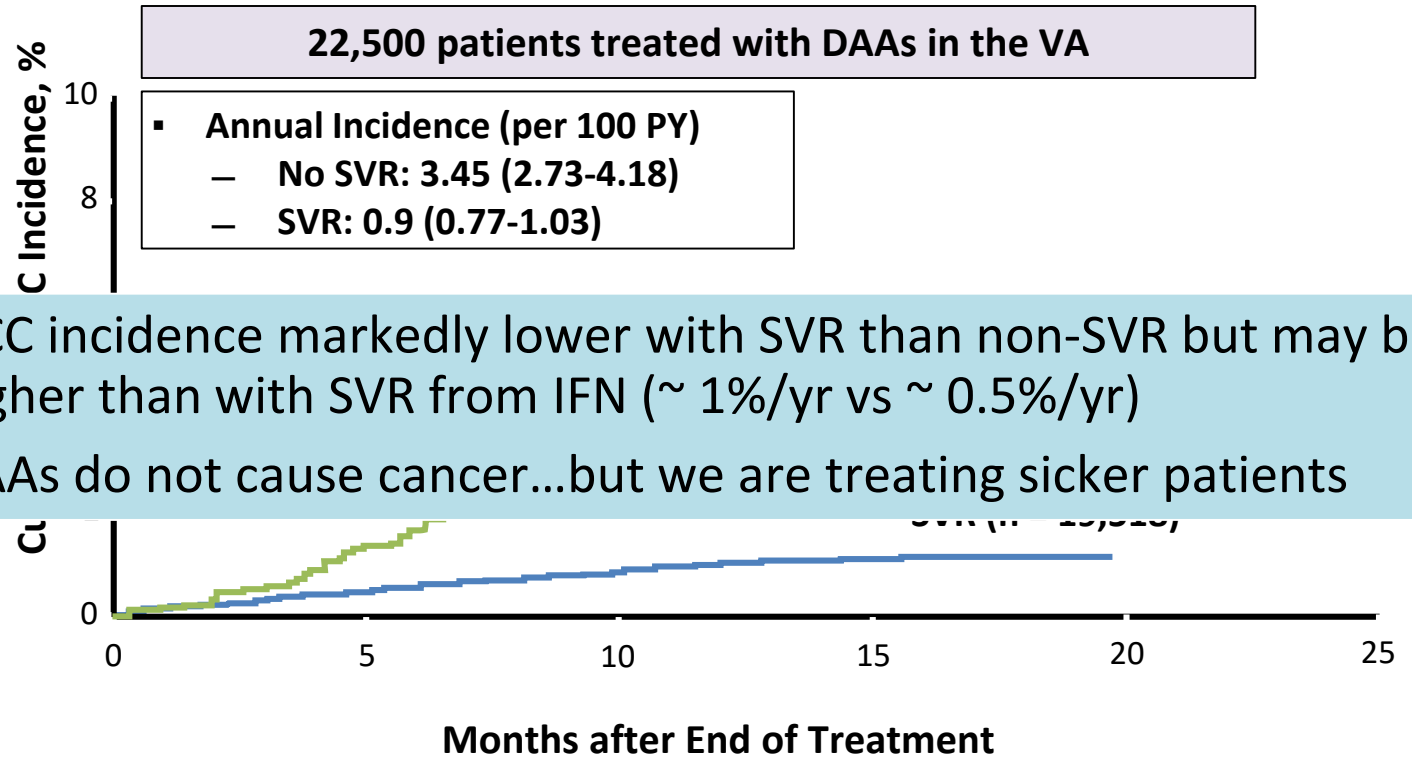


- No untreated control group, but annual HCC incidence after SVR with DAAs lower than reported incidence with no treatment (1-4%/yr)[2,3]
- HCC incidence MUCH higher with decompensated cirrhosis

Slide credit: clinicaloptions.com

Muir. AASLD 2016. Abstr 880.

VA Data is Helpful (large number)



- HCC incidence markedly lower with SVR than non-SVR but may be higher than with SVR from IFN (~ 1%/yr vs ~ 0.5%/yr)
- DAAs do not cause cancer…but we are treating sicker patients

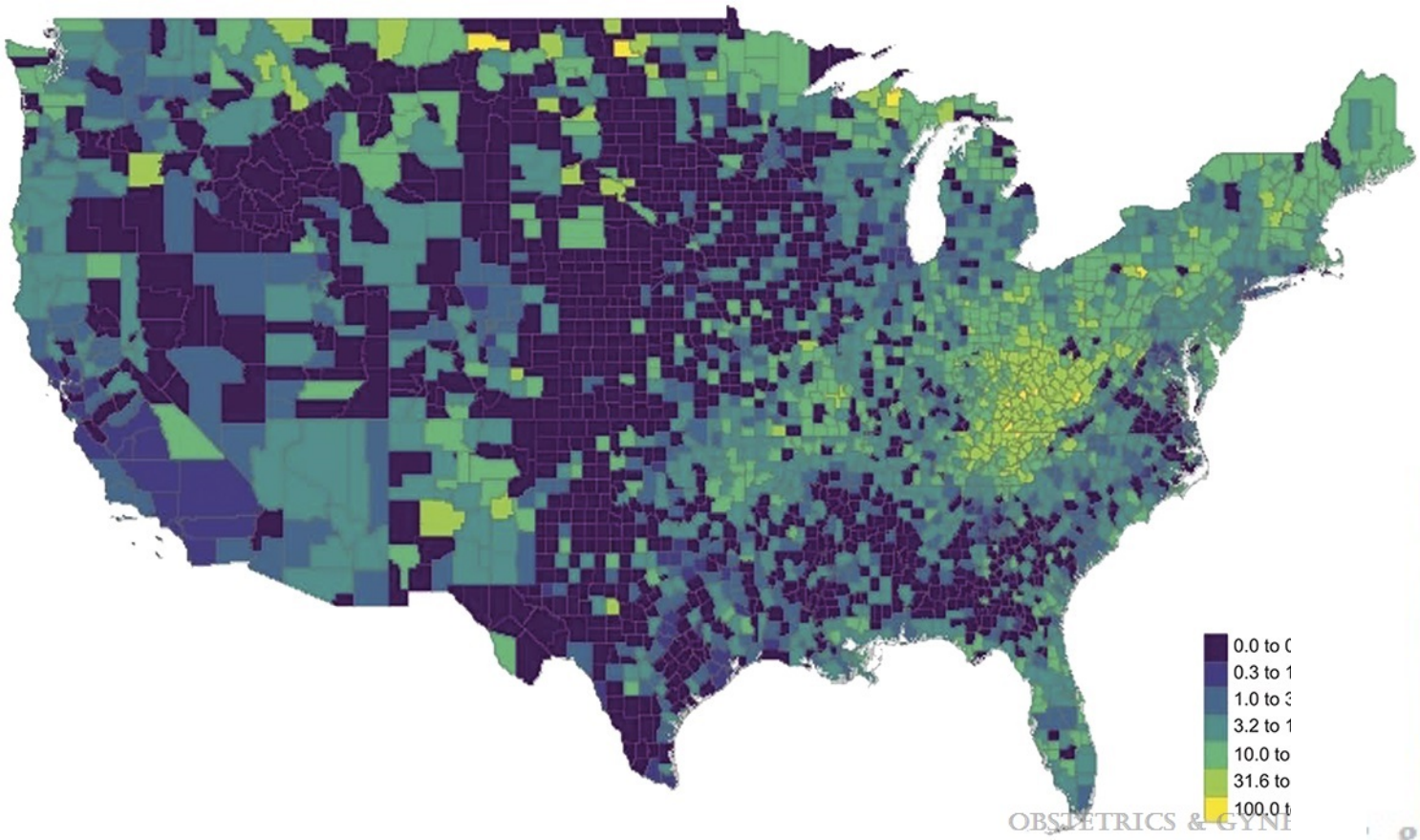
Patients at Risk, n (N HCC)

Achieved SVR	19,518	(85)	19,372	(68)	14,364	(29)	6128	(1)	0	(0)	0
No SVR	2982	(35)	2453	(36)	1617	(14)	636	(3)	5	(0)	0

Slide credit: clinicaloptions.com

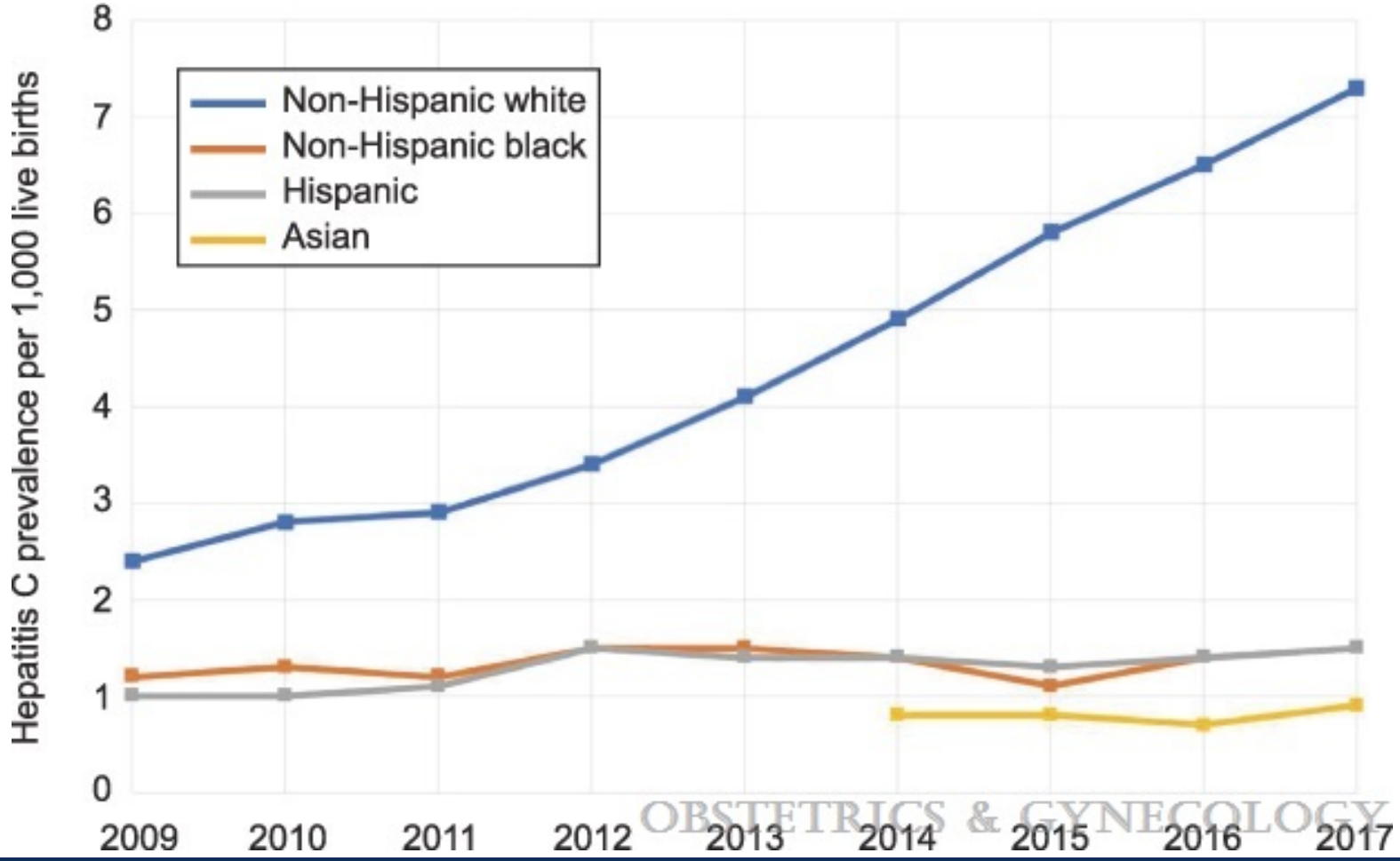
HCV in Pregnancy

Maternal HCV prevalence (per 1,000 live births) at the county level-- United States in 2017



Obstetricians and Gynecologists
Rossi. Maternal Hepatitis C Trends in the United States. Obstet Gynecol 2020.

Racial trends in maternal HCV prevalence per 1,000 live births



Rossi. Maternal Hepatitis C Trends in the United States. Obstet Gynecol 2020.

AASLD/IDSA Guidance: Testing for HCV During Pregnancy

Recommendation for Universal Hepatitis C Screening in Pregnancy	
RECOMMENDED	RATING
As part of prenatal care, all pregnant women should be tested for HCV infection with each pregnancy, ideally at the initial visit. (See Recommendations for Initial HCV Testing and Follow-Up.)	IIb, C

- Testing at the initiation of prenatal care is considered optimal to maximize opportunities for education, referral, and appropriate testing for the exposed infant
- Early identification is key as women living with HCV and their exposed infants are at significant risk for not linking to appropriate HCV evaluation or care.
- Women should be tested with an HCV-antibody test. If positive, this should be followed with testing for HCV RNA.
- HCV-infected pregnant women should be linked to care so that antiviral treatment can be initiated at the appropriate time

Key Points Regarding HCV in Pregnancy

- Today HCV in pregnancy should be considered a biomarker for opioid use disorder
- Assess for OUD and engage in MAT
- HCV treatment in pregnancy not yet approved
- There are no large-scale clinical trials evaluating the safety of direct-acting antivirals (DAAs) in pregnancy
  - A small study evaluating the pharmacokinetics of sofosbuvir in pregnancy demonstrated 100% SVR12 and no safety concerns (Chappell, 2019).
  - An international case series of 15 pregnant women treated with ledipasvir/sofosbuvir reported 100% SVR12 and no early safety concerns in the women or their infants (Yattoo, 2018).
  - Currently, there are no available data on the use of pangenotypic regimens during pregnancy.
- Despite the lack of a recommendation, treatment can be considered during pregnancy on an individual basis after a patient-physician discussion about the potential risks and benefits.

Pregnancy and Post Partum Recommendations

Recommendation Regarding HCV Treatment and Pregnancy	
RECOMMENDED	RATING
For women of reproductive age with known HCV infection, antiviral therapy is recommended **before** considering pregnancy, whenever practical and feasible, to reduce the risk of HCV transmission to future offspring.	I, B

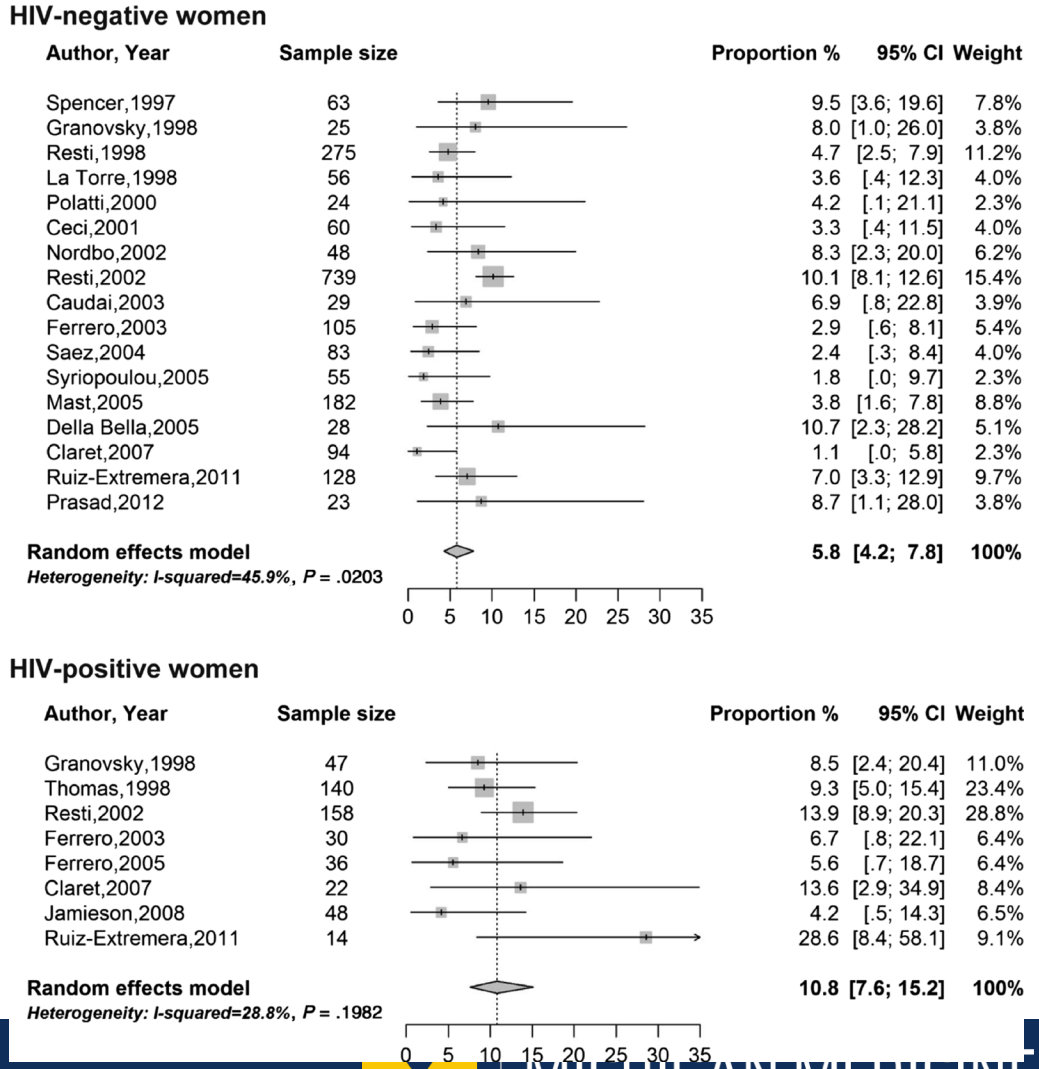
Recommendations Regarding Breastfeeding and Postpartum Care for HCV-Infected Women	
RECOMMENDED	RATING
Breastfeeding is not contraindicated in women with HCV infection, except when the mother has cracked, damaged, or bleeding nipples, or in the context of HIV coinfection.	I, B
Women with HCV infection should have their HCV RNA reevaluated after delivery to assess for spontaneous clearance.	I, B

HCV Treatment in Pregnancy

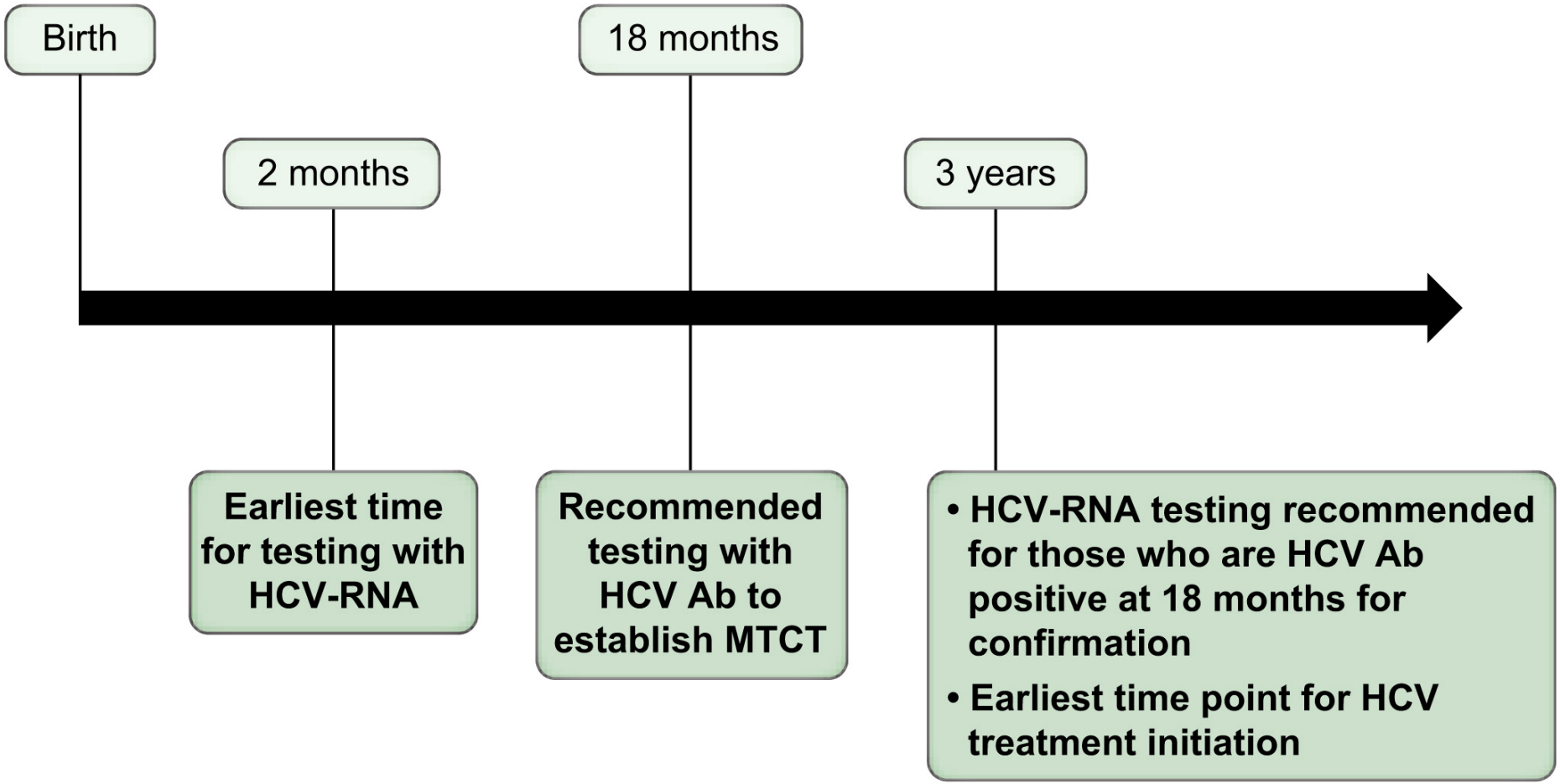
- Women who become pregnant while on DAA therapy (with or without ribavirin) should discuss the risks versus benefits of continuing treatment with their physicians
- Ribavirin is contraindicated in pregnancy due to its known teratogenicity
- In addition, the risk for teratogenicity persists for up to 6 months after ribavirin cessation and applies to women taking ribavirin and female partners of men taking ribavirin

Vertical transmission of HCV Mother-to-Child

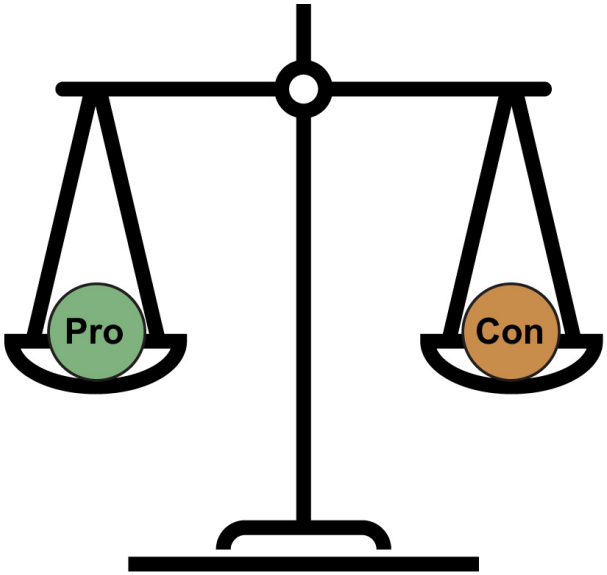
- Leading cause of HCV infection in children
- One third to one half of MTCT of HCV occur in utero prior to the last month of pregnancy, remainder occurs in the last month of pregnancy or delivery
- A meta-analysis examining rates of vertical transmission of HCV, stratified by whether women were coinfected with HIV.
  - Pooling 17 studies of women with chronic HCV infection who were HIV-negative, the risk of vertical transmission was 5.8%
  - The risk of vertical transmission in HIV-positive women, based on the results of 8 studies, was 10.8%



Assessment of mother-to-child transmission



Treatment with DAA During Pregnancy



1. Maternal cure while engaged in pregnancy care
2. Possible decrease in MTCT
3. Maternal treatment while under insurance coverage
4. Decrease in community transmission
5. Potential decrease in HCV-associated adverse pregnancy outcomes?

1. Human safety in pregnancy not established
2. Safety during breastfeeding not established
3. More established data for treatment prior to pregnancy or children starting at age 3
4. Difficulty in accessing DAA therapy in time (prior to delivery)
5. Cost-effectiveness not established

Kushner T, Reau N. J Hepatolog 2020

What Is the Effect of HCV Infection on Pregnancy?

- HCV may have negative effects but difficult to tease apart from effects of associated factors (eg, injection drug use)

Meta-analysis of > 4,000,000 women with > 5000 HCV infection cases[1,2*]

Birth Outcome	OR With vs Without HCV (95% CI)
Preterm birth[1]	1.62 (1.48-1.76)
Intrauterine fetal growth restriction[2]	1.53 (1.40-1.68)
Low birth weight[2]	1.97 (1.43-2.71)

Swedish Birth Registry: > 1 million women, > 2000 births to HCV+ women, 2001-2011[3]

Birth Outcome	aRR With (n = 1,091,913) vs Without (n = 2056) HCV (95% CI)
Preterm birth	1.32 (1.08-1.60)
Late neonatal death	3.79 (1.07-13.79)

*1. 4,186,698 participants with 5218 HCV infection cases; 2. 4,185,414 participants with 5094 HCV infection cases.

- Multicenter observational US study to assess outcomes in pregnant women with HCV (N = 772) and their infants launched in 2012[4,5]

1. Huang. J Viral Hepat, 2015;22:1033. 2. Huang. Medicine (Baltimore). 2016;95:e4777.
3. Stokkeland. Eur J Epidemiol. 2017;32:617. 4. NCT01959321. 5. Prasad. Obstet Gynecol. 2020;135:778

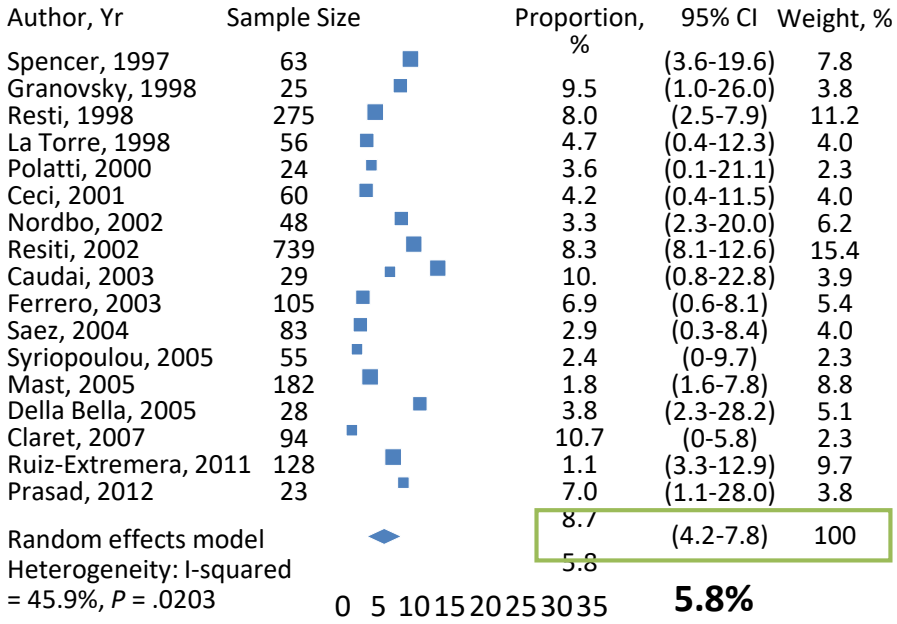
Why Consider Antiviral Therapy During Pregnancy?

- Potential to reduce risk of MTCT; similar to HBV
- Pregnancy is often a time when women have health insurance and engaged in health care
  - Opportune time to treat HCV concurrent with pregnancy care
- Provides opportunity to cure HCV in women with high-risk behaviors to prevent transmission to others, including injecting partners

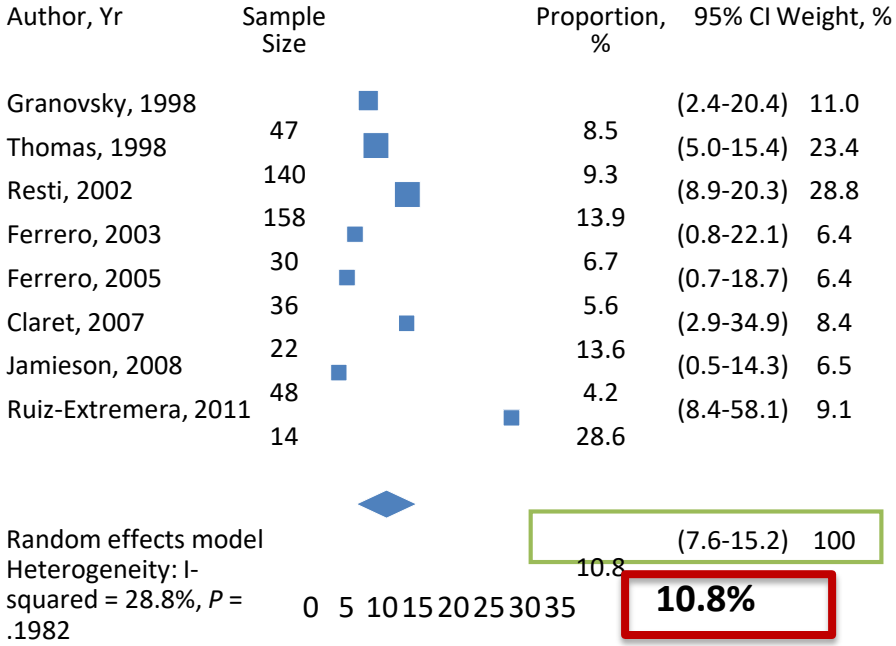
Risk of MTCT of HCV by Maternal HIV Serostatus

- Systematic review and meta-analysis of 109 studies with HCV Ab+, HCV RNA+ mothers

HIV-negative women



HIV-positive women



Benova. Clin Infect Dis. 2014;59:765.

Slide credit: clinicaloptions.com

Recommendations of Society of Maternal and Fetal Medicine Regarding Prevention of MTCT of HCV

Recommendation	Grade of Recommendation
Amniocentesis is recommended over chorionic villus sampling given the lack of data on the latter	2C
We recommend against cesarean delivery solely for the indication of HCV infection.	1B
We recommend that obstetric care providers avoid internal fetal monitoring, prolonged rupture of membranes, and episiotomy in managing labor in HCV-positive women	1B
We recommend that providers not discourage breastfeeding based on a positive HCV infection status	1A

Hughes. Am J Obstet Gynecol. 2017;217:B2.

MTCT Most Common Cause of HCV in Children

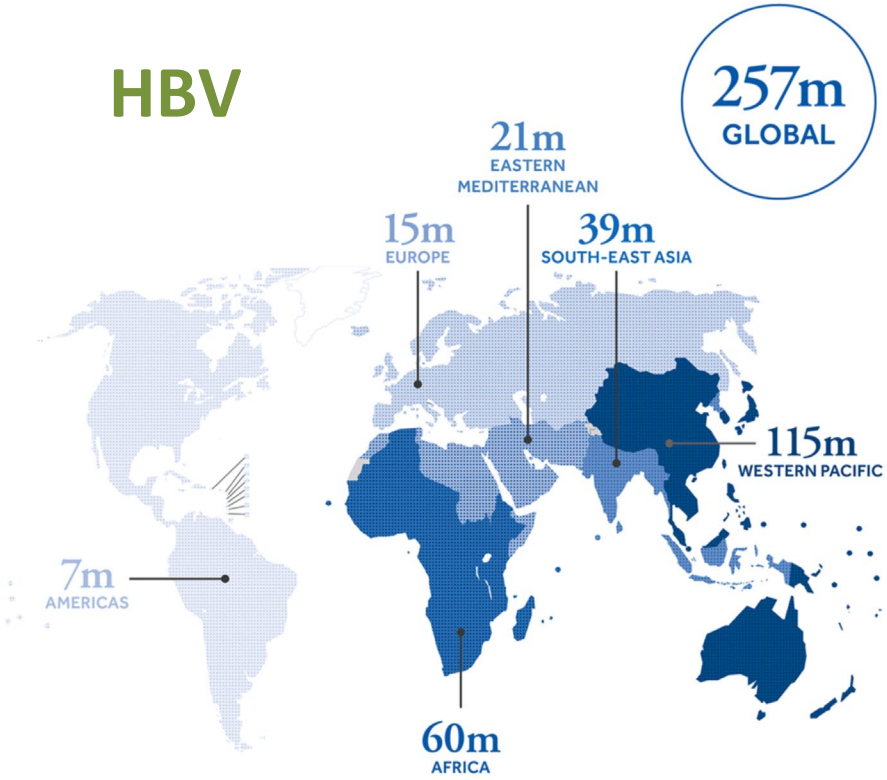
- 25% to 40% of infants clear HCV by 2-3 yrs of age[1]
- Impact of HCV infection in children on quality of life[1,2]
  - Reduced physical functioning[1,2]
  - Executive function impairment in 20% of children with HCV[1]
  - Worse cognitive functioning vs children without HCV[1]
    - Parental emotional impact and decrement in parental quality of life[1]
- Higher rates of cirrhosis in children who acquire HCV through MTCT[1]
- Hepatocellular carcinoma is second most common hepatic malignancy in children[1,3]

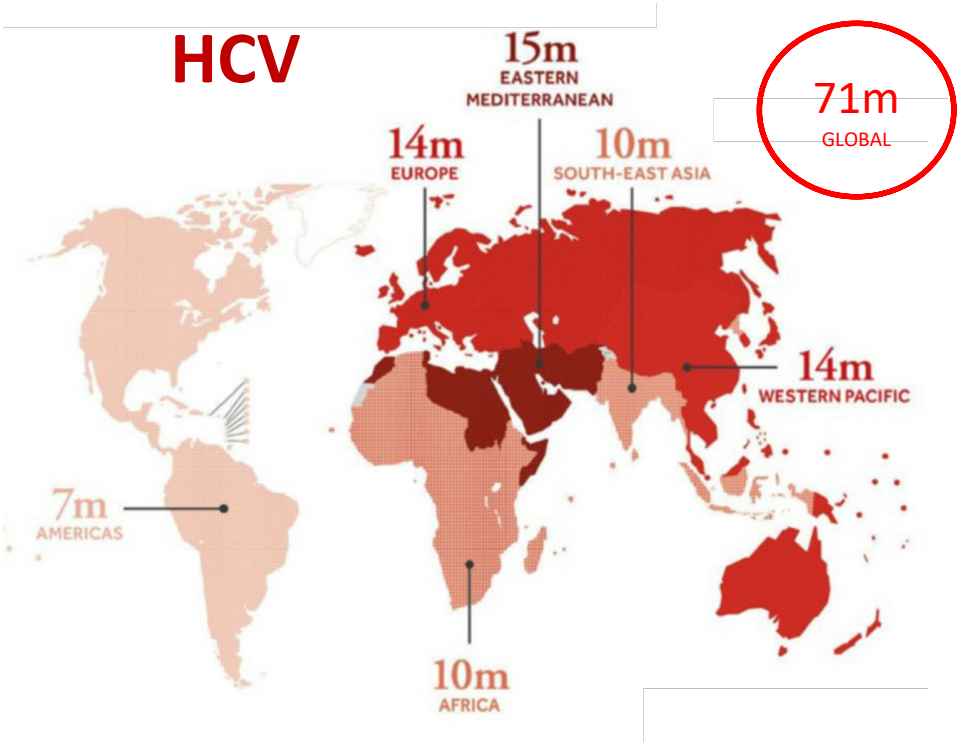
1. Murray. Diseases of the Liver in Children. Springer. 2014. 2.Nydegger. J Gastroenterol Hepatol. 2008;23:226. 3. Modin. J Hepatol. 2019;70:371.

Slide credit: clinicaloptions.com

Hepatitis B and C: Coinfection & Reactivation

Putting Viral Hepatitis B and C into a Global Perspective

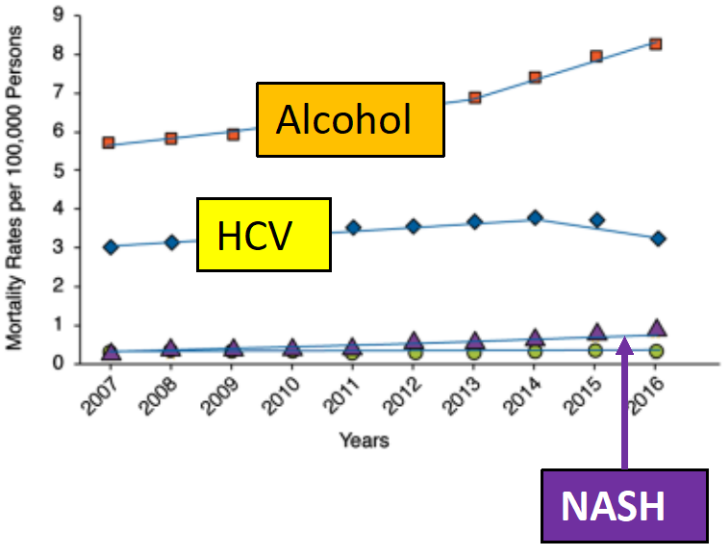




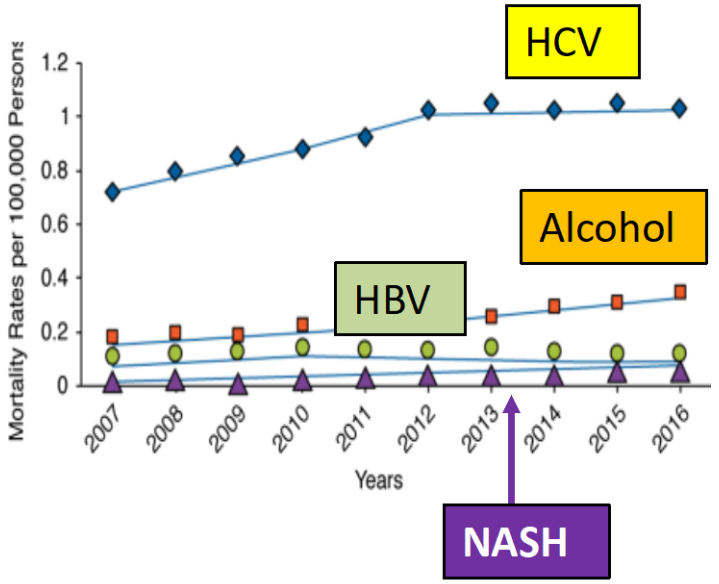
WHO, Global hepatitis report 2017

Viral Hepatitis Remains a Major Source of Mortality in the United States

In the US, approximately 2.4 million living with HCV infection[1] and 840,000 living with HBV infection[2]



Cirrhosis
Age-standardized Mortality[3]

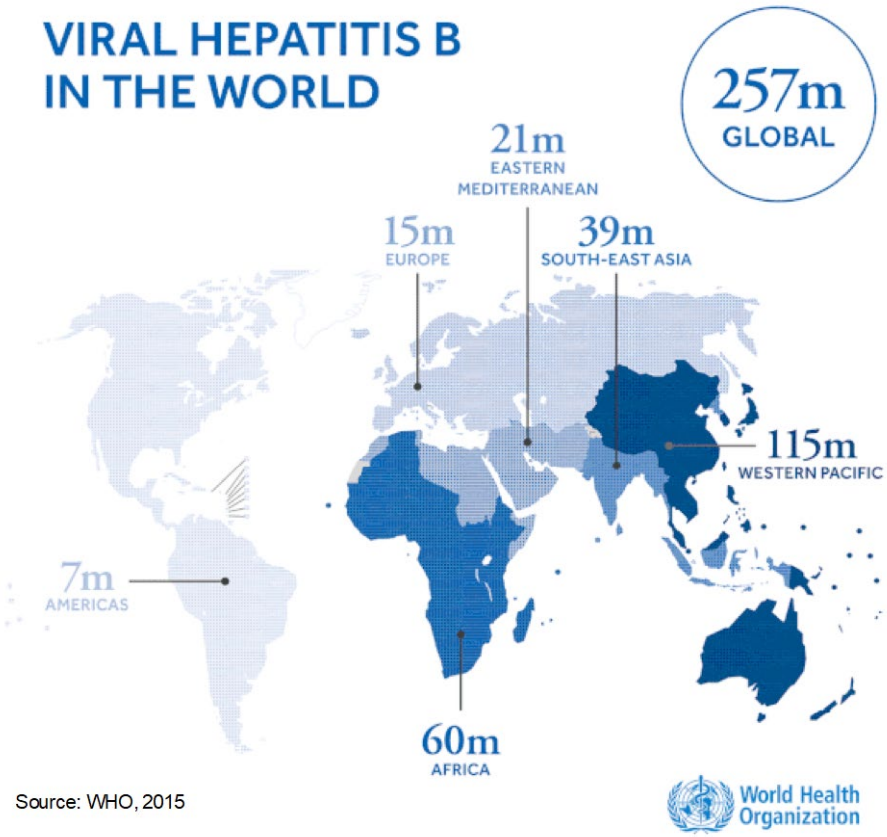


HCC
(Age-standardized Mortality)[3]

1. Hofmeister MG et al. Hepatology 2019
2. Le MH, et al. Hepatology 2019
3. Kim, et al, Hepatology, Volume: 69, 2019

Hepatitis B Epidemiology

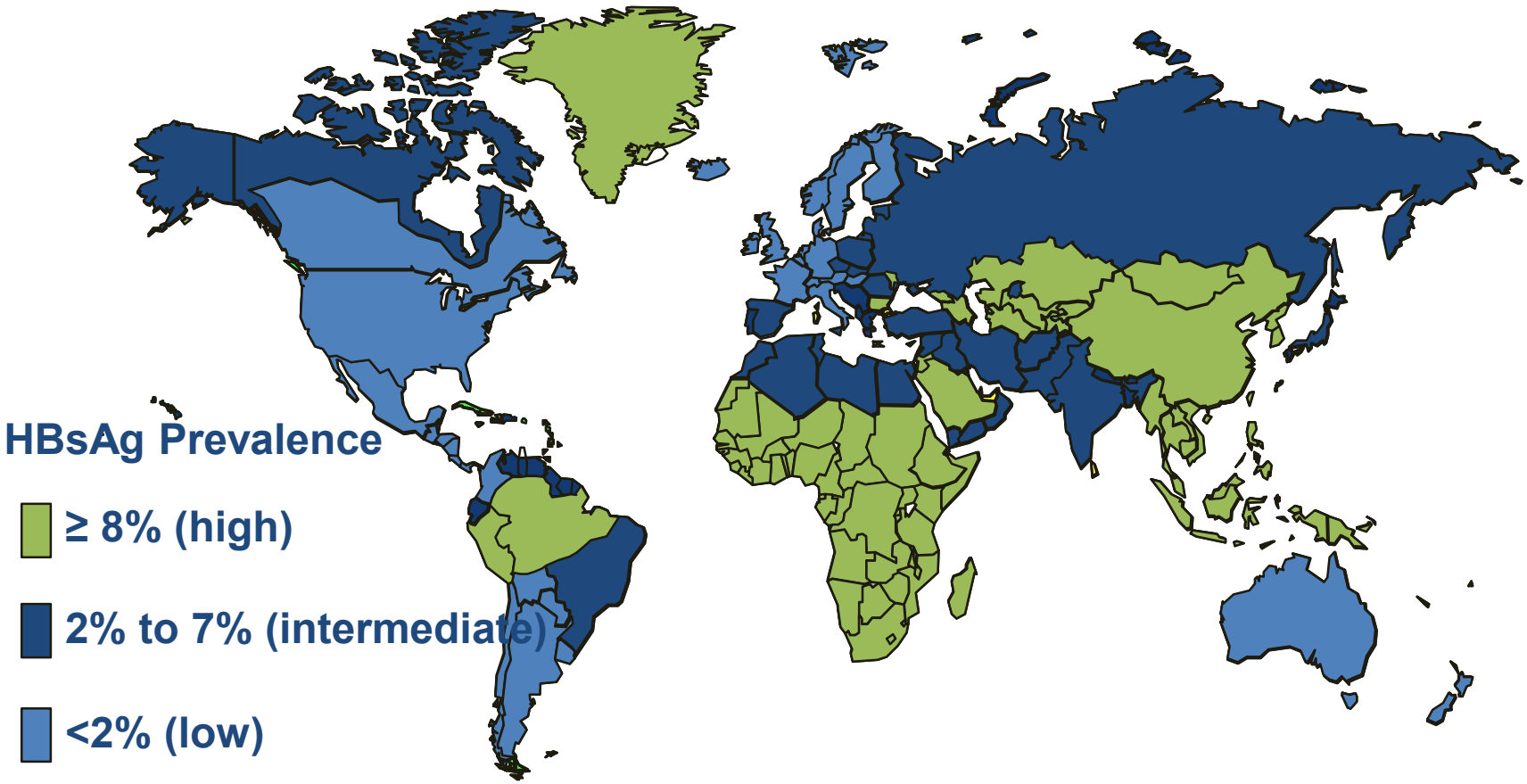
Identifying at-risk populations



In 2015:

- 257 million persons (3.5% population) infected
- 68% in Africa and Western Pacific
- 2.7 million co-infected with HIV
- Most infected persons born before HBV vaccine was widely used in infancy
- Leading cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide
- 30%-50% of HCC associated with HBV in the absence of cirrhosis
- HBV is second to tobacco in causing cancer deaths
- HBV 50-100 times more infectious than HIV

Geographic Distribution of Chronic HBV Infection

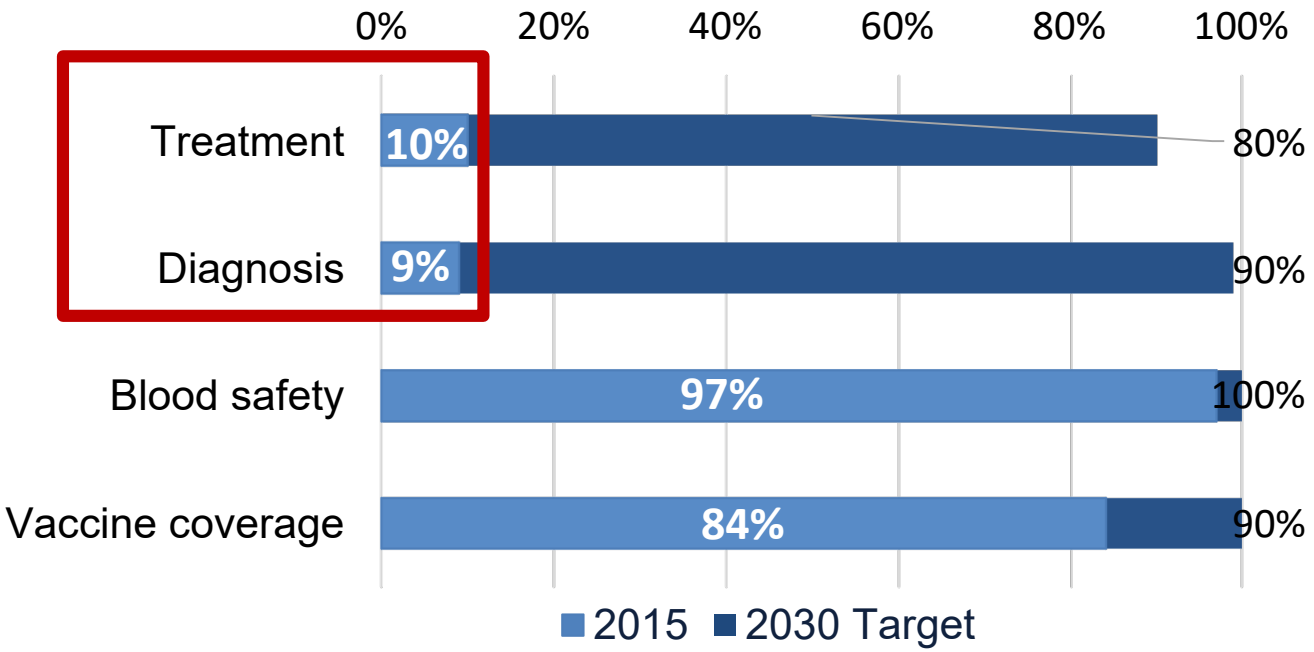


HBsAg=Hepatitis B surface antigen

Source: Weinbaum CM, et al. MMWR Recomm Rep. 2008;57(RR-8):1-20.

Global and U.S. Goals for Elimination of HBV as Public Health Threat by 2030

– **By 2030, 90% reduction in new infections and 65% reduction in deaths**



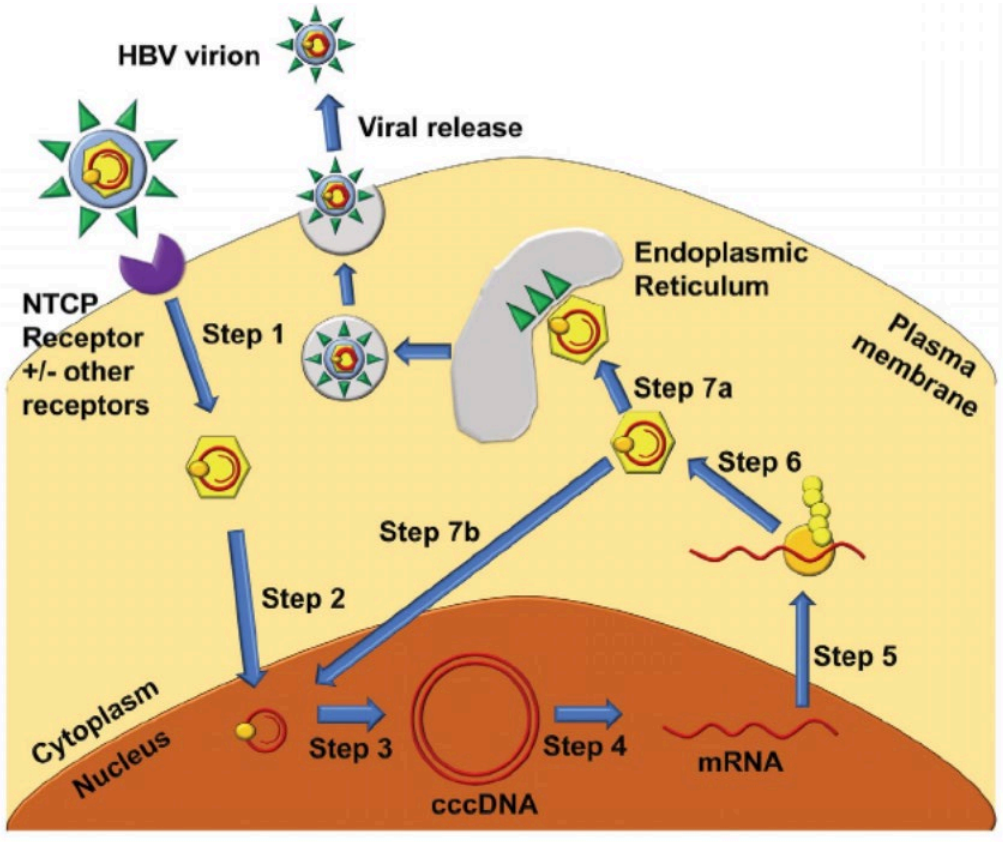
Source: https://www.who.int/hepatitis/publications/hepatitis-service-coverage-targets/en/.

HBV modes of transmission

ENDEMIC COUNTRIES	NONENDEMIC COUNTRIES
• Mother to baby at time of birth (~50% of cases, most common among Asians)	• Adult sexual activity (~54% of cases, most common)
• Horizontal within household during early childhood (Virus can survive at least 7 days outside body)	• IV drug use (~20% of cases)
• Health care (Re-use of non-sterilized needles and syringes in resource-poor areas, contaminated blood products)	
• Traditional medicine (Acupuncture, coining, cupping, scarification, etc.)	

HBV Key Points

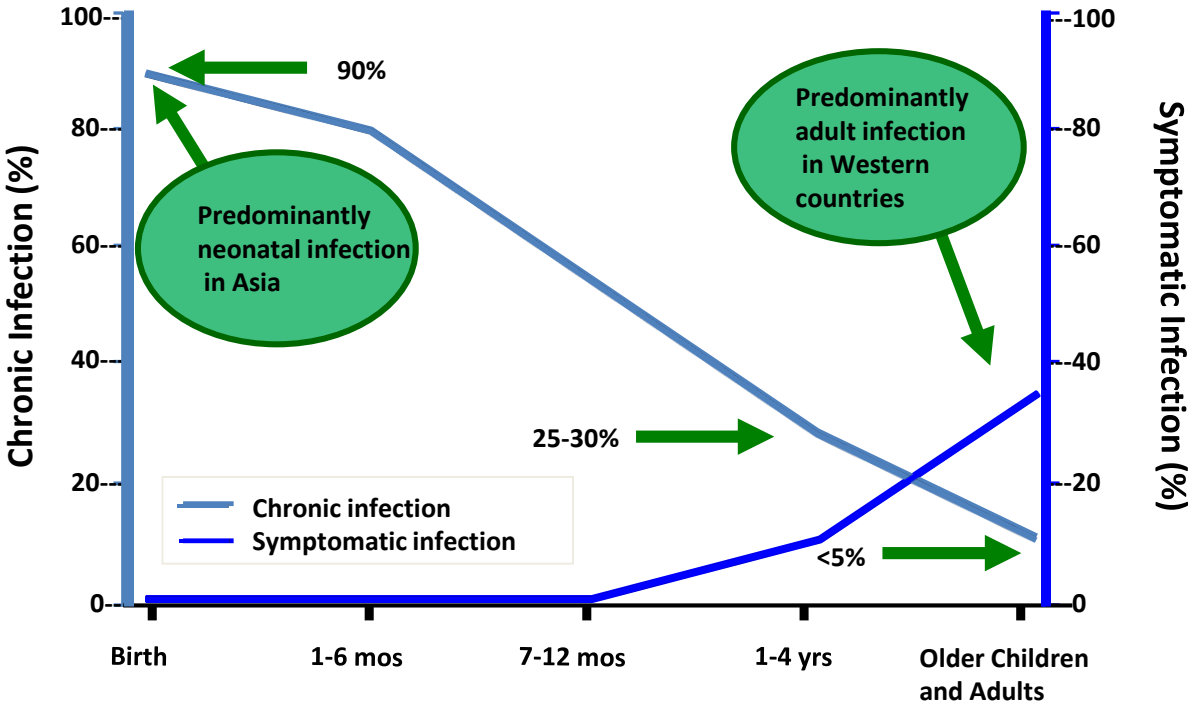
- Unlike HCV, HBV incorporates DNA in host
- Not everyone recommended for treatment
- Treatment aimed at viral suppression
- Treatments have evolved- safe and effective
- No current curative therapy for HBV although many drugs being studied in pipeline



New England Journal of Medicine. Copyright 2014. Massachusetts Medical Society.

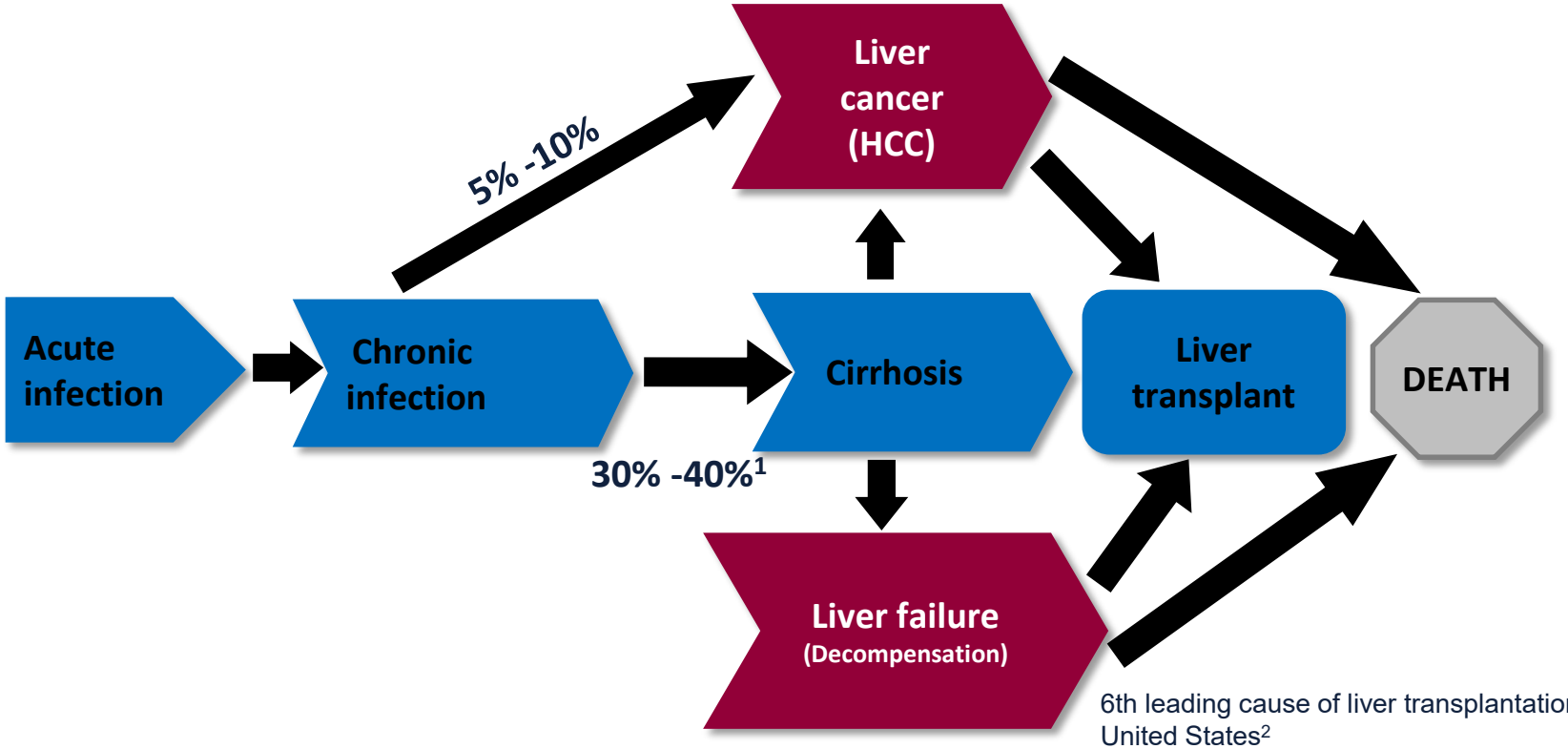
Outcome Of HBV Infection by Age Of Transmission

- Chronic infection in >90% of newborns infected at birth
- Chronic infection in only 3% to 5% of adults
- 40% of men and 15% of women with perinatally acquired HBV **will die** of liver cirrhosis or HCC
- Safe and effective vaccine has been available since 1981



Source: Stanford Asian Liver Center 2007. Physician's Guide to Hepatitis B

Hepatitis B Disease Progression



6th leading cause of liver transplantation in the United States[2]

Source: 1. Moyer LA, Mast EE. Am J Prev Med. 1994;10(suppl):45-55. 2. Perrillo RP, et al. Hepatology. 2001;33:424-432.

HBV Epidemiology in the United States

ESTIMATED 862,000 (95% confidence interval [CI], 668,000–1,056,000) people living with hepatitis B (2016)

11% INCREASE in rate of acute cases (2014–2018)

3,322 REPORTED ACUTE CASES (2018)

AGES 30-49

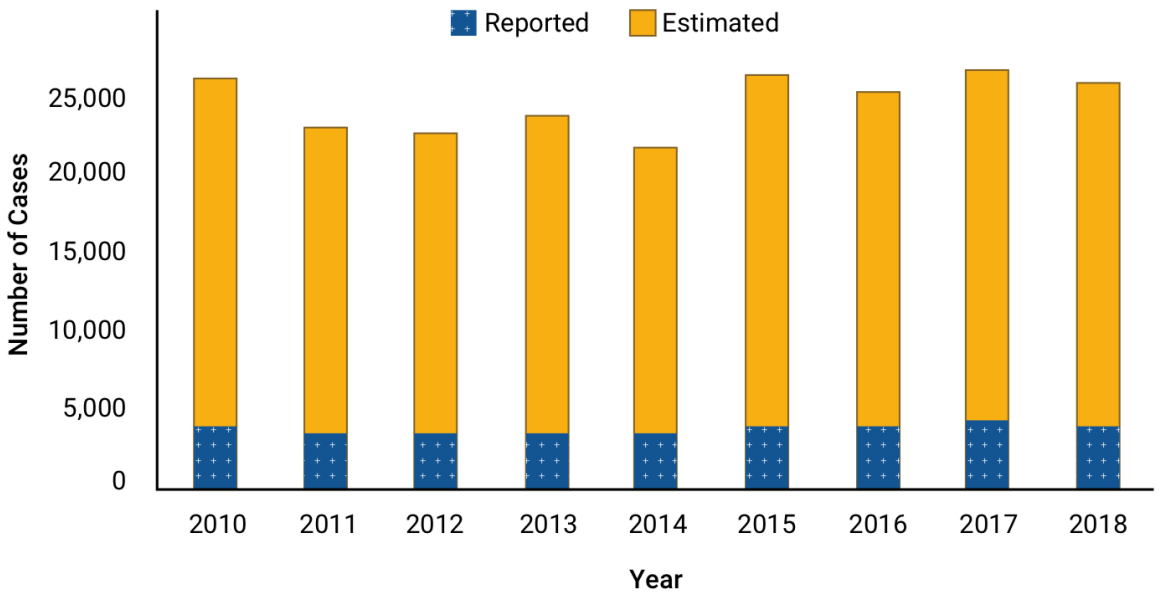
MORE THAN ONE-HALF OF ACUTE HEPATITIS B CASES (2018) were among persons aged 30–49 years and were due to low vaccination rates and the opioid crisis

21,600 ESTIMATED ACUTE INFECTIONS (2018)

UP TO 70% OF CHRONIC HEPATITIS B INFECTIONS in the United States are among non-U.S.-born populations, with the highest prevalence among people from Asia (58%) and Africa (12%)

https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf

Reported and estimated number of acute HBV cases – US, 2010-2018



Populations Disproportionately Impacted

- Acute
  - » People who inject drugs
- Chronic/Morality
  - » Asian and Pacific Islander
  - » Black, non-Hispanic

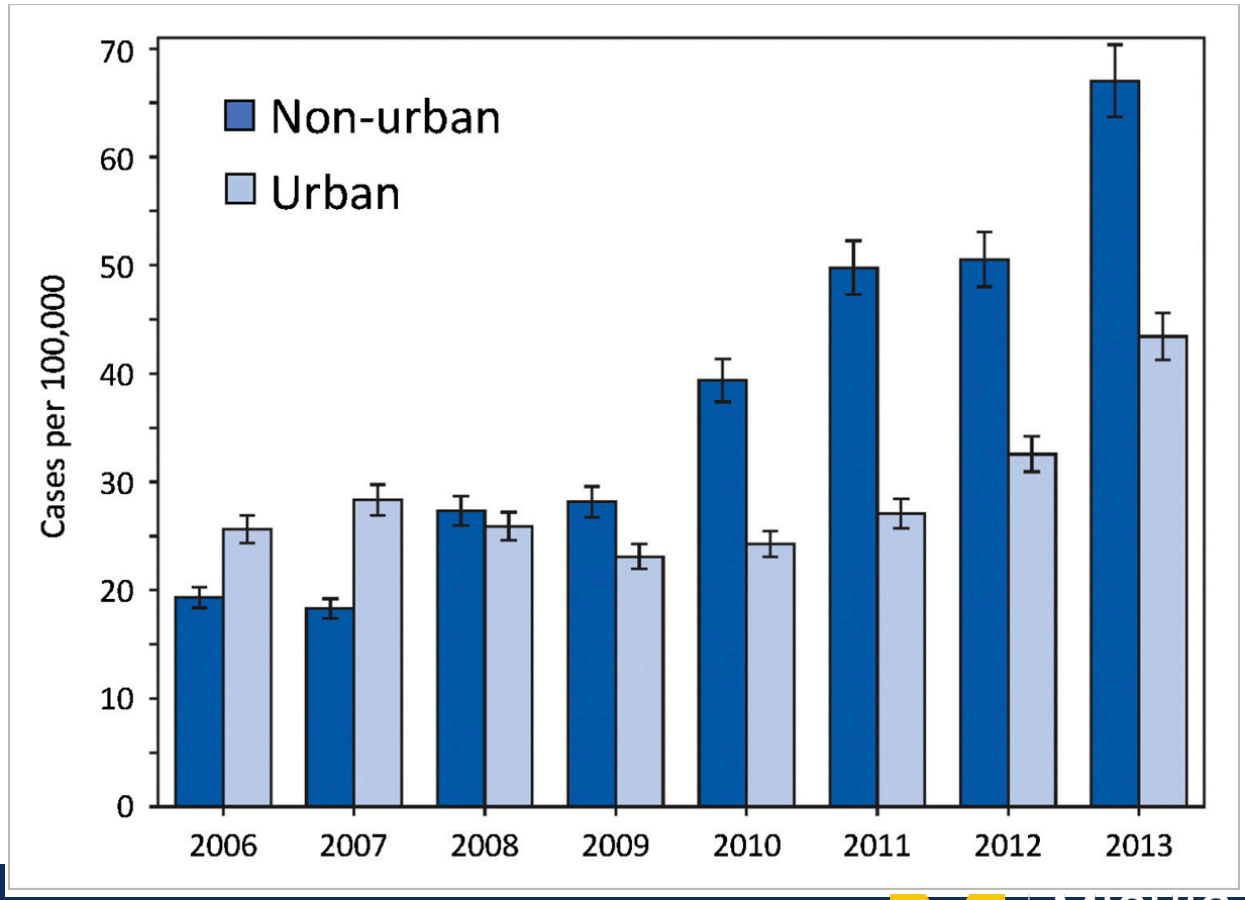
Current Challenges

- Acute
  - » Injection drug use
  - » Low adult vaccination rates
- Chronic
  - » Perinatal transmission
  - » Lack of awareness of infection
  - » Testing and linkage to care
  - » Price of treatment
  - » No curative treatment

https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategi[illegible]-2020-2025.pdf

Recent increase of acute HBV in the US

Incidence of acute HBV in Kentucky, Tennessee, and West Virginia



USPSTF Screening Recommendations For HBV Infection In High-risk Individuals

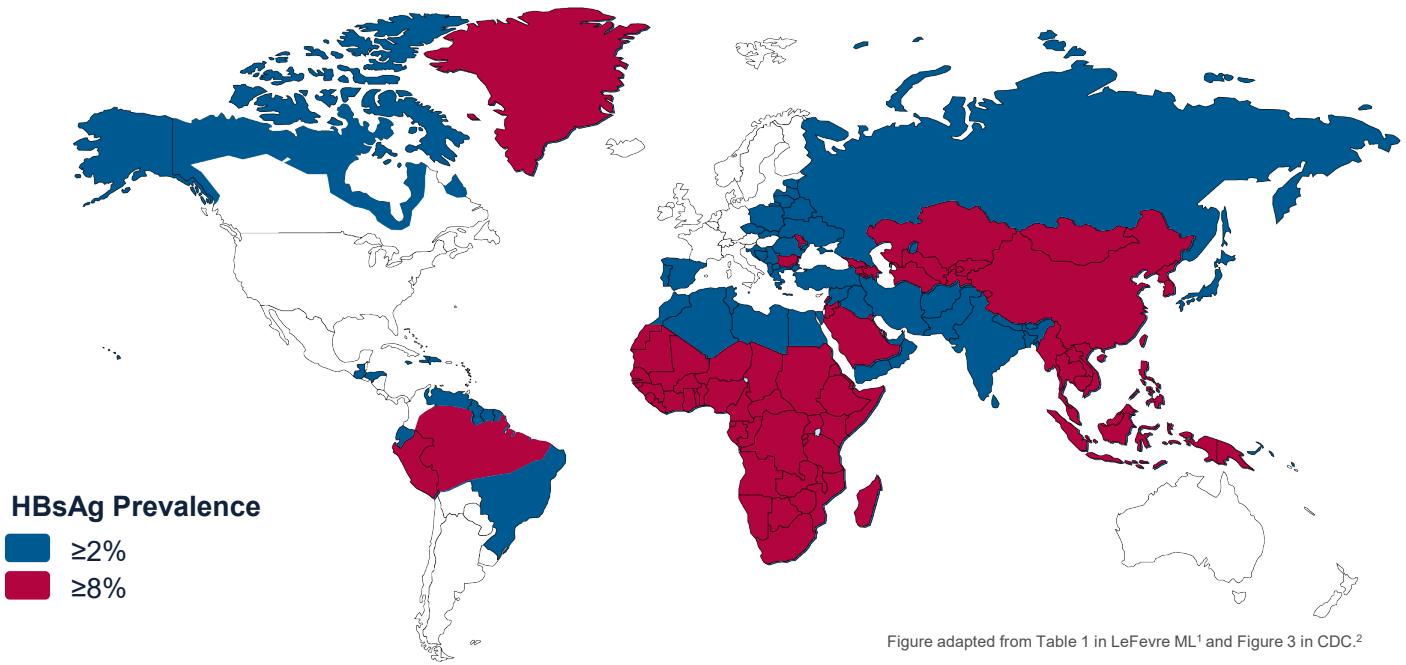


Figure adapted from Table 1 in LeFevre ML[1] and Figure 3 in CDC.[2]

- People born in regions with prevalence of HBV infection of ≥2%[1]
- US-born people not vaccinated as infants whose parents were born in regions with prevalence of HBV infection of ≥8%[1]

Sources: 1. LeFevre ML; USPSTF. Ann Intern Med. 2014;161:58-66; 2. CDC. Hepatitis B FAQs for Health Professionals.

Who Should Be Screened For HBV?

- Persons born in high and intermediate endemic areas (≥2% prevalence)
- US-born children of immigrants from high endemic areas (≥8%; only if not vaccinated as infants in the US)
- Household and sexual contacts of HBV carriers
- Persons who have injected drugs
- Persons with multiple sexual partners or history of STIs

- Men who have sex with men
- Inmates of correctional facilities
- Individuals with chronically elevated ALT/AST
- Individuals infected with HIV or HCV
- Patients undergoing dialysis
- Patients who are immunosuppressed
- All pregnant women
- Infants born to HBV carrier mothers

How common is HBV in the United States?

- >90% of cases in the US occur in immigrants from endemic parts of the world
- Most new cases of HBV in US are from sexual transmission or injection drug use
  - 46, 000 new cases each year
- 2000–4000 deaths yearly from the complications of chronic HBV infection, decompensated cirrhosis, and HCC
- 15% of HCC cases in the US are from HBV

Roberts H, et al. *Hepatology* 2016.

Diagnosis of Hepatitis B Virus

Hepatitis B Serology 101 – Step One Screening for HBV

- **HBsAg: Hepatitis B surface antigen**
  - Marker of active infection
  - Chronic HBV: HBsAg positive for at least 6 months
- **Anti-HBs (or HBsAb): Antibody to HBsAg**
  - Marker of immunity to hepatitis B
- **Anti-HBc: Total hepatitis core antibody (IgG)**
  - Previous exposure or false positive
- ***If acute HBV is suspected: IgM Anti-HBc**

Hepatitis B Serology 101 – Step Two If HBsAg is Positive

- **HBeAg: hepatitis B "e" antigen**
  - Surrogate marker of high viral load
- **Anti-HBe (or HBeAb): antibody to HBeAg**
  - Precore or basal core promoter mutation: associated with lower viral load
- **HBV DNA: active viral replication**

- 30-40% have active hepatitis that meets criteria for antiviral treatment

Currently approved therapies for HBV

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

Hepatitis B and Hepatitis C Coinfection

How common is HBV/ HCV coinfection?

- Depends on the patient population and regional prevalence
- 10-15% of HCV patients are coinfected with HBV (up to 30% in some settings)
- 5-20% of HBV patients are coinfected with HCV
- Shared routes of transmission

HBV and HCV dual infection – what are the issues?

1. Accelerated disease course
2. Treatment prioritization
3. Risk of HBV reactivation with HCV treatment

Viral interactions between HBV and HCV

3 main theories

1. Direct inhibition of HCV to HBV replication
2. Increase in available replication space after eradication of one virus
3. Loss of host immune responses to one of the viruses, usually HBV, or production of an immune inhibitory signal of one virus to improve replication over the other

Hepatitis B Reactivation

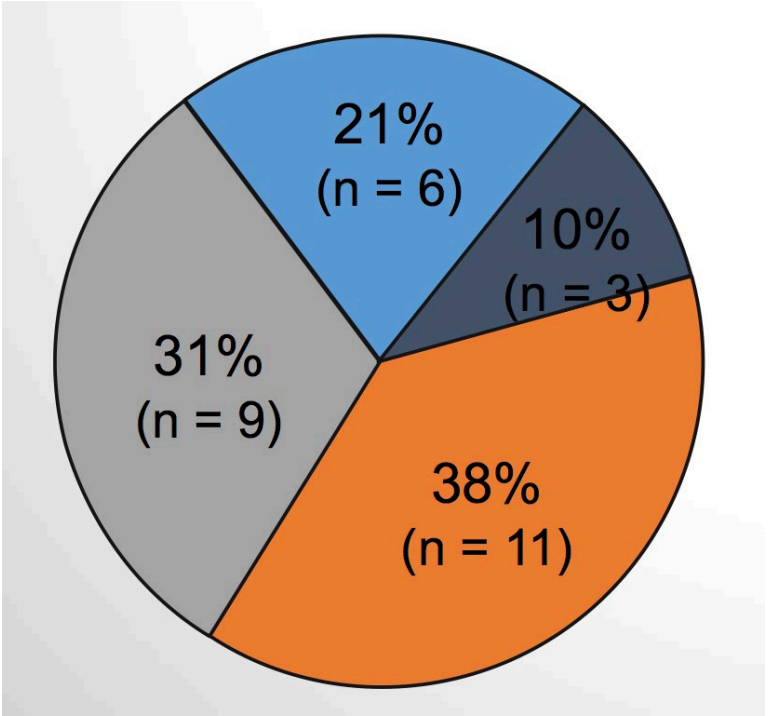
What is HBV reactivation?

- *Clinical syndrome characterized by sudden increase in HBV replication due to a loss in immune control.* Occurs in HBsAg+, anti-HBc+ or HBsAg–, anti-HBc+ patients
- A 1-log (10 fold) increase in HBV DNA in the serum or a return of HBV DNA viremia in a patient with undetectable HBV DNA at baseline.
- May include reverse seroconversion (return of HBsAg in a HBsAg-negative individual)

Manifests as Wide Clinical Spectrum:
Silent reactivation, elevated viral load without overt hepatitis
HBV-associated hepatitis, elevated viral load and evidence of clinical, biochemical, or histological hepatitis
Fulminant liver failure, elevated viral load with hepatic synthetic dysfunction, encephalopathy, and coagulopathy

Hepatitis B reactivation: An (unwanted) affect of HCV treatment

- FAERS database search 11/22/13 – 10/15/16
  - 29 cases identified (5 in USA, 19 in Japan, 5 other); 3 decompensated: 2/3 death; 1/3 underwent liver transplant
- Mean time to reactivation 53 days (most 4–8 wks)
- No specific DAA regimen the culprit; no specific HCV genotype
- 14 patients had possible delay in care
  - **The FDA now requires a boxed**



	GLP/PIB	LED/SOF	SOF/VEL
Entecavir	♦	♦	♦
Tenofovir alafenamide	♦	♦	♦
Tenofovir-DF (HBV)	♦	▮	▮

Perello et al. Clin Gastro and Hep 2016;14:1682-86

HBV reactivation in HCV patients on DAAs

Theories:

1. HCV core protein interferes with HBV gene expression; Once HCV is treated, HBV replicates
2. Increase in available replication space after eradication of HCV allows replication of HBV
3. HCV can induce an interferon-abundant state that inhibits HBV replication; once HCV is gone, interferons “relax”

HBV reactivation during DAA compared to IFN therapy

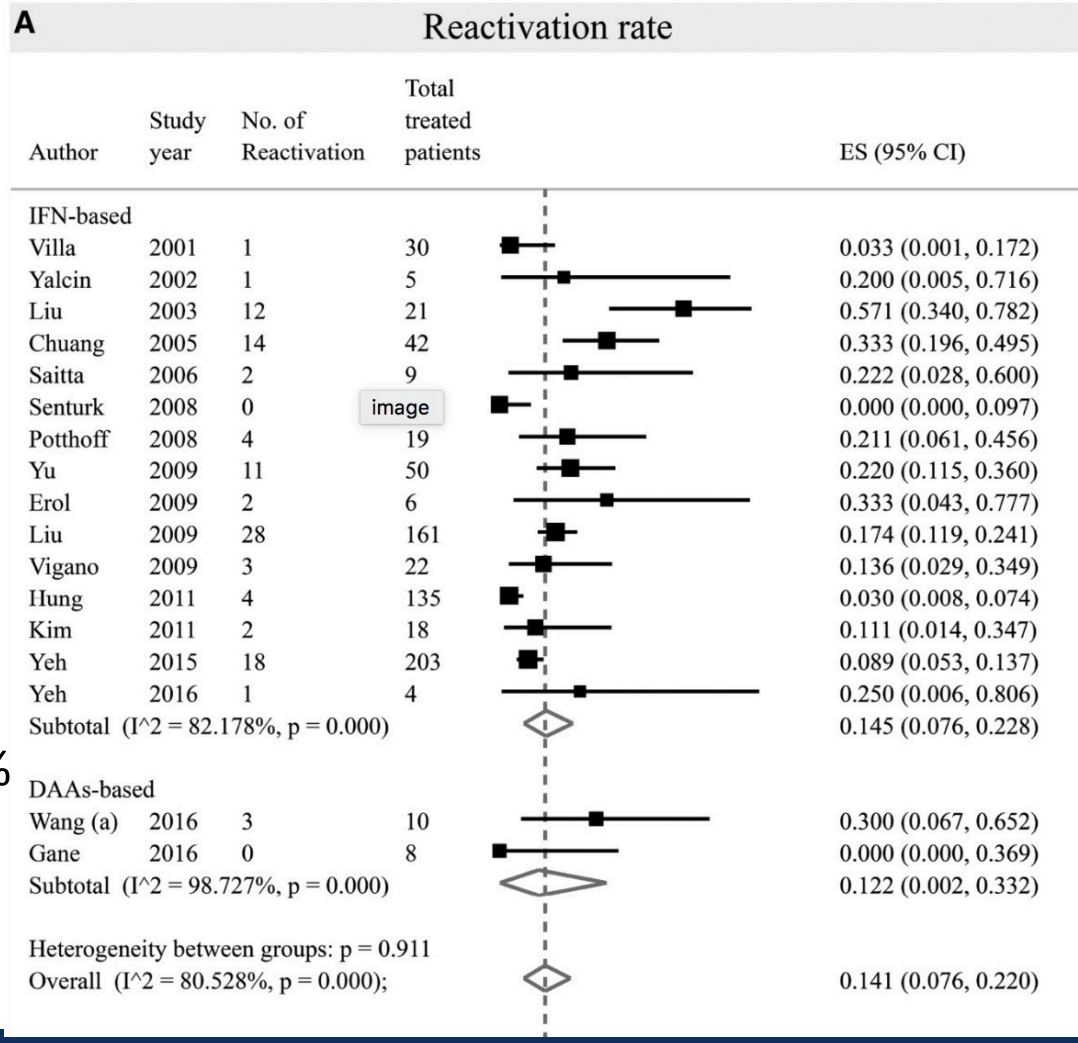
28 studies; 884 HBV and 292 resolved HBV infection

Endpoints:

1. Hepatitis B reactivation
2. Occurrence of hepatitis 2/2 HBV reactivation

Results:

- Pooled HBV reactivation rate **14.1%**
- IFN-based vs. IFN free DAA (14.5% vs. 12.2%; *P* = 0.03)
- Occurred sooner with DAA than with interferon treatment



Chen, G, et al. *Hepatology* 2017.

Another meta-analysis

- 17 studies; 242 with chronic HBV and 1379 with resolved HBV infection
- Risk of HBV reactivation 24% in patients with untreated chronic HBV infection and 1.4% with resolved HBV infection.
- Risk of HBV-reactivation-related hepatitis 9% with chronic HBV infection, and no HBV-related hepatitis with resolved infection.

Mucke M, et al. [illegible] Gastroenterol Hepatol 2018.

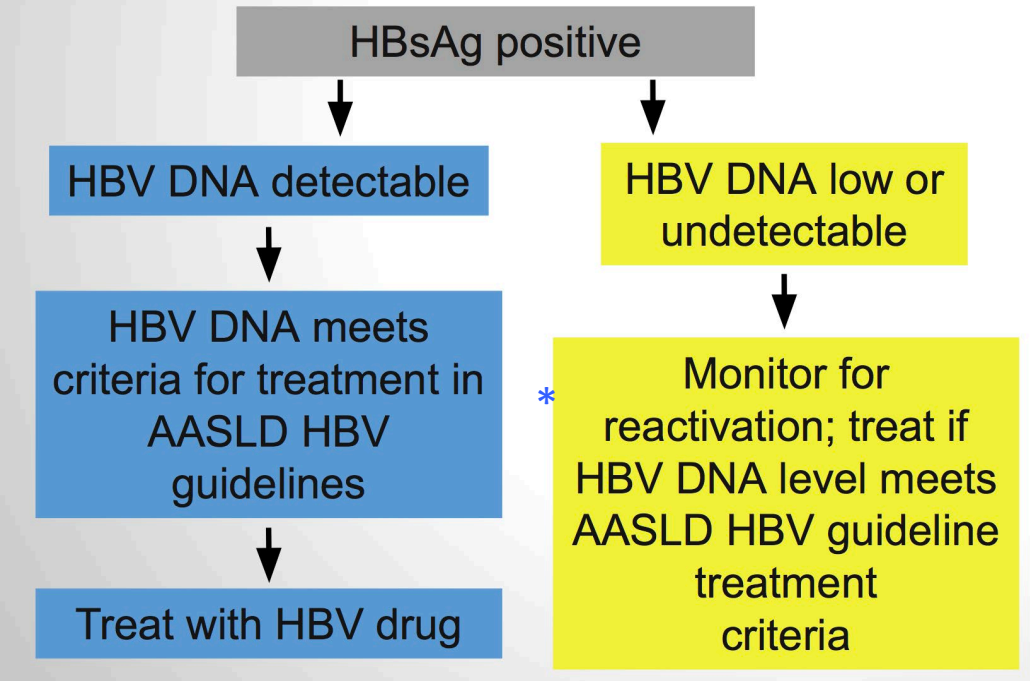
Be Proactive: Look For It!

- Prevention of HBV reactivation is critical
  - Screen patients about to receive IS therapies
  - Stratifying risk based on virological data and
  - Immunosuppression regimen
  - Tailor management

How do we prevent reactivation?

- Test all patient initiating HCV therapy for HBV

  HBsAg, anti-HBc, and anti-HBs



**possibility of HBV reactivation should be considered in patients in the event of an unexplained increase in liver aminotransferase levels during and/or after completion of DAA therapy.

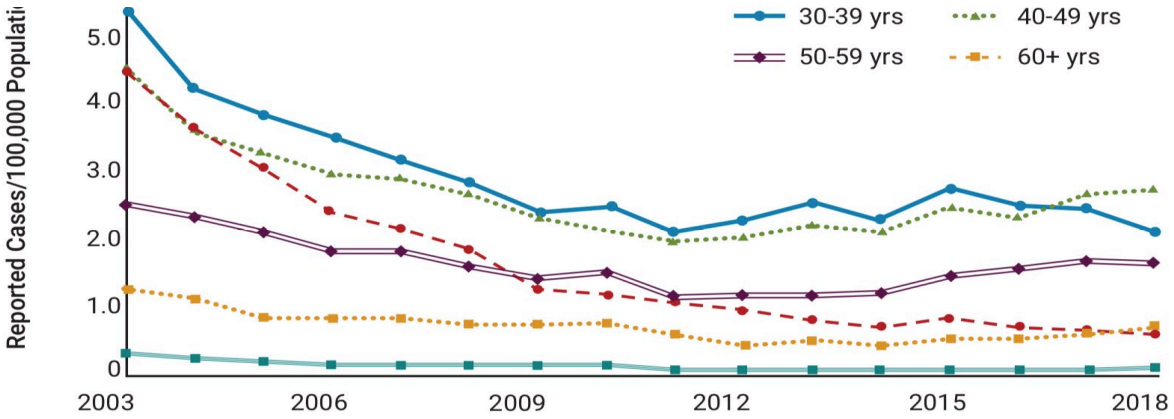
*If monitoring is elected, HBV treatment should be started if the HBV DNA level increases >10-fold or is >1000 IU/mL in a patient with undetectable or unquantifiable HBV DNA prior to DAA treatment.

Hepatitis B and Hepatitis C Clinical Management

When should HBV treatment be started?

- Start on HBV treatment at the same time or before HCV DAA therapy is initiated
- Can treat during DAA treatment until assessment for SVR 12
- If stopping HBV therapy, monitor closely for HBV flare

Should HBV coinfection impact selection of HCV medications?



	GLP/PIB	LED/SOF	SOF/VEL
Entecavir	◆	◆	◆
Tenofovir alafenamide	◆	◆	◆
Tenofovir-DF (HBV)	◆	▬	▬

"Sofosbuvir/velpatasvir increased tenofovir AUC by ~30-80% when administered with various regimens containing tenofovir-DF. No effect on the pharmacokinetic parameters of sofosbuvir, GS-331007 or velpatasvir was observed. Monitor for tenofovir-associated adverse reactions"

Coadministration with tenofovir alafenamide alone has not been studied but no clinically significant interaction is expected."

Conclusions

- Post treatment monitoring with HCC screening is recommended for patients with advanced fibrosis prior to HCV treatment
- A diagnosis of HCV in pregnancy is a biomarker for opioid use disorder
  - Optimal timing for treatment should be tailored to the patient although robust treatment in pregnancy data is lacking
- All patients should be screened for HBV prior to initiation of HCV infection given the risk of co-infection and risk of reactivation

QUESTIONS?