



Updates in Viral Hepatitis

Sean G. Kelly, MD

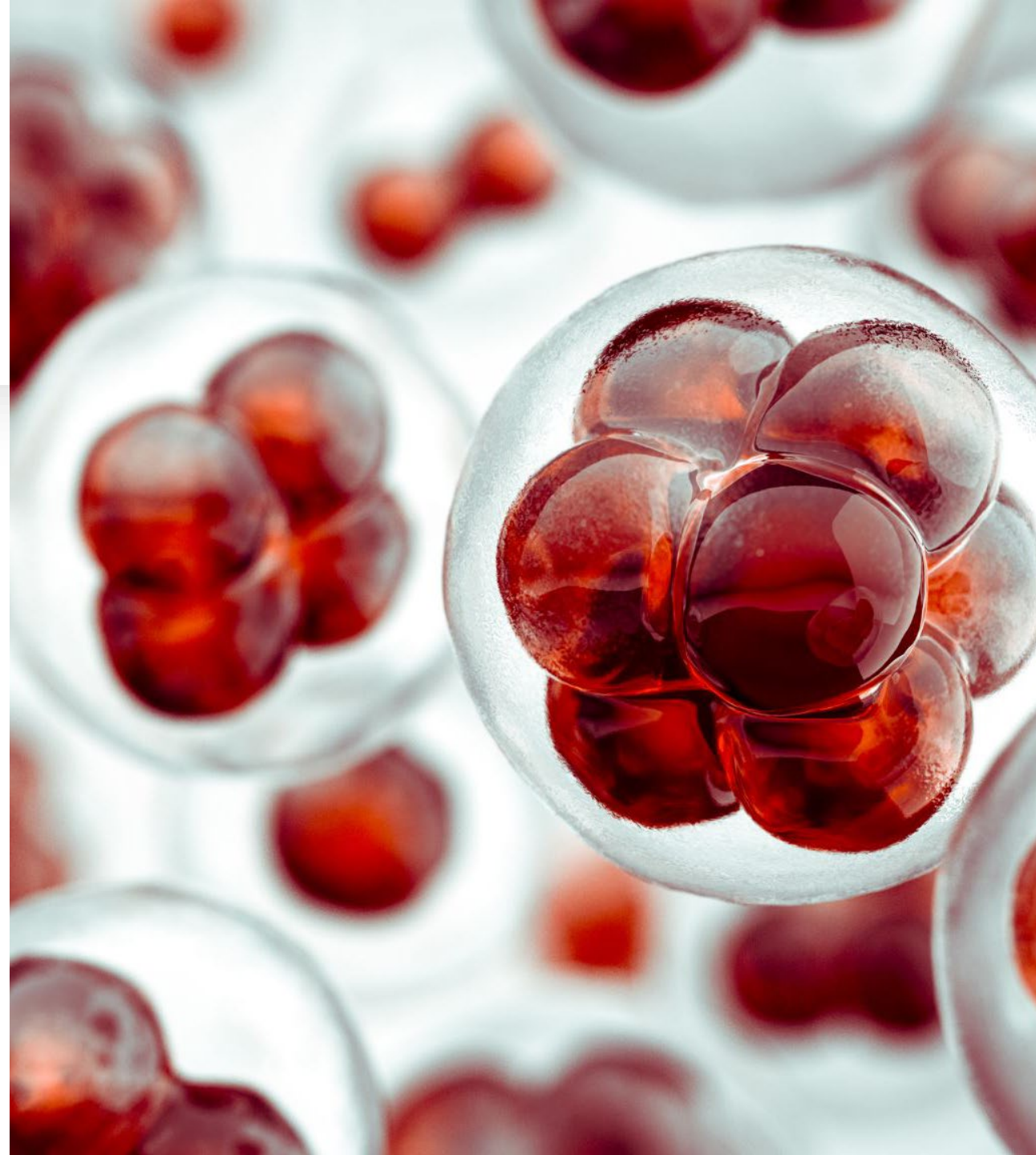
Medical Director, Liver Transplant Program

Associate Professor, Division of Gastroenterology, Hepatology and Nutrition

November 6, 2024

Lecture Objectives / Outline

- Approach to atypical viral infections affecting the liver
- Discuss the current status of viral hepatitis
- Hepatitis A through D...
 - Where are we now?
 - What are we doing to improve?
 - What are our barriers?



40 Years
*of life-saving
liver transplants*



Liver Transplant Firsts at Ohio State

- 1984** — Liver transplant (first in Ohio)
- 2017** — Split liver transplant
- 2018** — Living donor liver transplant
 - Ex-vivo liver perfusion clinical study
- 2019** — Combined heart-liver transplant
- 2022** — OrganOx *metra* liver perfusion system

Liver Transplant Program

Ohio State Comprehensive Transplant Center



All-Time Volume:

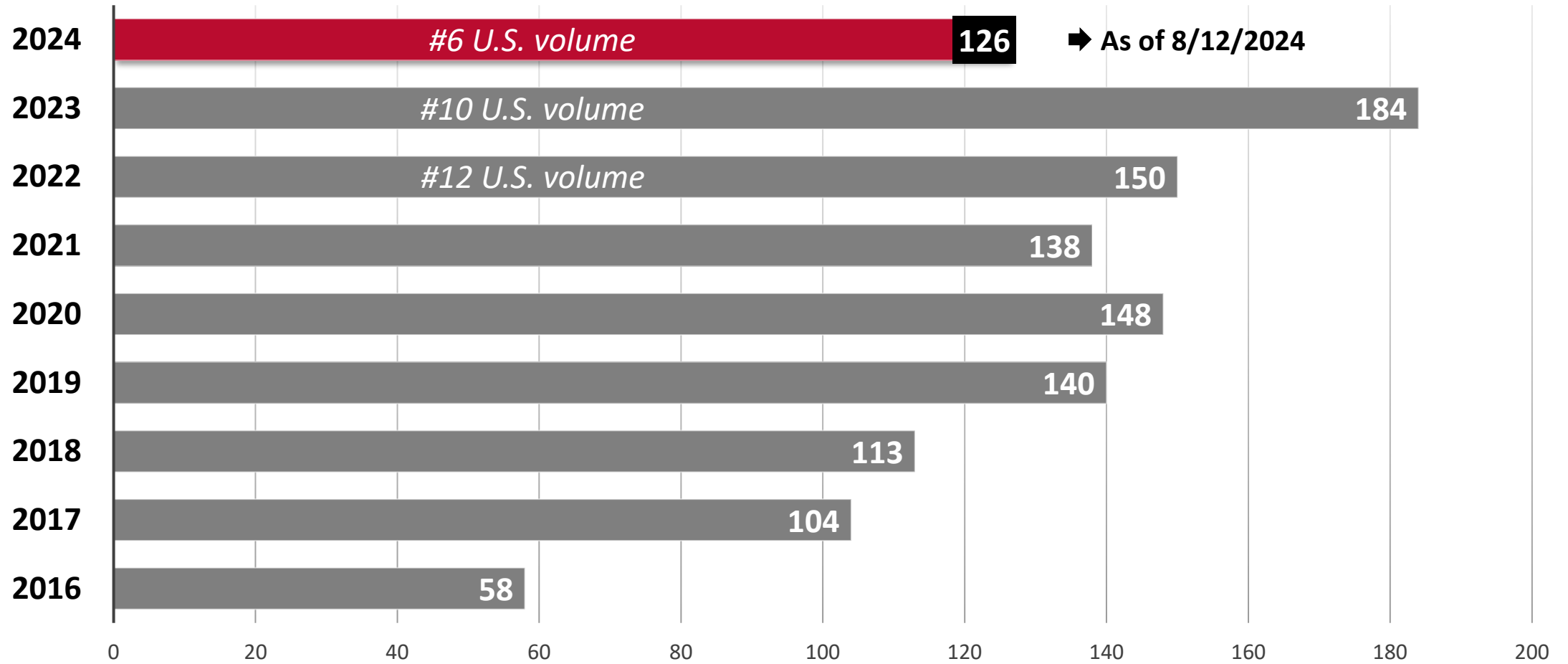
1,874

Volume Increase

2016 – 2023:

▲ 217%

Liver Transplant Volume (CY)



1-Year Patient and Graft Survival Outcomes

Ohio State Liver Transplant Program (data released Jan. 2024)

	1-Year Patient Survival			1-Year Graft Survival		
	OSUWMC EXPECTED	OSUWMC OBSERVED	National OBSERVED	OSUWMC EXPECTED	OSUWMC OBSERVED	National OBSERVED
Liver	94.40%	93.44%	93.95%	92.58%	92.28%	92.02%

- ✓ **Pre-transplant risk assessment**
- ✓ **Waitlist maintenance**
- ✓ **Peri- and post-transplant management**

OSUWMC Hepatology Team

Transplant Hepatologists



Lanla Conteh, MD,
MPH, MBA
Section Chief,
Hepatology



Sean Kelly, MD
Medical Director of
Liver Transplant



Chathur Acharya,
MBBS



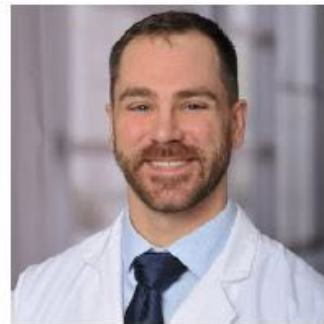
Vivek Mendiratta, MD



Khalid Mumtaz,
MBBS



Lindsay Sobotka, DO



Michael Wellner, MD



Erin Bouquet, MD

Gastroenterology / Hepatology



Na Li, MD, PhD



Guillermo Ortiz San
Juan, MD

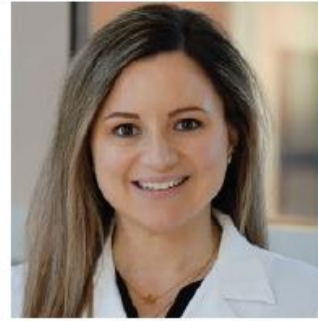
OSUWMC Hepatology Team – Nurse Practitioners



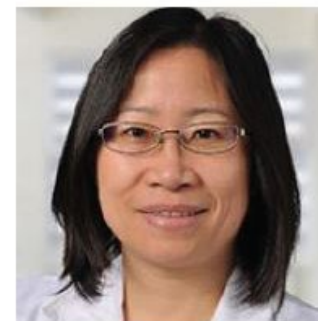
Nicole Gray,
APRN-CNP, Lead



Kathy Foreman,
APRN-CNP



Sarah Johnson,
APRN-CNP



Sherry Ma,
APRN-CNP



Maribeth Smith,
APRN-CNP

OSUWMC Liver Transplant Surgeons



Kenneth Washburn, MD
Executive Director,
Comprehensive Transplant
Center; Professor and
Director, Division of
Transplantation Surgery



Sylvester Black, MD, PhD
Professor, Division of
Transplantation Surgery
Surgical Director,
Liver Transplant



Musab Alebrahim, MD
Assistant Professor,
Division of Transplantation
Surgery



Ashley Limkemann, MD, MPH
Assistant Professor, Division
of Transplantation Surgery
Director, Abdominal Transplant
Surgery Fellowship Program



Austin Schenk, MD, PhD
Assistant Professor,
Division of Transplantation
Surgery



Navdeep Singh, MBBS
Assistant Professor,
Division of Transplantation
Surgery



**Sai Rithin
Punjala,
MBBS**

Acute hepatitis, ACLF, ALF – different management

	Acute hepatitis	ACLF	ALF
AST or ALT > 400	Yes	Yes	Yes
INR	Usually < 1.5	Variable	≥ 1.5
Encephalopathy	No	Possibly	Yes
Pre-existing liver disease	No	Yes	No

Epstein-Barr Virus (EBV)

- Infants / Children typically asymptomatic or mild disease
- Adolescents / Adults: Pharyngitis, fever, lymphadenopathy
 - EBV hepatitis more severe in adults > 30 years
 - Splenomegaly is common
- Liver involvement is nearly universal:
 - 90% have AST/ ALT / LDH elevations 2-3x normal
 - Rise over 1-2 wks, peak < 5x normal (lower than HAV, HBV)
 - 45% with high alk phos and mildly elevated bilirubin, LFTs typically normal in 1 month

EBV Diagnosis

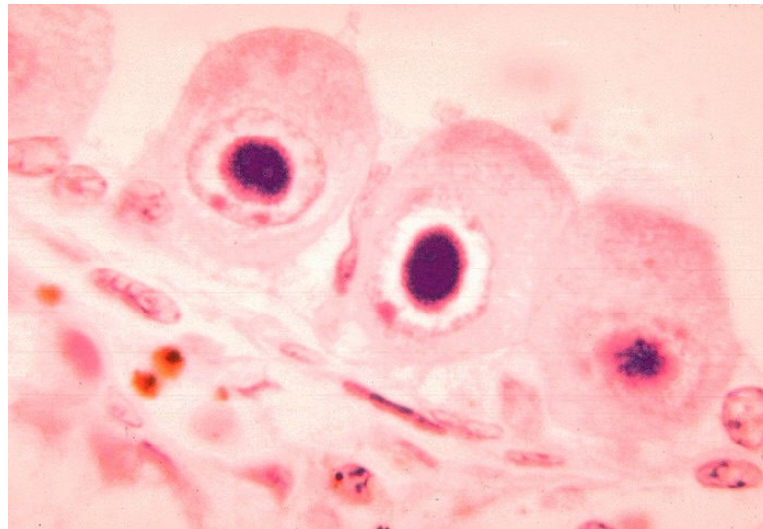
Monospot positive after ~10 days after infection

- Anti-EBV IgM peaks early, persists for months
 - EBV serum PCR
-
- Treatment is supportive: No benefit from Acyclovir; Ganciclovir not well studied

Other Viruses - CMV

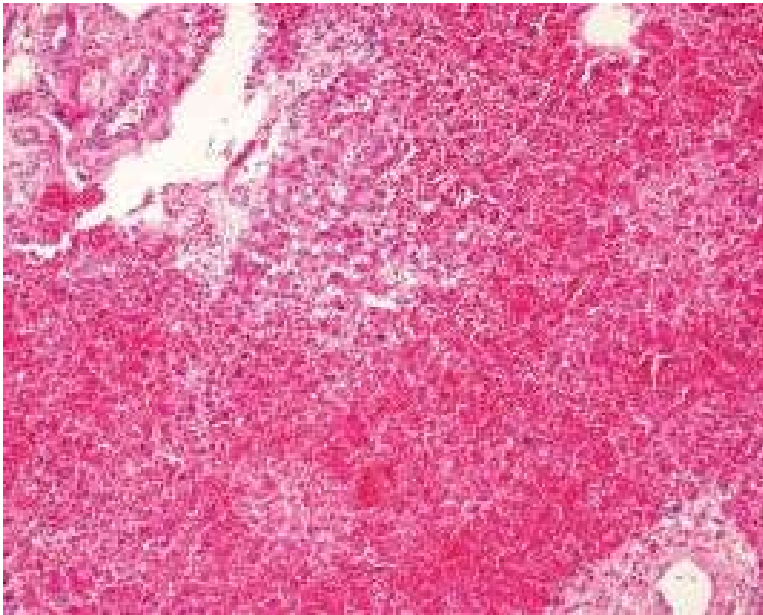
- Typically in the immunocompromised host
- Can effect multiple organ systems
- Elevated AST and ALT is the most common finding
- Can diagnose with PCR and/or biopsy.
- Treatment: antivirals (ganciclovir, valganciclovir)

Inclusion Bodies seen
at right; described as
owl's eye nuclei



Other Viruses - Herpes Simplex

- Higher risk groups: neonates, patients on steroids, transplant recipients; patients with cancer, HIV or pregnancy
- HSV hepatitis presents is usually fatal in untreated individuals (>80 percent mortality). [Acyclovir](#) can be life-saving.



Liver histology can reveal diffuse acute liver necrosis with multiple viral inclusion bodies. Immunostaining positive for HSV.

Hepatitis E

- **Acute HEV:** similar to acute HAV or HBV, most asymptomatic
 - Pregnancy (2nd / 3rd trimester) → ALF with mortality 5-25%
 - Increased rates of infection in pregnancy 9-19%
- Week 1: fever, abd pain, anorexia, aversion to smoking, vomiting, diarrhea, arthralgias, transient macular rash
- Weeks 2-4: jaundice, pruritus, dark urine / clay colored stools
- Weeks 4-8: spontaneous resolution

Hepatitis A



Historical Perspective



Molecular Virology



Prevention

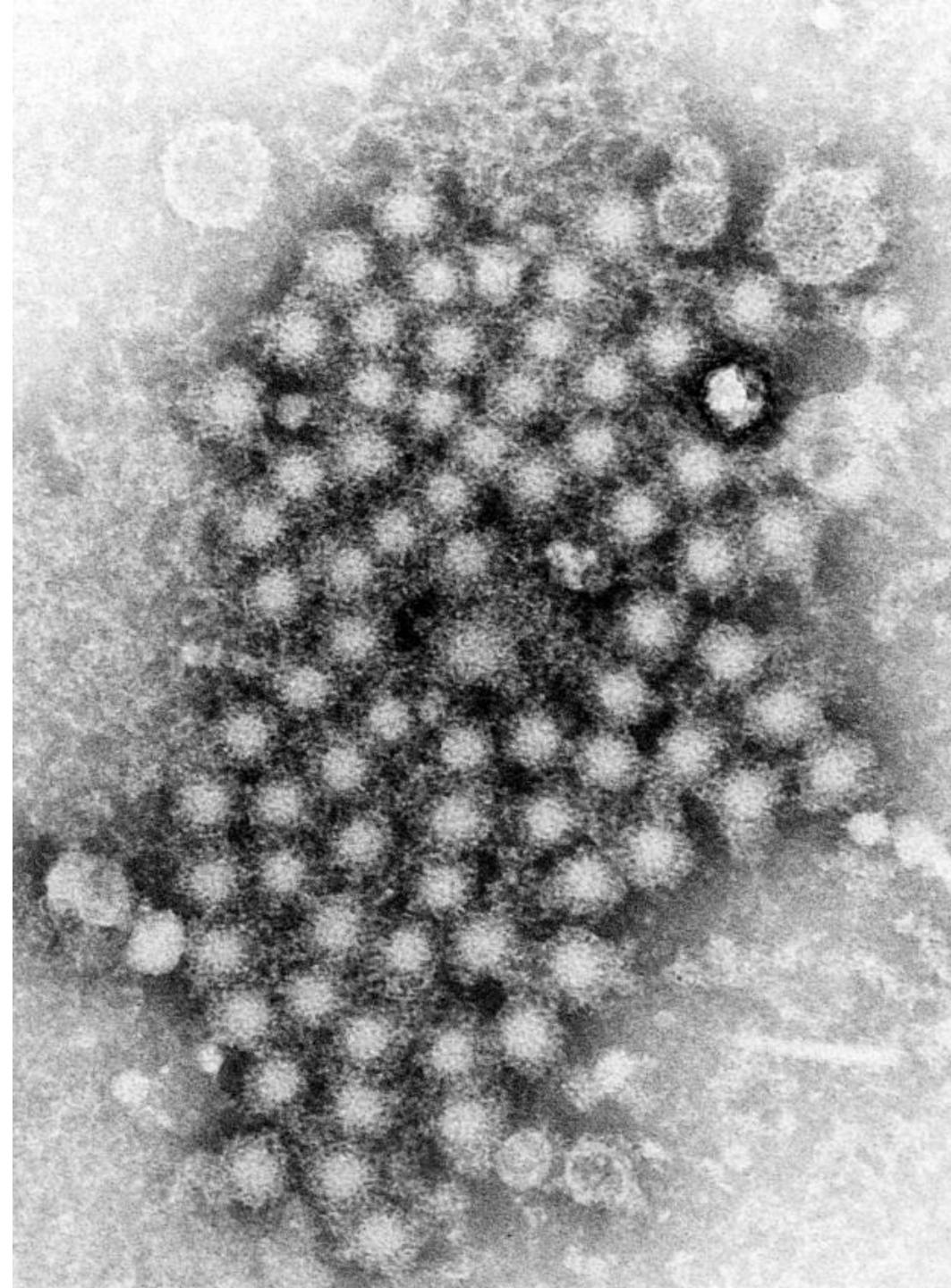
Hepatitis A: the Historical Perspective

- Epidemics of Jaundice
 - Reports from 5th century BC in Europe as far back as 5000 years ago in China
 - 19th century attributed to mucous plugging of the bile duct - catarrhal jaundice
 - Armies were notorious for outbreaks; known as "campaign jaundice"
- WWII
 - Differentiation of "serum jaundice" (HBV) from "epidemic infectious jaundice" (HAV)
- Isolation
 - Electron microscopy 1973 - Feinstone et al
 - RNA genome reverse transcribed 1987
 - Vaccine development 1990's

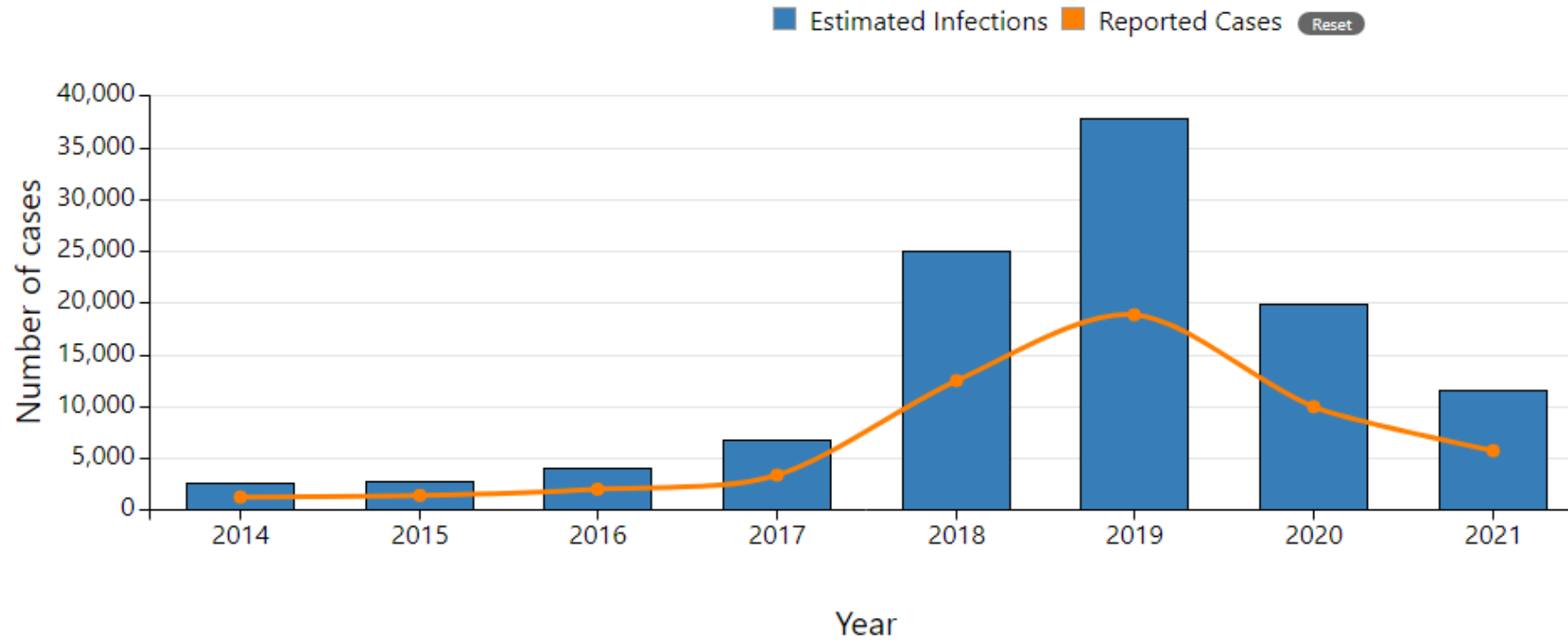


Hepatitis A: Virology

- Picornaviridae family and Hepatovirus genus
 - Viron-positive strand RNA in an icosahedral protein capsid
- Clinical course
 - Predominantly fecal-oral transmission
 - Incubation period 15-40 days
 - Malaise, fatigue, anorexia, vomiting, abdominal discomfort, diarrhea, pruritus and less common fever, headaches, arthralgia, myalgia
- Vaccine
 - All HAV vaccines contain HAV antigens derived from cell cultures of attenuated HAV strains
 - 95% effective with at least 20 years of efficacy



Hepatitis A: Where are we now?



	2014	2015	2016	2017	2018	2019	2020	2021
Reported Cases	1,239	1,390	2,007	3,366	12,474	18,846	9,952	5,728
Estimated Infections	2,500	2,800	4,000	6,700	24,900	37,700	19,900	11,500

Hepatitis B



Historical Perspective



Molecular Virology



Treatment and
Prevention

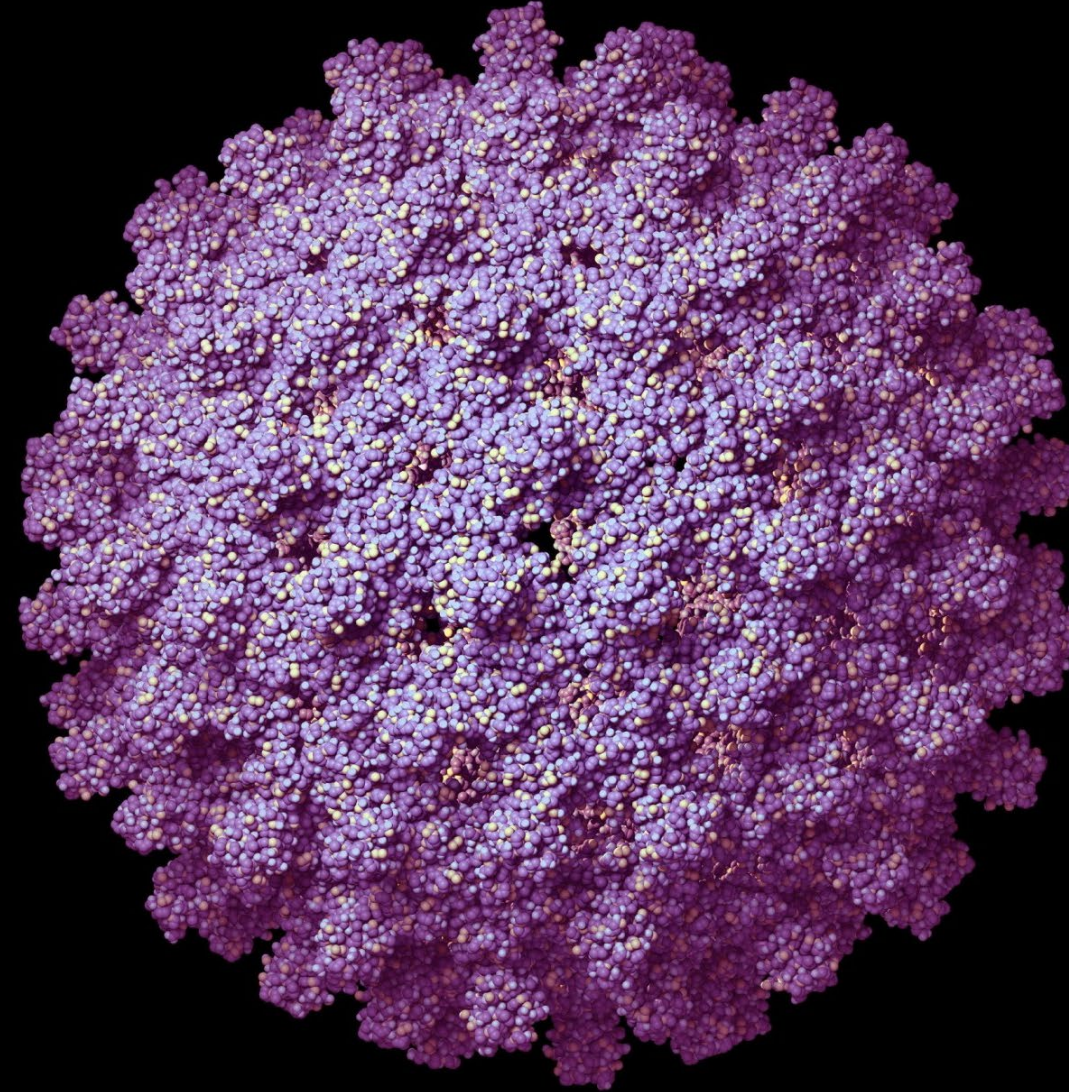
Hepatitis B: the Historical Perspective

- Isolation
 - First described epidemic was 1885
 - Discovered in 1965 by Dr. Baruch Blumberg
 - Screening transfusions began in 1971
- Global Impact
- Hepatocellular Carcinoma (HCC) risk prior to cirrhosis

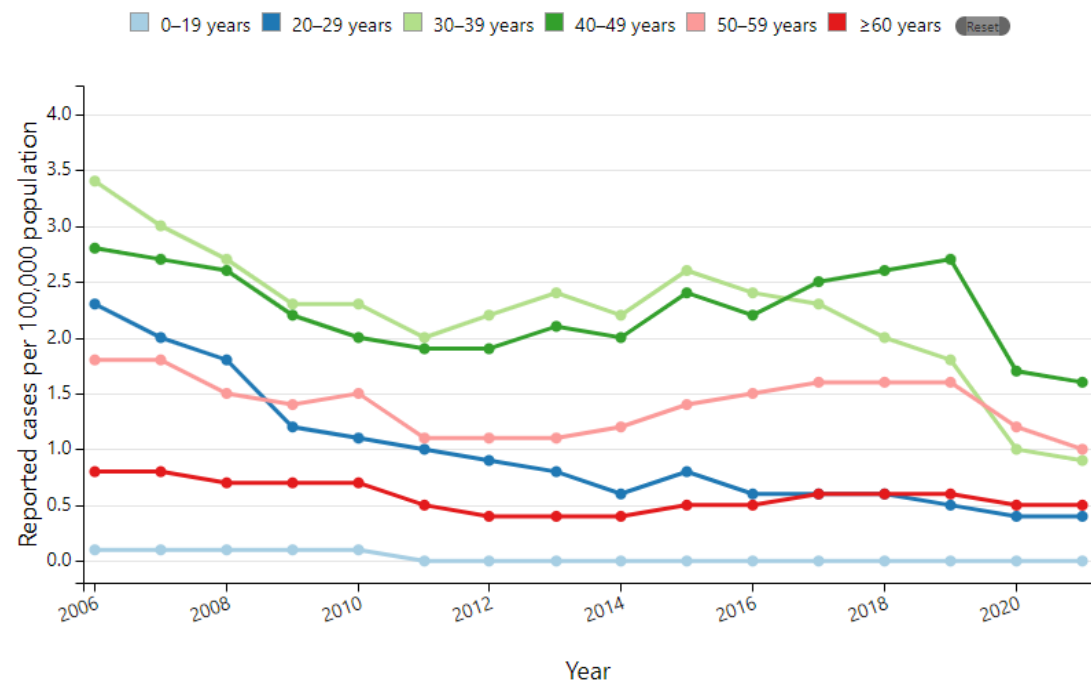
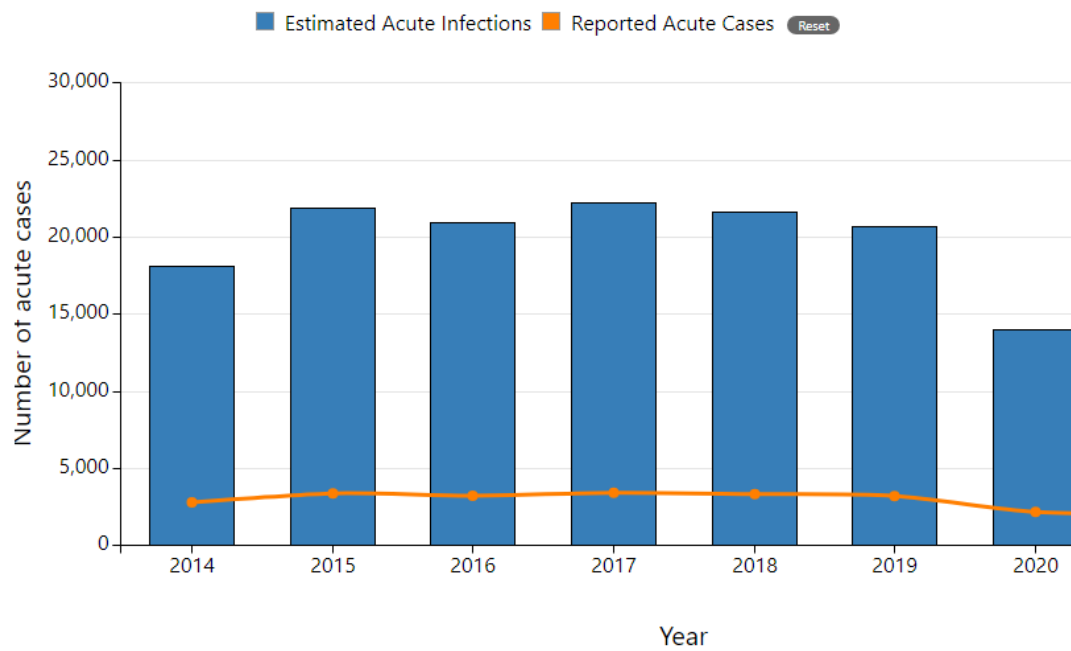


Hepatitis B: Virology

- Hepadnaviridae family Orthohepadnavirus genus
 - Partially DS DNA virus
 - Dane particle lipid outer layer, icosahedral nucleocapsid, viral DNA and DNA polymerase
 - 100 x more virulent than HIV 10 x more virulent than HCV
- Clinical course
 - Blood and body fluids
 - Incubation period 1-4 months
 - 70% subclinical hepatitis, 30% icteric hepatitis
 - Chronicity of infection depends on age
 - 90% perinatal
 - 20-50% ages 1-5
 - Less than 5% adults
- Nearly 1 million people die annually from complications of HBV



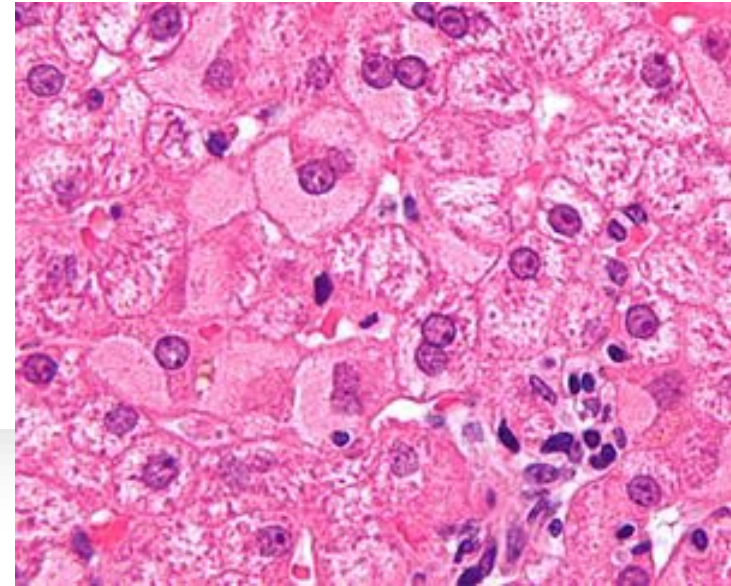
Hepatitis B: Where are we now?



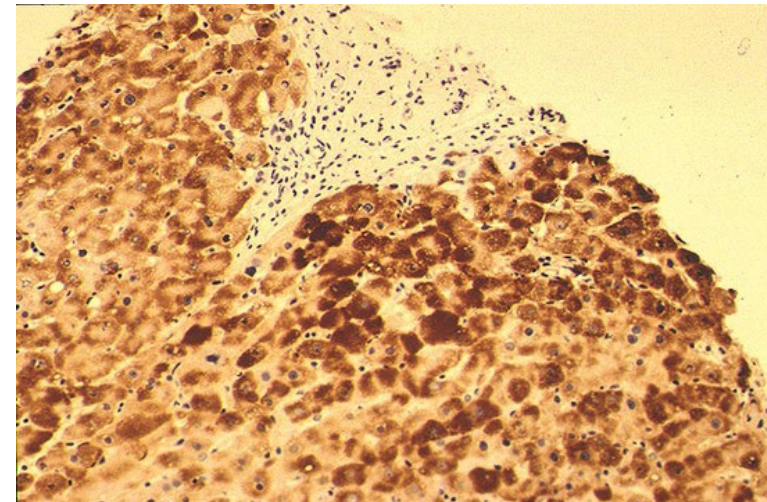
	2014	2015	2016	2017	2018	2019	2020	2021
Reported Acute Cases	2,791	3,370	3,218	3,409	3,322	3,192	2,157	2,045
Estimated Acute Infections	18,100	21,900	20,900	22,200	21,600	20,700	14,000	13,300

What about Chronic HBV?

- Estimated 880,000 (95% CI = 580,000–1,170,000) chronic HBV infections in the US
- Non-US-born residents accounted for 69% of the population with chronic HBV infection and were 9 times more likely to be living with chronic hepatitis B, compared with US-born persons
- Despite increasing immunization, the prevalence of chronic HBV has remained stable at 0.3% since 1999



Ground glass hepatocytes
(HBV surface Ag in endoplasmic reticulum)



HBV surface Ag stain

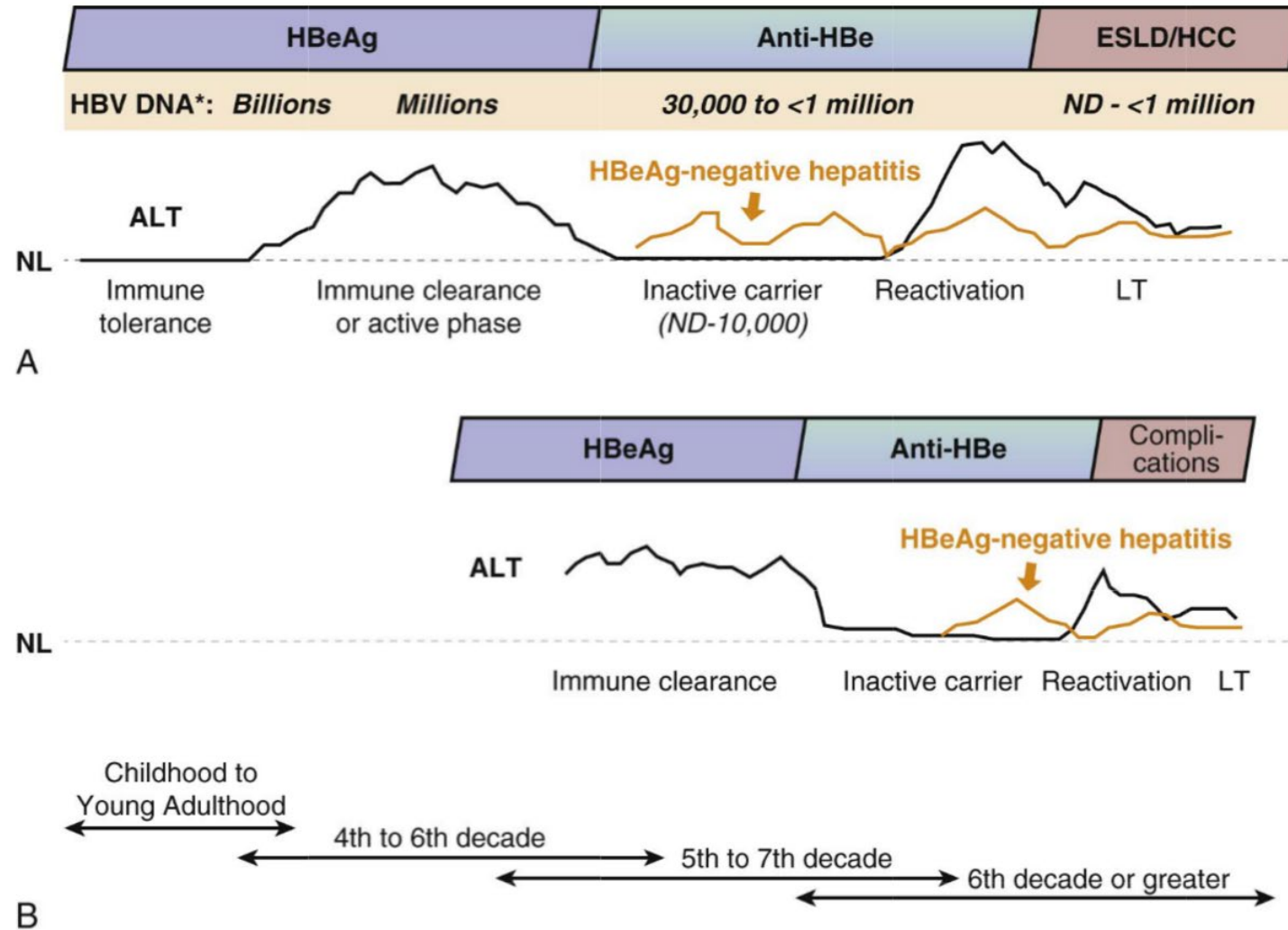
An Ounce of Prevention...

- Among adults aged ≥ 25 years in the US, an estimated 155 million persons (or 73%) were susceptible to HBV infection
- Hepatitis B vaccination is only 30% among adults over age 19; Even among healthcare professionals the rate is only 67%
- Despite the World Health Organization goal to eliminate viral hepatitis as a public health problem by 2030, annual global deaths from HBV are projected to increase by 39% from 2015 to 2030

Table 2. Estimated deaths averted due to vaccination from 2001 to 2030, 194 countries (in million).

	Deaths averted due to vaccination		
	2001–2010	2011–2020	2021–2030
Total	29.7 (26.6–33.1)	39.5 (36.7–42.4)	51 (48.5–53.7)
<i>By pathogen</i>			
Hepatitis B virus	9.7 (8.4–11.6)	13 (11.1–15.7)	14 (11.5–16.9)

HBV – Natural History



Keeping it Simple: Screening and Workup

CONSULT WITH HBV SPECIALIST

- Cirrhosis and/or liver mass
- Platelets $< 100 \times 10^9/L$
- HDV, HCV, and/or HIV coinfection
- Pregnancy
- Lack of response to treatment or rebound of HBV DNA levels^j

SCREENING

Universal, one-time HBV screening in all adults^a
(HBsAg, anti-HBs, and total anti-HBc)

HBsAg positive

DIAGNOSTIC WORKUP

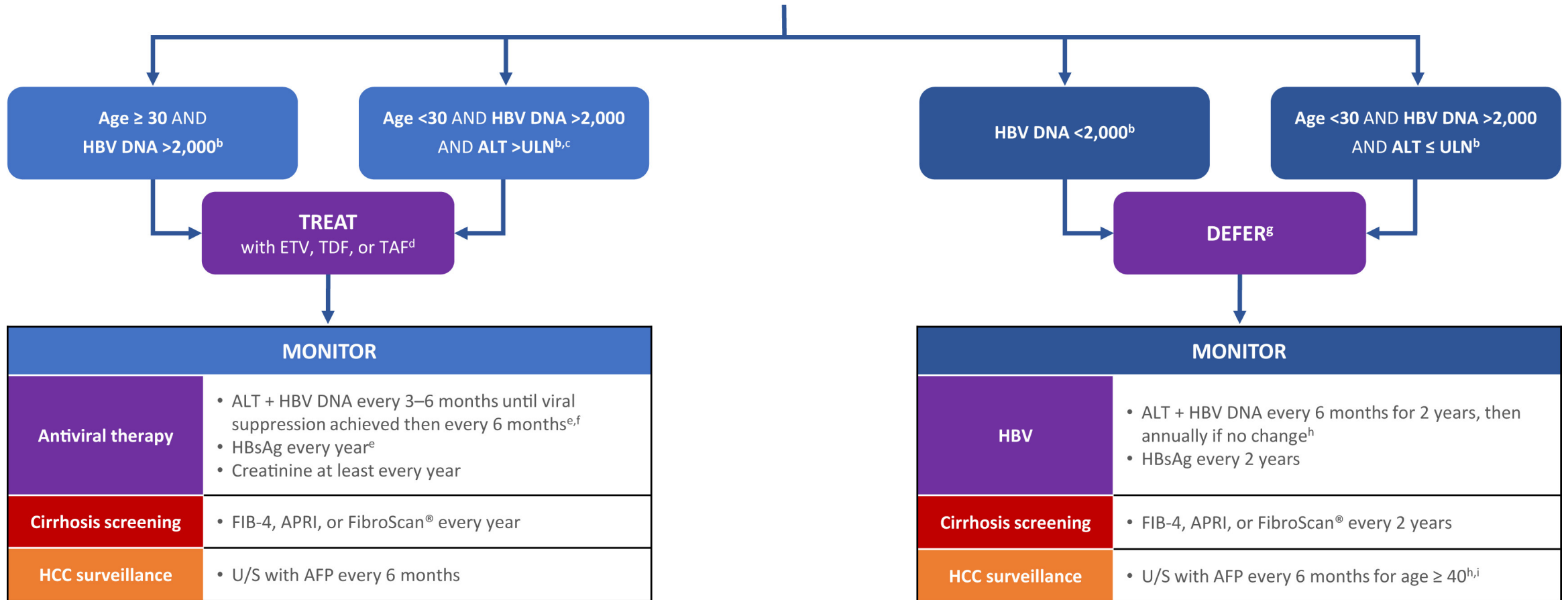
At minimum (*see Table 2 for full evaluation*)

HBV: HBV DNA, ALT, AST, platelets

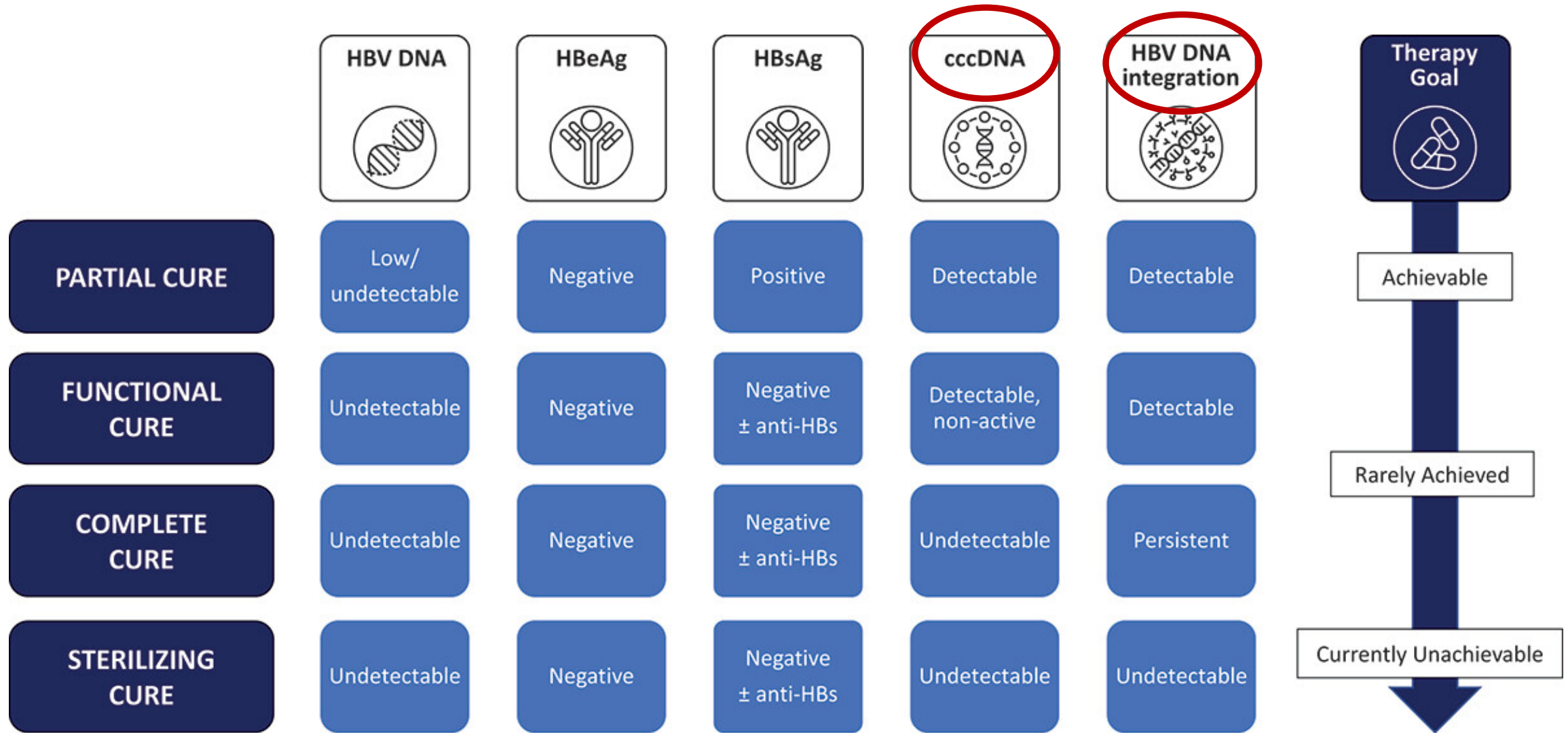
Cirrhosis screening: Noninvasive tests such as FIB-4, APRI, or FibroScan

HCC surveillance: Baseline U/S of liver with AFP

Keeping it Simple: 2K HBV DNA Threshold



Hepatitis B Management



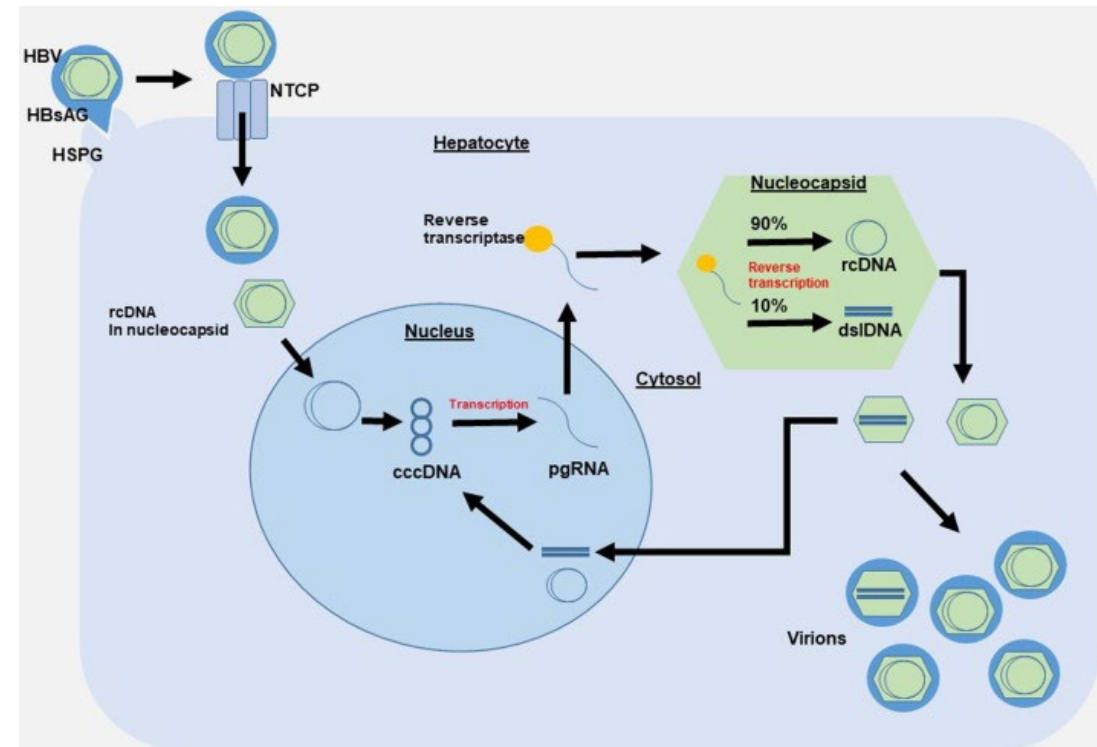
OSUWMC Clinical Practice Guideline - January 2023

HBV Screening and Prophylaxis for Patients Requiring Immunosuppression - **cccDNA (covalently closed circular DNA)**

HBsAg	Negative	<ul style="list-style-type: none"> • Prior exposure without chronic infection (Low risk for reactivation) • Reactivation rates are 8-18% in cancer therapy and 2% in rheumatic therapy 	<ul style="list-style-type: none"> • Prophylaxis needed if patient receiving CD 19/20 directed-monoclonal antibody (e.g., rituximab), jak/stat inhibitors (e.g., ruxolitinib), or stem cell transplant • If using immunosuppression that is NOT a CD 19/20 directed-monoclonal antibody or jak/stat inhibitor, monitor with HBsAg, HBV DNA, and ALT every 3 months until 6-12 months after completing immunosuppression
Anti-HBc	Positive		
Anti-HBs	Negative		
HBsAg	Negative	<ul style="list-style-type: none"> • Prior exposure without chronic infection (Very low risk for reactivation) • Surface antibody does not confer immunity in this case 	
Anti-HBc	Positive		
Anti-HBs	Positive		

True Cure in the Future

- Aims
 - Induce HBsAg loss,
 - Prevent new hepatocyte infection,
 - Regain host immune function, and
 - Entirely eliminate HBV DNA
- Current areas of exploration
 - HBV regulatory X protein - pre-clinical
 - Epigenetics DNA methylation, histone acetylation
 - Immune system - nivolumab, TLR, APOBEC
 - Gene editing CRISPR
 - HBSAg inhibitors
 - Viral entry inhibitors
 - Small molecule cccDNA inhibitors – Bepirovirsen; sustained HBsAg and HBV DNA loss occurred in 9–10% of patients who received bepirovirsen for 24 weeks



Hepatitis C



Historical Perspective



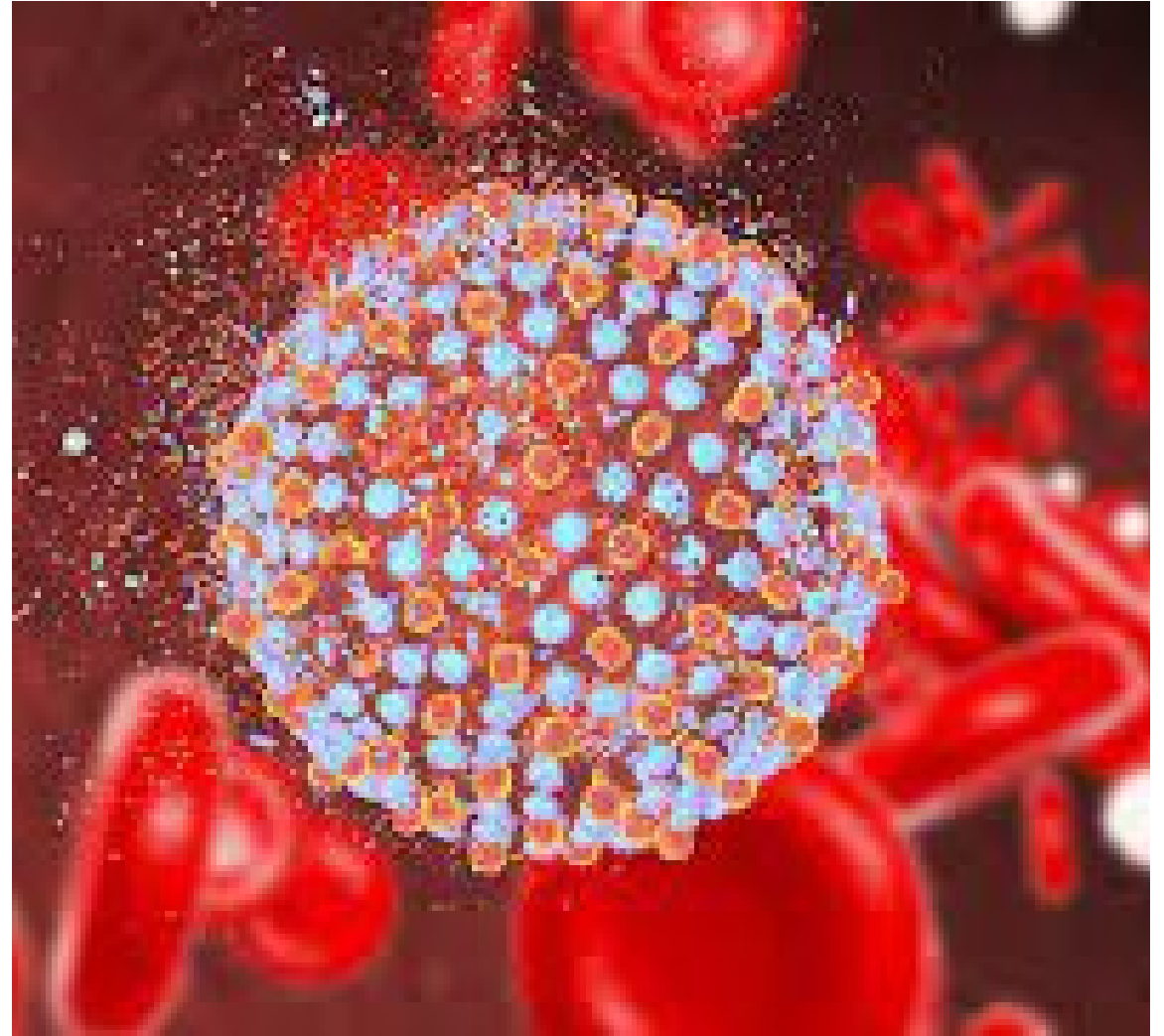
Molecular Virology



Future Directions

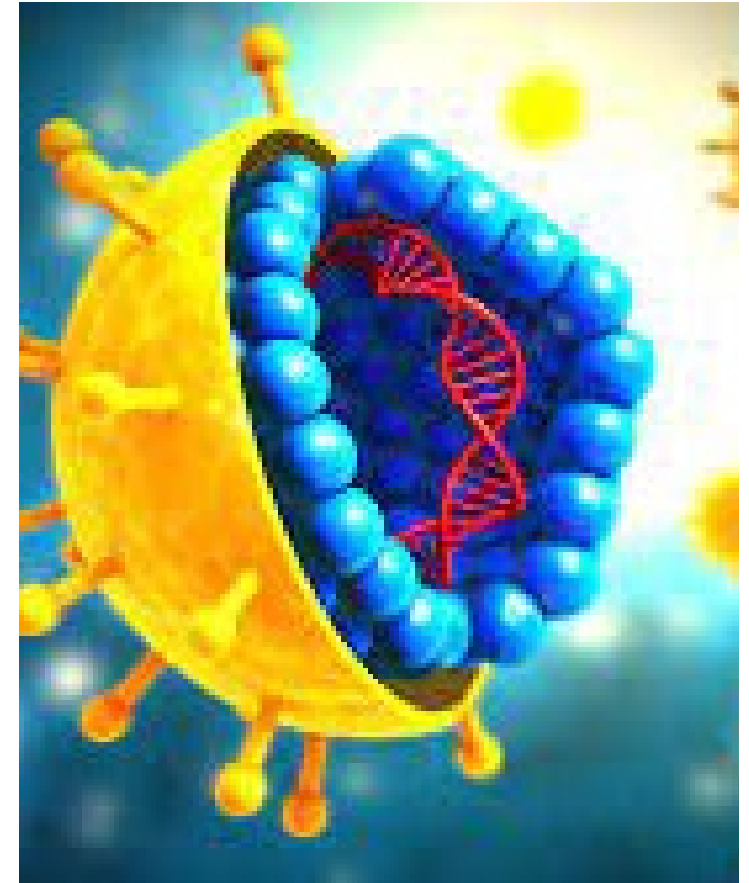
Hepatitis C: the Historical perspective

- First recognized as non-A non-B hepatitis (NANBH) in 1975
- 1989 Houghton et al cloned and sequenced the genome
- Ancient history
 - According to some experts HGV/GBV-C could be a relative of the hepatitis C virus affecting Old and New World primates. If true, then the origins of HCV can be traced back 35 million years.
 - The six types of genotypes or strains of hepatitis C virus likely have a common ancestor that existed some 400 years ago.

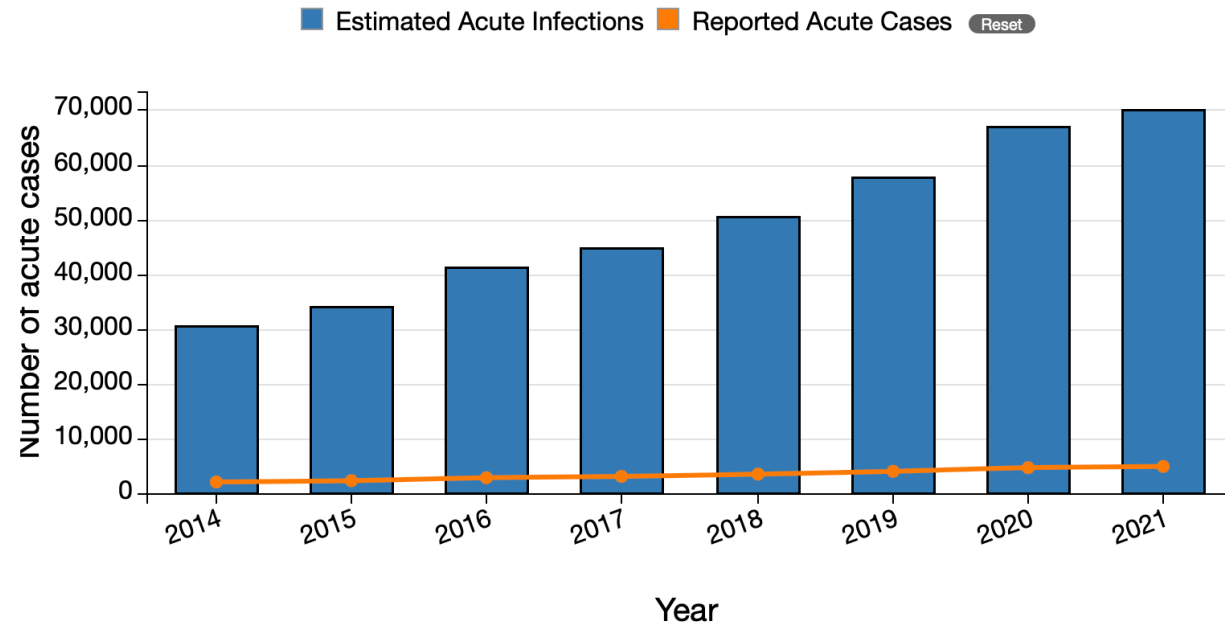


Hepatitis C Virology

- Hepacivirus, a member of the family Flaviviridae
 - Single stranded RNA virus
- Clinical course
 - Predominantly bloodborne transmission
 - 20% manifest an acute infection 70% develop chronic
 - Incubation period of 4-12 weeks
- Treatment
 - 1991 interferon
 - Direct acting antivirals
 - 2011 first agents
 - 2014 first DAA alone treatment
 - 2015 first pan-genotypic treatments



Hepatitis C: Where are We Now?



	2014	2015	2016	2017	2018	2019	2020	2021
Reported Acute Cases	2,194	2,436	2,967	3,216	3,621	4,136	4,798	5,023
Estimated Acute Infections	30,500	33,900	41,200	44,700	50,300	57,500	66,700	69,800

The Path to Clearance

- Mortality from Hepatitis C has declined since 2019, driven by an increase in HCV treatment ten times that of the strategy baseline
- Barriers
 - 20-40% of chronic HCV infections are undiagnosed
 - Stigma
 - Access
- Strategies
 - Micro-elimination
 - Increased access to testing and emphasis on point-of-care testing
 - Education and expansion providers who can treat HCV
 - Policy maker investment for health initiative and justice-involved populations

Hepatitis Delta



Historical Perspective



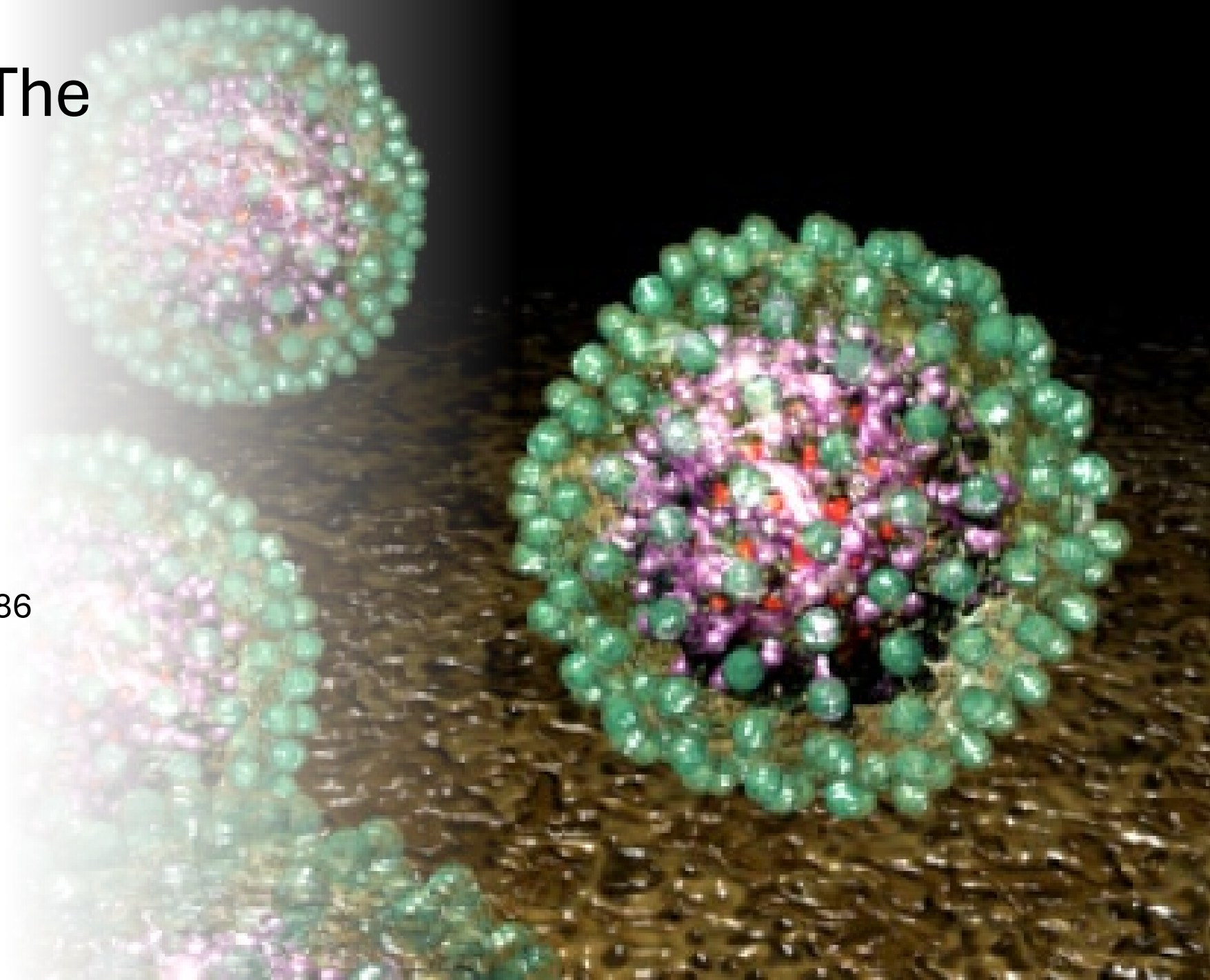
Molecular Virology



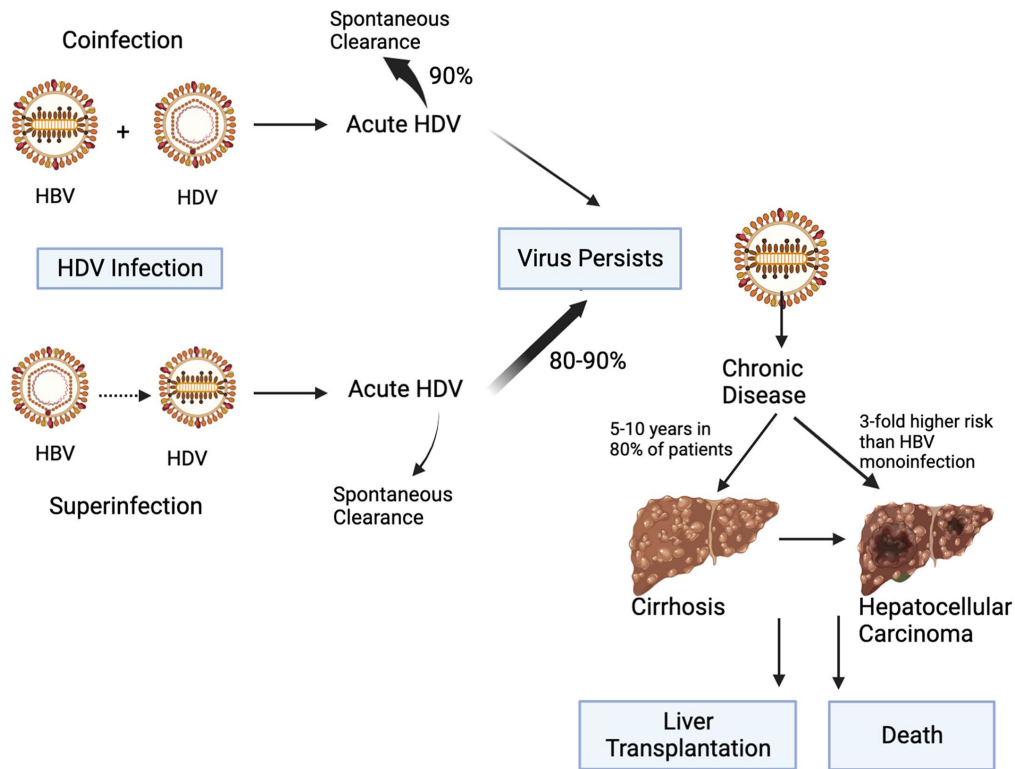
Treatments and
Prevention

Hepatitis Delta: The Historical Perspective

- Lábrea fever described in the 1950's
- HDV was discovered in 1977 originally thought to be an antigen of HBV
- Cloned and sequenced in 1986



Hepatitis Delta: Virology



- Its own genus: Deltavirus
- Single stranded RNA genome
- At least 8 genotypes with studies suggesting a common ancestor
- Clinical course
 - Highest fatality rate

Hepatitis D:
Where are
we now?



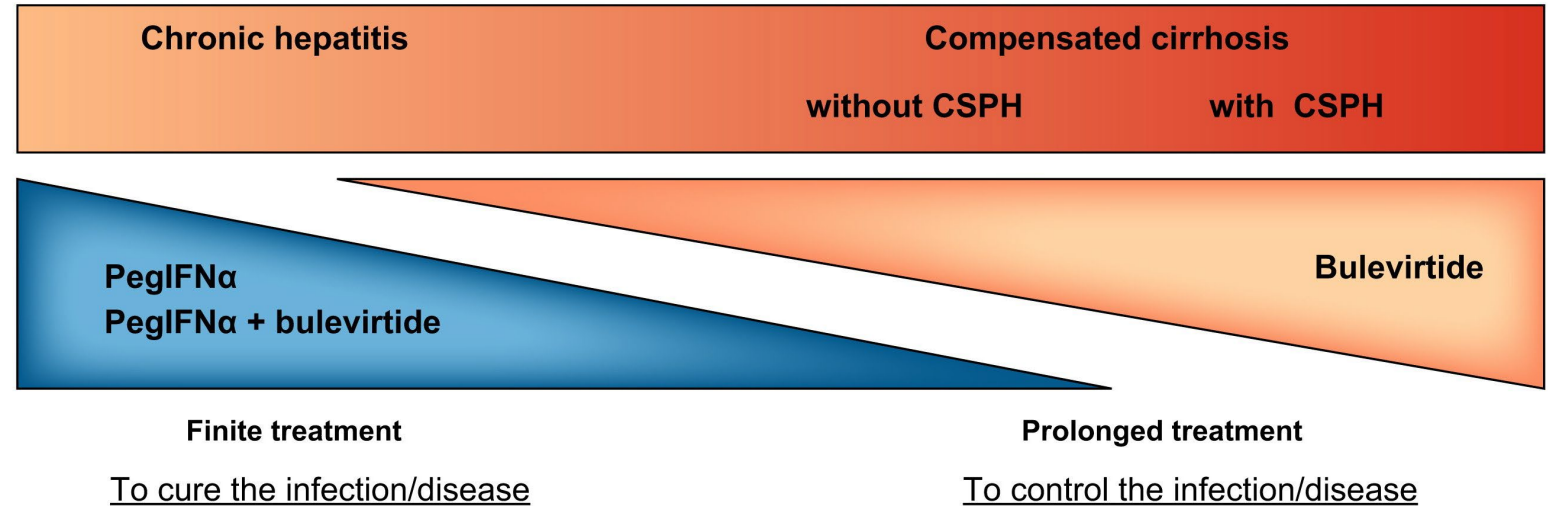
HDV: Estimates

- Global estimates - 0.16% of the population or ~ 12 million
- 4.5% of those with hepatitis B
- A few studies have specifically evaluated HDV prevalence in the United States among unique cohorts, including:
 - Veterans Affairs (VA) Cohort (HDV prevalence of 3.4%)
 - Northern California (8%), the Midwest (3.3%)
 - Among injection drug user population in Baltimore (11%)
- Rates of testing for HDV in the United States vary widely
 - 8.5% to 42% among persons with HBV



Hepatitis Delta: Treatment

- Prevention
- FDA approved
 - Interferon
- Bulevirtide
 - FDA rejected
 - EMA approved
 - first in class HBV entry inhibitor
 - Duration?
 - French multicenter ANRS HDV cohort, 65 patients 39% of patients achieved a virological response (8% HDV RNA undetectable)
 - Data are scarce regarding long-term BLV monotherapy





In Conclusion

- Elimination is possible with our current tools
- Barriers exist with recognition and education being the greatest



References

- https://en.wikipedia.org/wiki/Hepatitis_D
- Melnick, Joseph L. "History and epidemiology of hepatitis A virus." *Journal of Infectious Diseases* 171.Supplement_1 (1995): S2-S8.
- Martin, Annette, and Stanley M. Lemon. "Hepatitis A virus: from discovery to vaccines." *Hepatology* 43.S1 (2006): S164-S172.
- Oancea, Carmen Nicoleta, et al. "Global hepatitis C elimination: history, evolution, revolutionary changes and barriers to overcome." *Romanian Journal of Morphology and Embryology* 61.3 (2020): 643.
- Abdelwahed, Ahmed H., Brent D. Heineman, and George Y. Wu. "Novel Approaches to Inhibition of HBsAg Expression from cccDNA and Chromosomal Integrants: A Review." *Journal of Clinical and Translational Hepatology* 11.7 (2023): 1485.
- Roberts, Henry, et al. "Prevalence of HBV Infection, Vaccine-Induced Immunity, and Susceptibility Among At-Risk Populations: US Households, 2013-2018." *Hepatology* 74.5 (2021): 2353-2365.
- Lu, Peng-Jun, et al. "Surveillance of vaccination coverage among adult populations—United States, 2018." *MMWR Surveillance Summaries* 70.3 (2021): 1.
- Carter, Austin, et al. "Modeling the impact of vaccination for the immunization Agenda 2030: Deaths averted due to vaccination against 14 pathogens in 194 countries from 2021 to 2030." *Vaccine* (2023).
- Altman, Jessica D., et al. "Factors affecting vaccine attitudes influenced by the COVID-19 pandemic." *Vaccines* 11.3 (2023): 516.
- Razavi-Shearer, Devin, et al. "Cost-effectiveness of treating all hepatitis B—positive individuals in the United States." *Journal of Viral Hepatitis* (2023).
- Wong, Robert J., et al. "Simplifying treatment criteria in chronic hepatitis B: reducing barriers to elimination." *Clinical Infectious Diseases* 76.3 (2023): e791-e800.
- Hsu, Yao-Chun, Daniel Q. Huang, and Mindie H. Nguyen. "Global burden of hepatitis B virus: current status, missed opportunities and a call for action." *Nature Reviews Gastroenterology & Hepatology* (2023): 1-14.
- Cui, Fuqiang, et al. "Global reporting of progress towards elimination of hepatitis B and hepatitis C." *The Lancet Gastroenterology & Hepatology* 8.4 (2023): 332-342.
- <https://www.cdc.gov/hepatitis/statistics/2021surveillance/index.htm>
- Shouval, Daniel, and Oren Shibolet. "Hepatitis A virus." *Viral Infections of Humans: Epidemiology and Control*. New York, NY: Springer US, 2023. 1-47.
- Melnick, Joseph L. "History and epidemiology of hepatitis A virus." *Journal of Infectious Diseases* 171.Supplement_1 (1995): S2-S8.
- Martin, Annette, and Stanley M. Lemon. "Hepatitis A virus: from discovery to vaccines." *Hepatology* 43.S1 (2006): S164-S172.
- Feinstone SM, Kapikian AZ, Purcell RH. Hepatitis A: detection by immune electron microscopy of a viruslike antigen associated with acute illness. *Science* 1973; 182: 1026-1028
- Degasperi, Elisabetta, Maria Paola Anolli, and Pietro Lampertico. "Bulevirtide-based treatment strategies for chronic hepatitis delta: A review." *Journal of Viral Hepatitis* (2023).
- Forbes, Carol, et al. "Global Importance of New Treatment Strategies to Efforts to Control Hepatitis B Virus." *Expert Review of Anti-infective Therapy* just-accepted (2023).
- Brunetto, Maurizia Rossana, et al. "EASL Clinical Practice Guidelines on hepatitis delta virus." *Journal of Hepatology* (2023).
- Kushner, Tatyana. "Delta hepatitis epidemiology and the global burden of disease." *Journal of viral hepatitis* 30 (2023): 4-10.
- Dieterich, Douglas, et al. "It is time for a simplified approach to hepatitis B elimination." *Gastro Hep Advances* 2.2 (2023): 209-218.
- Nathani, Rohit, et al. "The Delta Delta: Gaps in screening and patient assessment for hepatitis D virus infection." *Journal of Viral Hepatitis* 30.3 (2023): 195-200.
- Weng, Mark K., et al. "Universal hepatitis B vaccination in adults aged 19–59 years: updated recommendations of the Advisory Committee on Immunization Practices—United States, 2022." *American Journal of Transplantation* 22.6 (2022): 1714-1720.
- **Special Thanks to Dr. Michael Wellner**