

Viral Hepatitis A-E: Perspective 2022 “Controversies”

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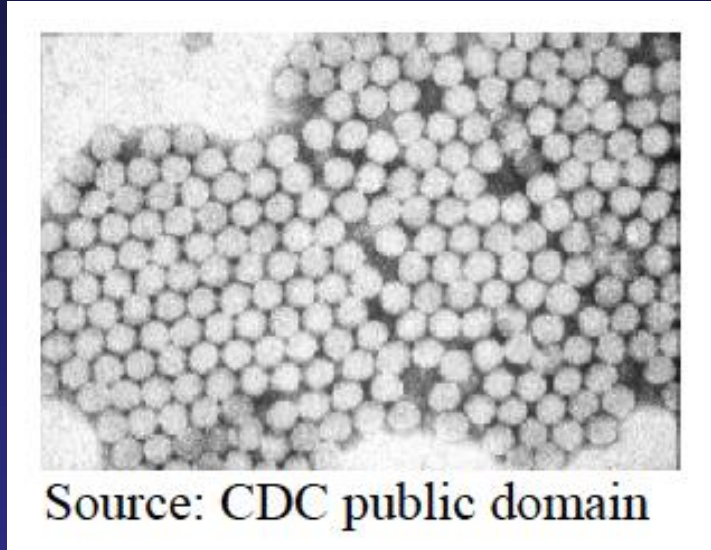
Dallas, TX

Disclosures: Research support from BMS, Gilead, Merck

Overview Viral Hepatitis: Progress is being made

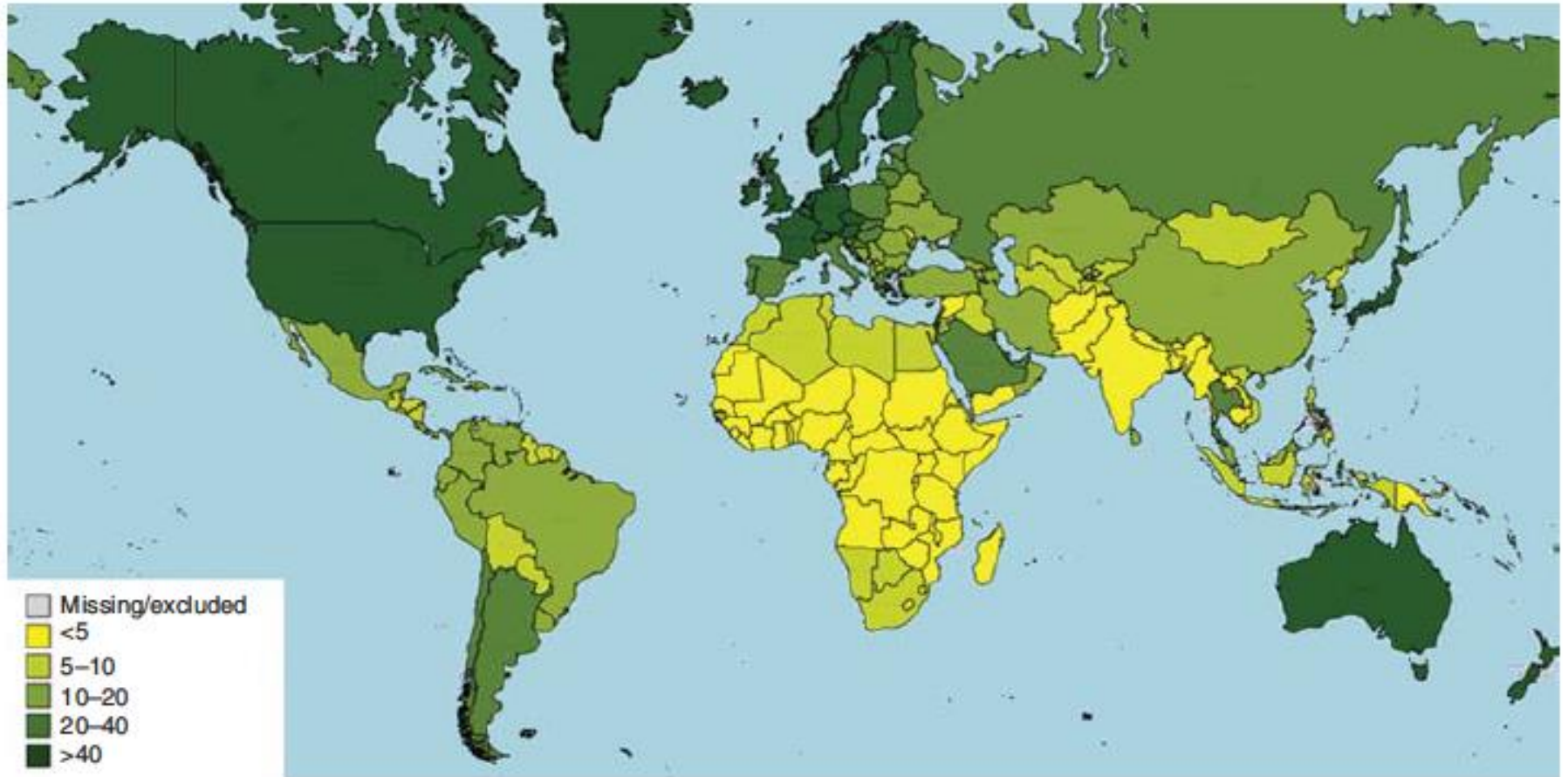
- Hepatitis A: Still around, sporadic/epidemic
- Hepatitis B: Worldwide problem, seeking a cure—new drugs coming.
- Hepatitis C: Major progress, still need to find additional cases.
- Hepatitis D: No progress here, but new drugs possibly effective
- Hepatitis E: Interesting developments

Hepatitis A Virus (HAV)



- *Picornaviridae* member that primarily infects liver cells
- Food and sanitation, also sex contacts
- Most have inapparent infection, < 1% ALF
- Never chronic

Epidemiology of Hepatitis A



Midpoint age of immunity

Jacobsen, K, cship.org

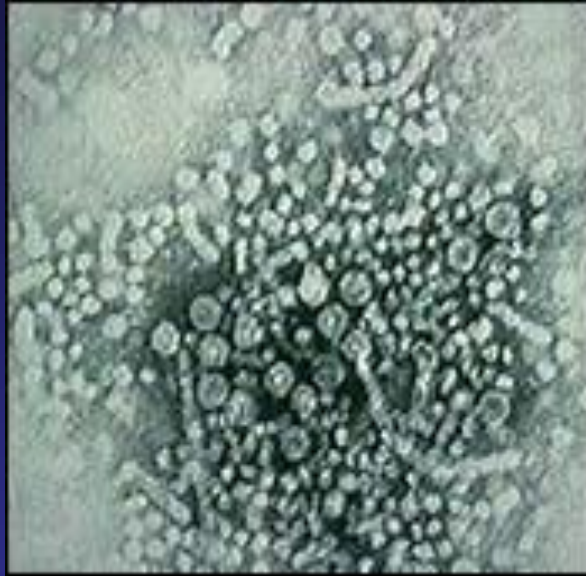
Recent Outbreaks Hepatitis A

- Among San Diego homeless, also LA, Michigan and Ohio, related to IDU and homelessness
- Over 600 hospitalized in San Diego alone
- Related to poor sanitation
- Remedy: more public toilets, hand washing, vaccination
- Food borne epidemics occur sporadically
- Points out that fewer young Americans are immune

Take Home Message: Evolving Natural History

- Developed vs. Third world epidemiology
- Currently seen in MSM, homeless, IDU settings—one case a week at least at PMH
- Food borne epidemics less frequent
- *Vaccination recommended for all* with chronic liver disease: think fatty liver disease, any form of cirrhosis.

Hepatitis B Virus (HBV)



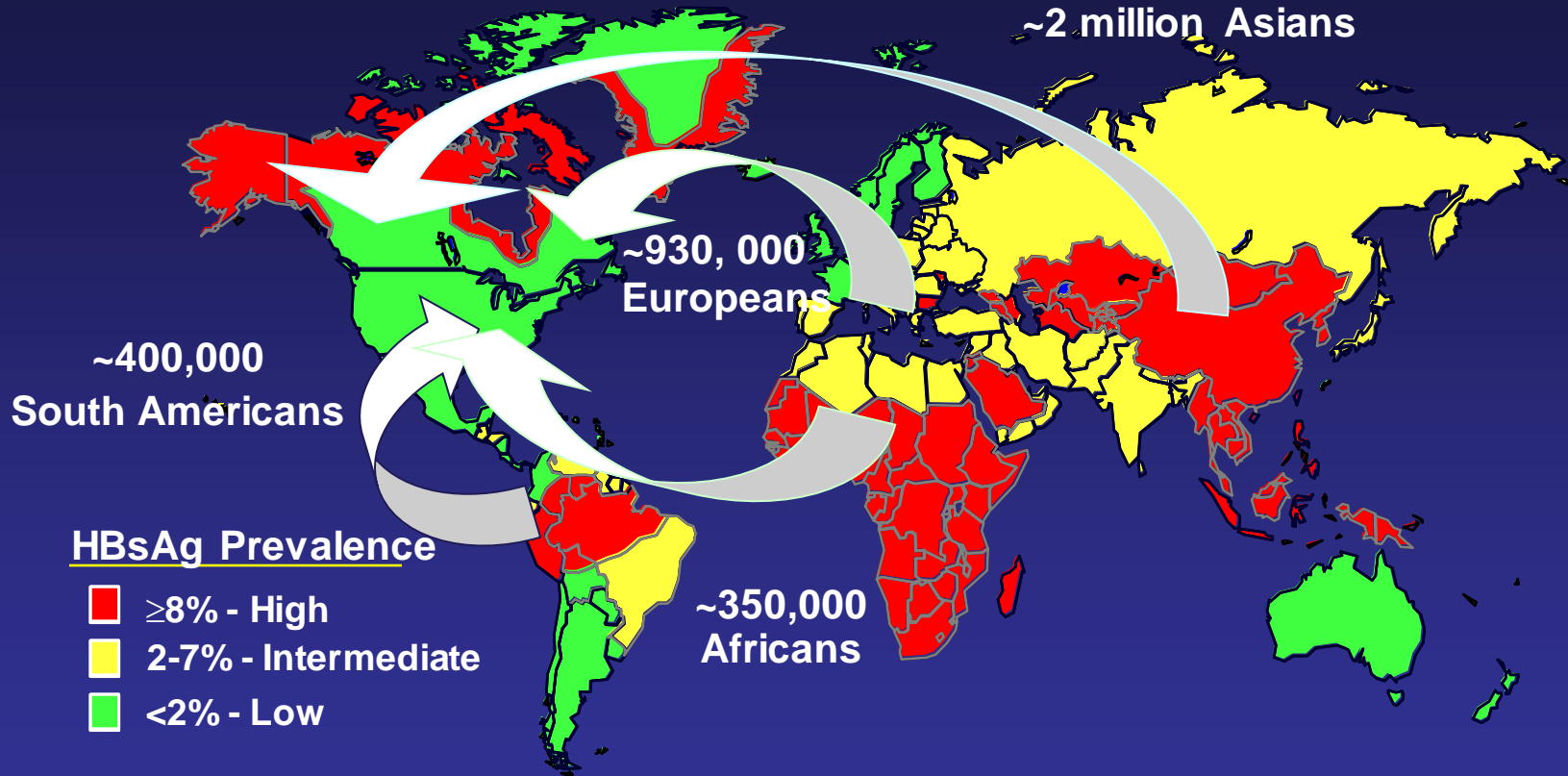
- *HepaDNAviridae* member that primarily infects liver cells
- 100 times more infective than HIV
- Found in blood and body fluids
 - Able to survive in dried blood for >1 week

Ott et al. *J Pediatr Health Care*. 1999;13(5):211-216.

Ribeiro, et al. *Microbes and Infection*. 2002;4:829-835.

MMWR. 2003;52:1-33.

Geographic Prevalence of Chronic Hepatitis B May Be Impacted by Migration



Immigration numbers summed by continent from 1996-2002

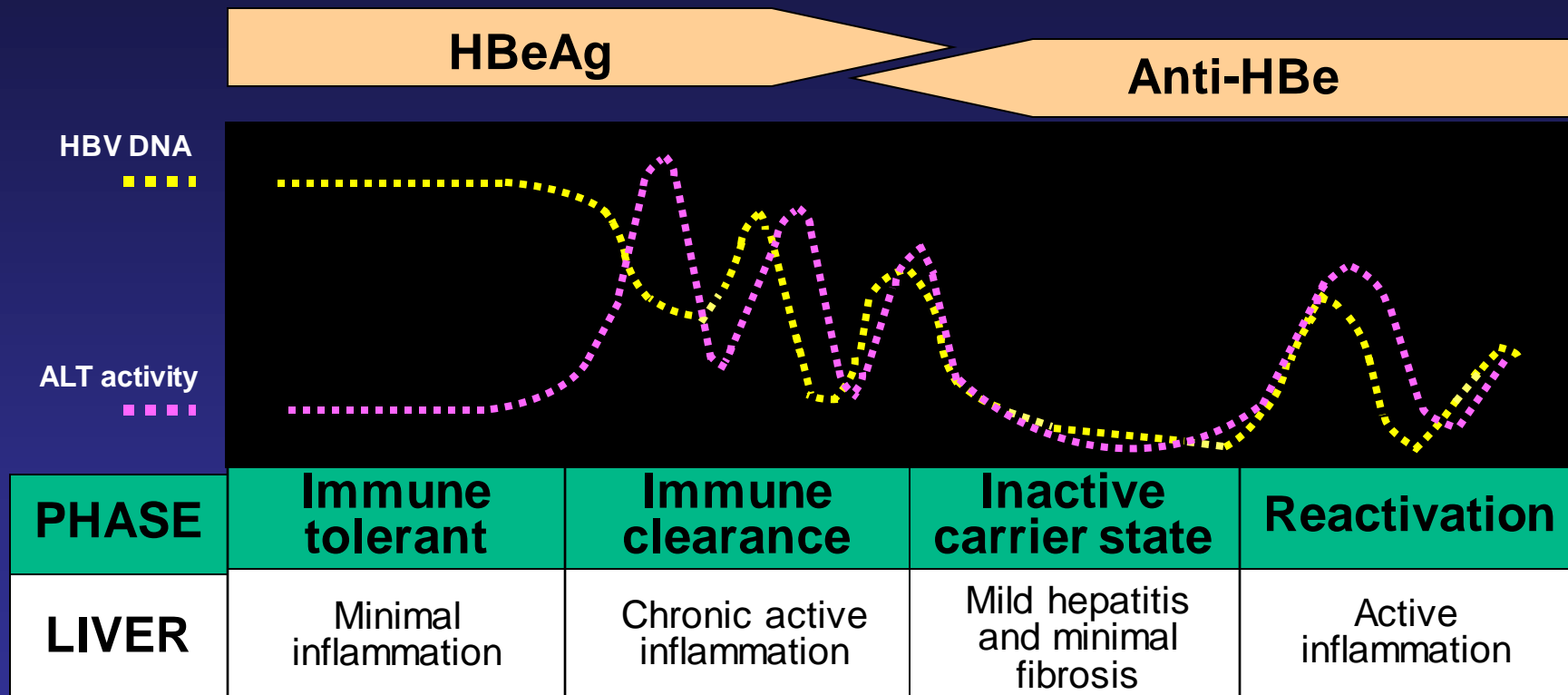
World Health Organization. Geographic Prevalence of HBsAg. Data from 1996 (unpublished).
<http://www.who.int/vaccines-surveillance/graphics/htmls/hepbprev.htm>. Accessed: September 13, 2004.

2002 Yearbook of Immigration Statistics.

<http://uscis.gov/graphics/shared/aboutus/statistics/IMM02yrbk/IMM2002list.htm>. Accessed: September 22, 2004.

Mahoney FJ. *Clin Microbiol Rev.* 1999;12:351-366.

Phases of Chronic HBV Infection



↑ Optimal treatment times ↑

ALT, alanine aminotransferase
HBeAg, hepatitis B e antigen

Yim and Lok. *Hepatology*. 2006;43:S173-S181.

Drugs Currently in Use for Hep B

- Entecavir (Baraclude®) 0.5 and 1.0 mg/d
- Tenofovir disoproxil (Viread) 300 mg/d
- Tenofovir alafenamide (Vemlidy) 25 mg/day
- **Benefits: safety profile great, long term use safe, virtually no drug resistance seen**

Newly recognized entity: Hep B reactivation in the setting of chemo/immunotherapy

- Many do not know that they have hep B if it is inactive, begin chemotherapy, disease flares, fatal outcome- testing prior to chemoRx is mandated
- **Totally preventable if HBV treatment begun prior to beginning chemoRx.**
- **NEW ENTITY:** Reactivation following DAA treatment, rare but worth mention.

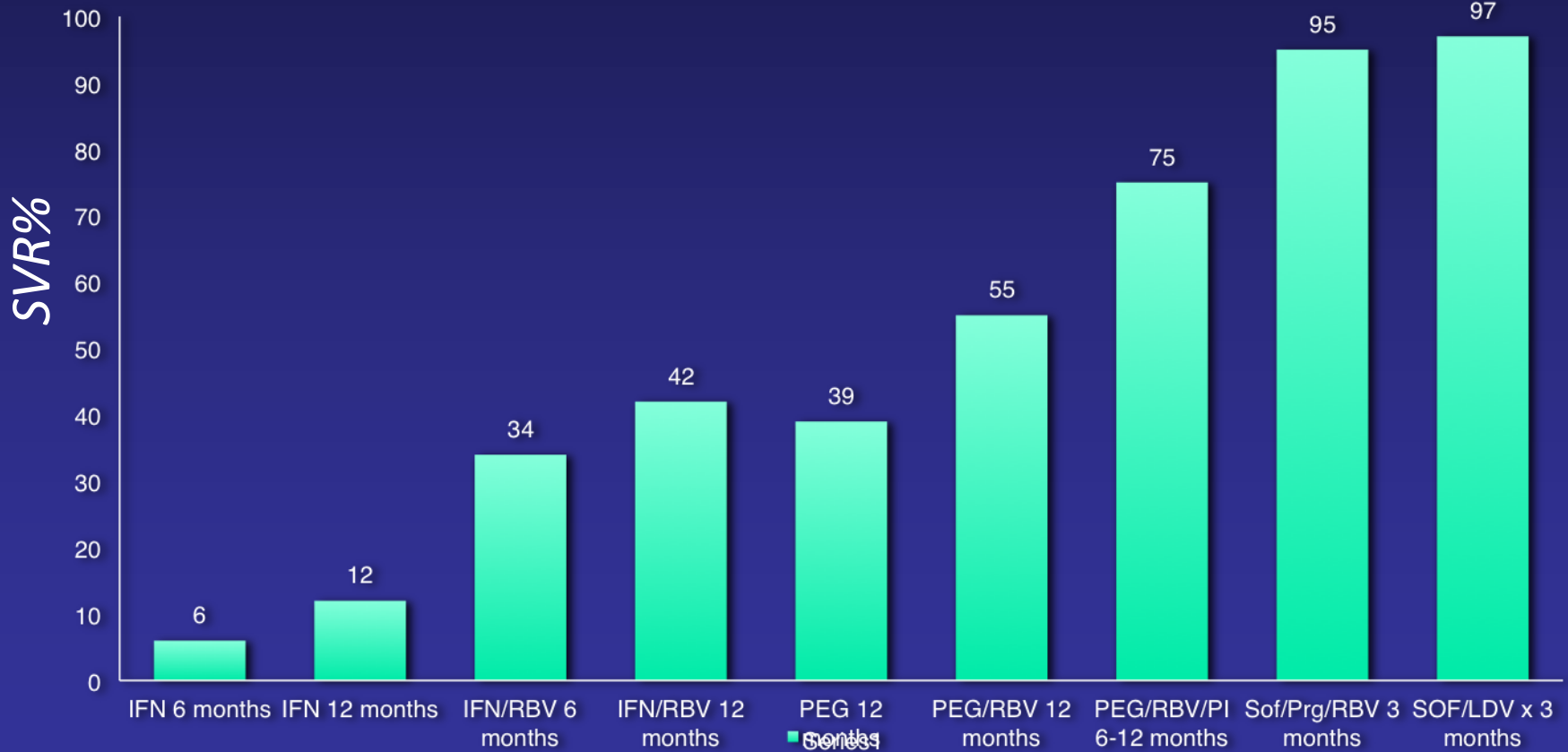
HBV controversies: When to treat, when to stop, why can't we get this cured?

- Treatment is highly effective, safe but costly
- Patients still want a cure which we don't have.
- If we wait for HBsAg negativity it is a long wait: 3%/year
- But in most instances, stopping Rx leads to relapse
- Cost an issue for Vemlidy: best drug for safety but also costs ~\$600 per month for many insured patients. Viread, earlier tenofovir, has some risk of CKD/osteopenia

Hepatitis C Virus (HCV) Update Outline

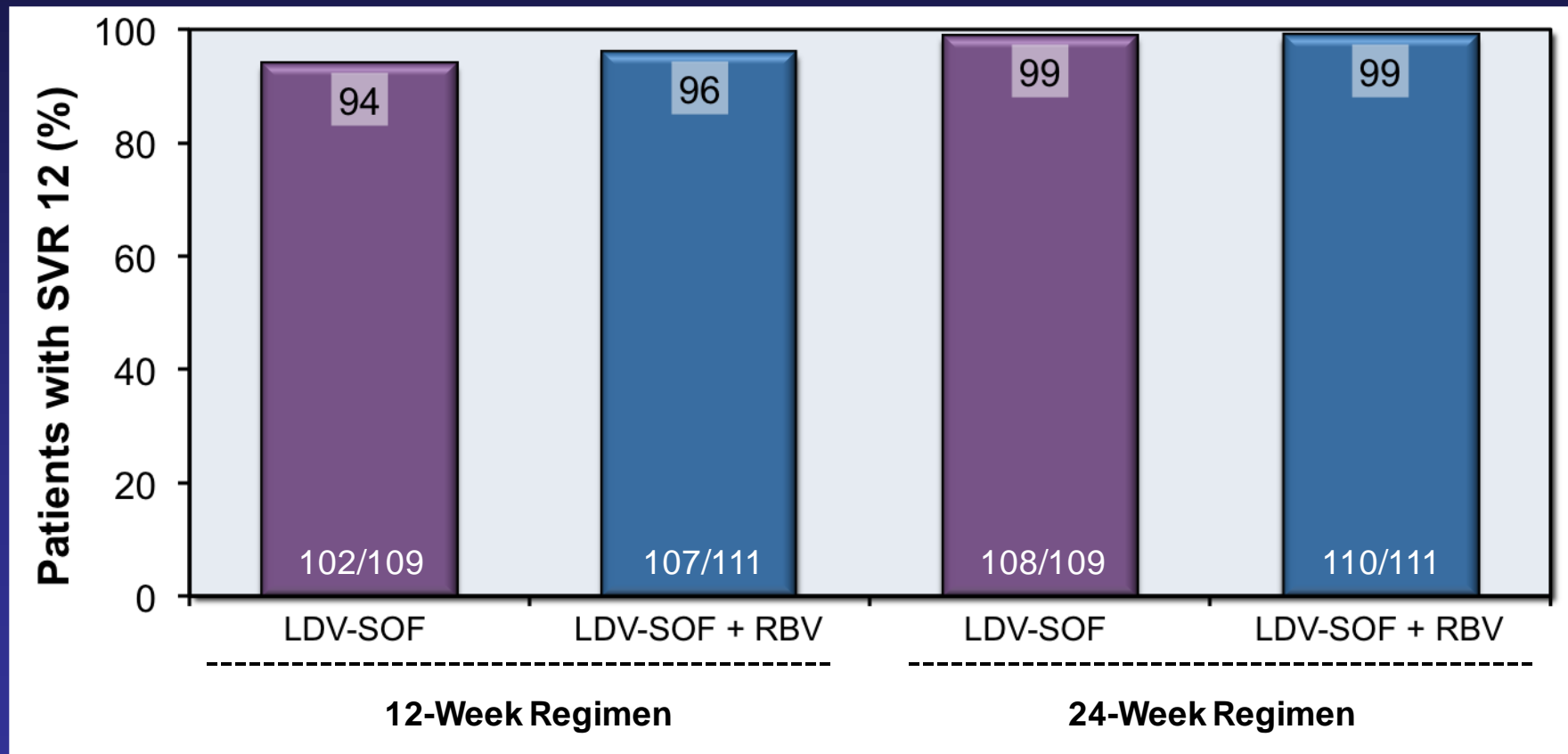
- **Historical perspective: what is the virus, where is it?**
- **Targeting Baby Boomers: diagnosing hepatitis C**
- **Treatment since 1990: stepwise improvement**
- **Dramatic improvement in the last 8 years**
- **Current recommendations/challenges**

Timeline of HCV Therapeutics



Ledipasvir-Sofosbuvir +/- Ribavirin in Treatment-experienced HCV GT 1 ION-2 Study: Results

ION-2: SVR 12* by Treatment Duration and Regimen



Abbreviations: LDV-SOF= ledipasvir-sofosbuvir; RBV = ribavirin

*Primary end-point by intention-to-treat analysis

Source: Afdhal N, et al. *N Engl J Med.* 2014;370:1483-93.

Current Era of HCV Treatment

- No interferon or ribavirin-no side effects
- Near 100% cure rate for almost all patients
- Principal drugs: Mavyret and Epclusa-maybe Vosevi for the few failures.
- Currently Rx 10/mon vs. 50+/mon in 2014.
- Now, we are 'mopping up' other groups: homeless, IDU, immigrants, etc.
- **Need: Identify those with unrecognized HCV**
- Detailed information: www.HCVguidelines.org

Hepatitis C: Take Home Messages

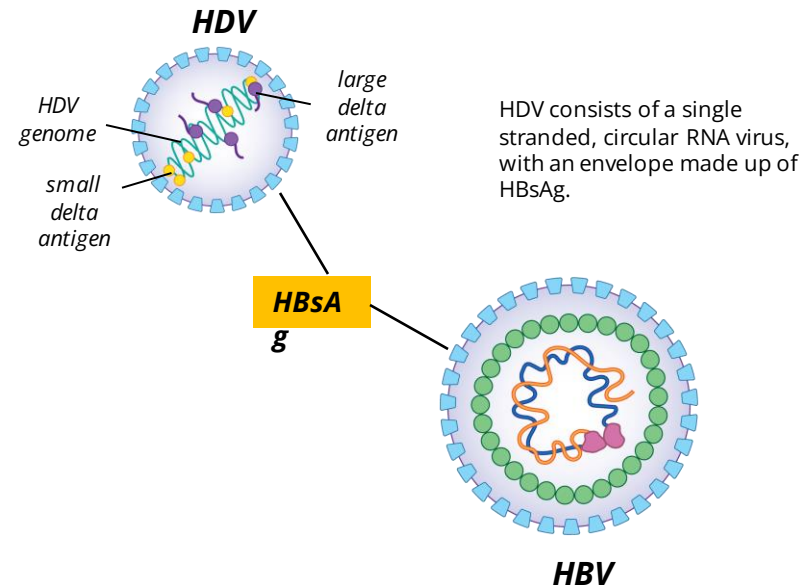
- Current treatments are incredible
- Hepatitis C will still be with us:
 - If patients are not identified, **or increased new infections**
- Cirrhosis and its complications live on:
 - Particular reminder: ***the cured patient with cirrhosis still needs cancer surveillance lifelong!***
 - 6-monthly sonograms will suffice in most cases.



HEPATITIS DELTA VIRUS (HDV)

OVERVIEW

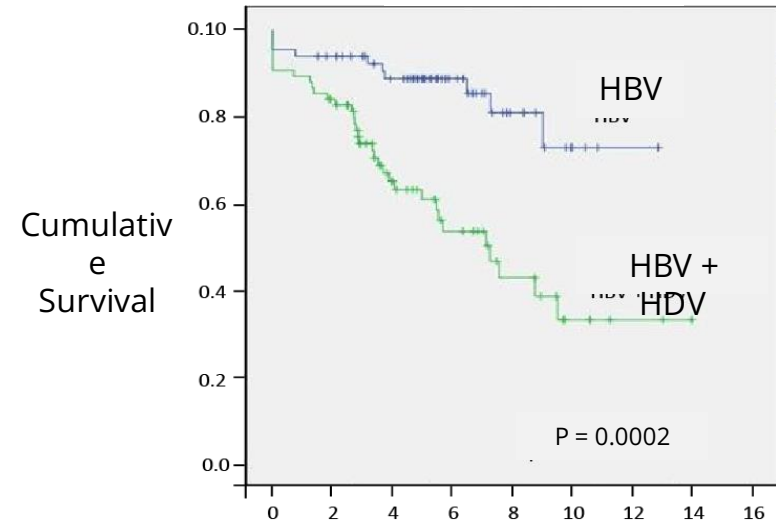
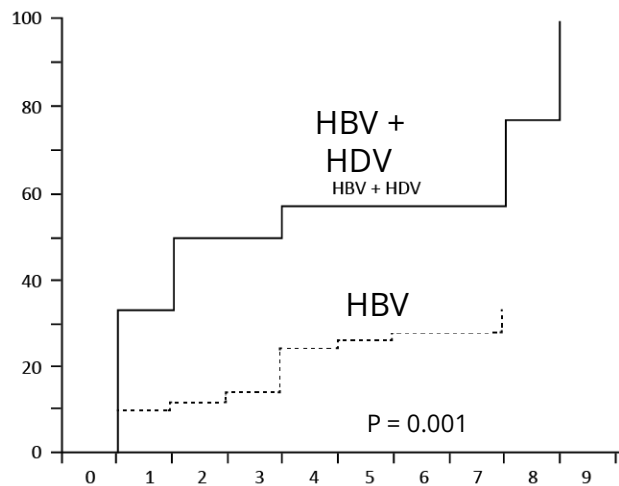
- HDV is the most severe form of human viral hepatitis
- HDV is always a co-infection with HBV
 - HBsAg acquired through protein prenylation
- 4-6% of HBV infected patients co-infected with HDV
- HDV causes more rapid disease progression
 - Compared to HBV mono-infection
- No FDA approved Rx
- 15-20 M HDV infected patients worldwide
 - > 100K HDV patients in US; > 200K HDV patients in EU
 - > 2 Million HDV patients in China



- HDV requires HBsAg to complete virus assembly
- HBsAg acquired through **PROTEIN PRENYLATION**

AT DIAGNOSIS, >50% OF HDV PATIENTS ARE CIRRHOTIC

Risk of Hepatocellular Carcinoma, Decompensation, Mortality Increase



Fattovich et al, J Infect Dis, 1987; Fattovich et al, Gut, 2000. Serrano et al, EASL 2011

Hepatitis D (delta, HDV): New Rx on the way

- Passenger RNA virus that accompanies Hep B infection
 - If no HBsAg, then no HDV is present
 - Test for HDV antibody and/or RNA-in everyone with HBV
 - Often have severe liver disease despite low HBV DNA
- No good treatment, long term interferon may have some value but poorly tolerated
- **Conquering hepatitis B will take care of delta**
- **Drug trials underway: we need to look harder and find more cases.**

Hepatitis E Worldwide

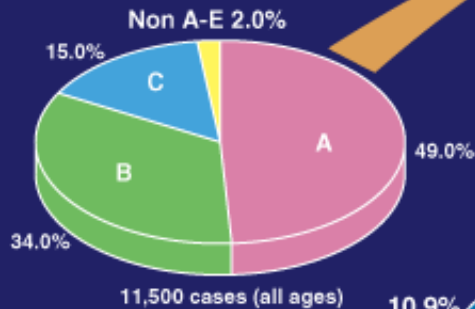
- Fifth form of viral hepatitis
- HEV: small single stranded RNA enterovirus: hepevirus
- Four genotypes described
 - Genotype 1 & 2, common cause of epidemic hepatitis E
 - Genotype 3 & 4, zoonoses found mostly in swine, but also in chickens, deer, rabbits
- Initially thought to be rare in the developed world but now more recognized 'autochthonous' cases, sporadic
- **Currently the most common cause of hepatitis worldwide!**

HEV

Important pathogen in tropical, subtropical regions

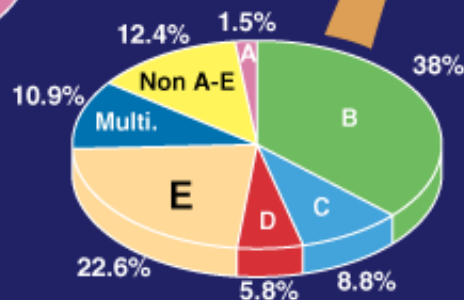


United States: All Ages
(Sentinel Counties)



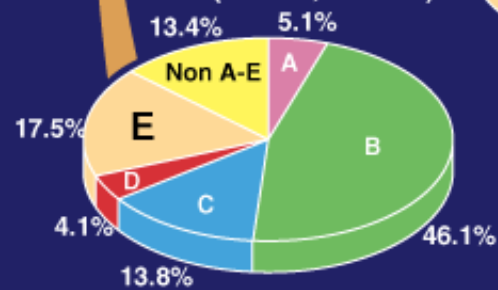
S. Goldstein et al., J. Inf. Dis., 2002

Egypt
(Cairo)



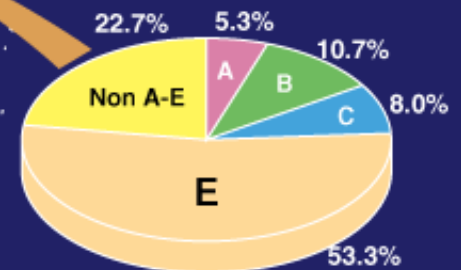
P. Gomatos et al., Egypt.J.Med.Micro., 1996

Saudi Arabia
(Jedda, Mecca)



T. Ghabrah et al., Clin. Inf. Dis., 1995

India
(New Delhi)



U. Poddar et al., J. Trop. Med., 2002

2nd or 1st most important cause of acute hepatitis in adults in the
Middle East, North Africa and Asia

(Purcell J Hepatology 2008; 48:494)

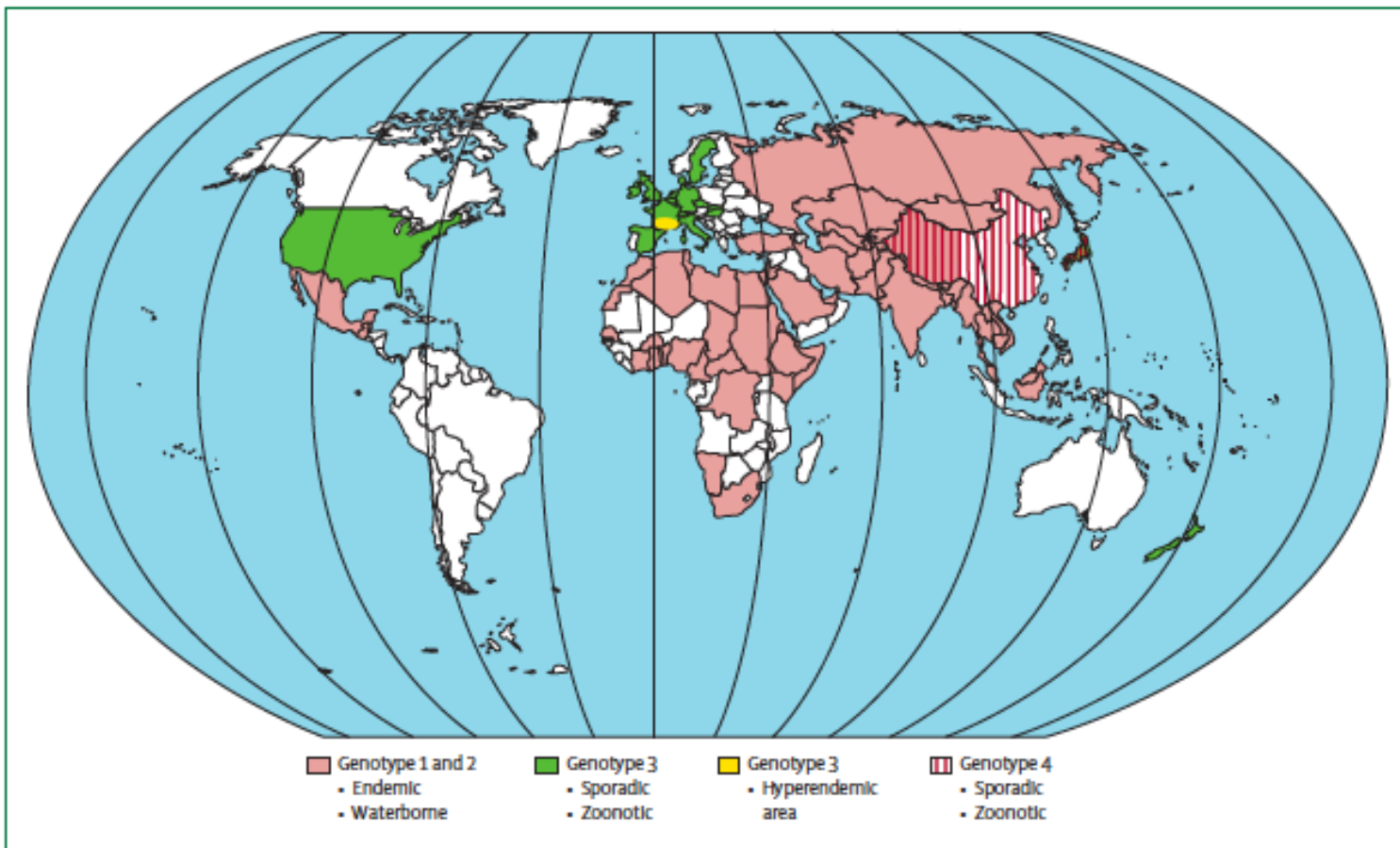
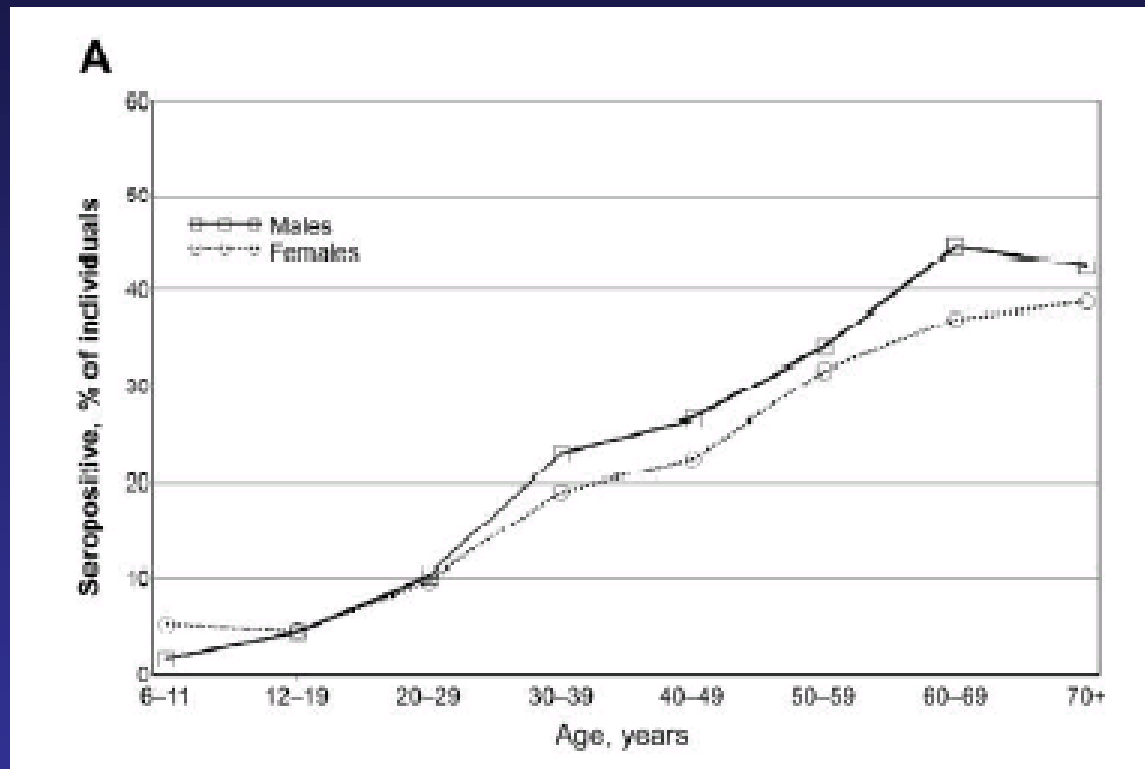


Figure 2: Worldwide distribution of clinical cases of HEV infection

Note, that in several countries, including in South America, there have been occasional reports of HEV3 infection. Countries left blank are those with insufficient data.

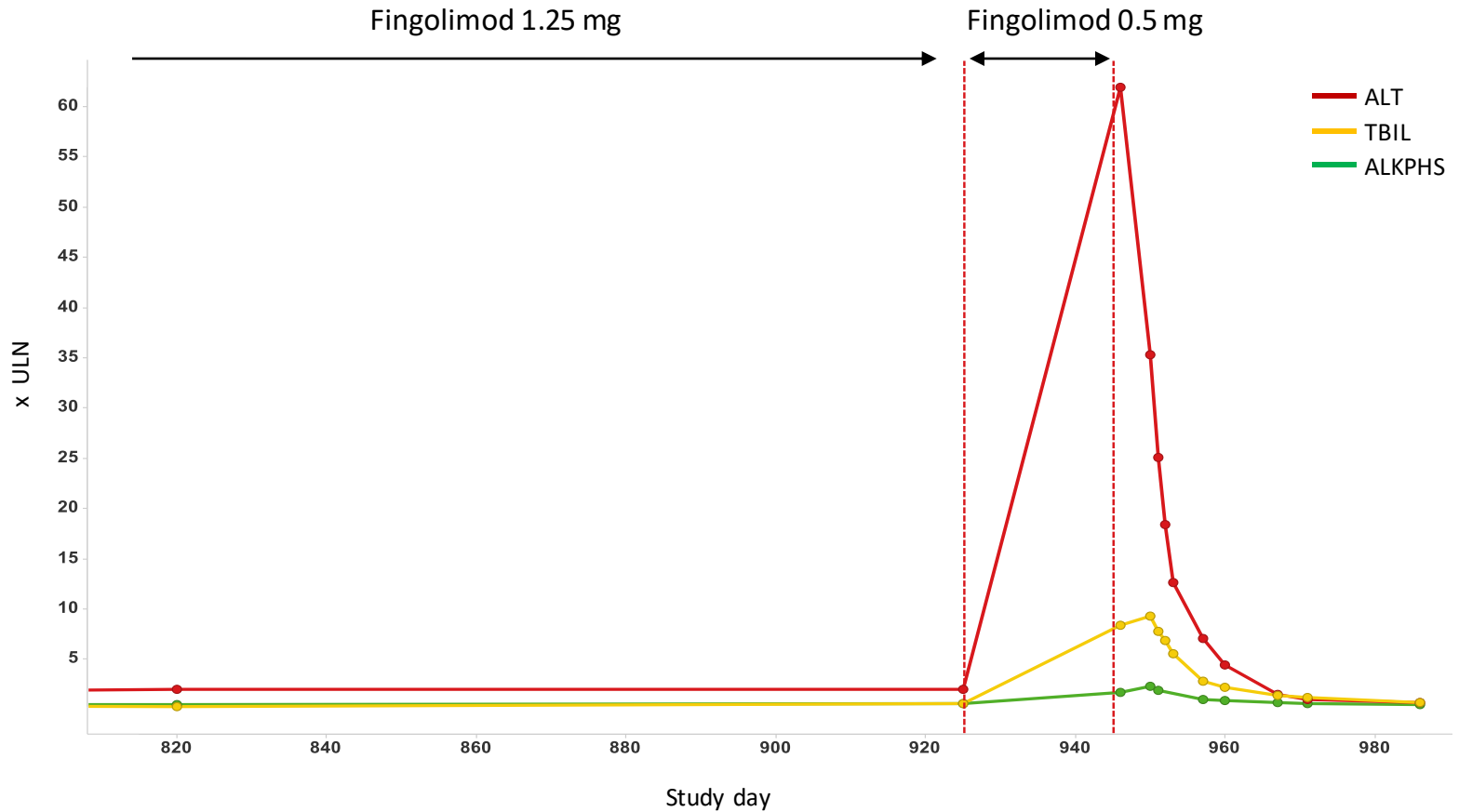
Epidemiology of Hepatitis E



Anti-HEV
prevalence by
age and sex in
the United States:
1988-94

Kuniholm et al. J Infect Dis
2009

Fig. 1b: Expanded view of liver test profiles during the episode of jaundice.



Hep E IgG Ab
 Hep E IgM Ab
 Hep E RNA PCR

-	-	+	+
-	-	+	+
-	+++	++	

Chronic Hepatitis E in Solid Organ Transplants

- Sizable numbers of cases in Europe have documented active acute and/or chronic infection in immunosuppressed transplant recipients.
 - At least 50% are chronic, some resolve
 - Antibodies may be absent/ use PCR for RNA to confirm the diagnosis
 - Reduction of immunosuppression is helpful
- Lung, heart, kidney and liver all implicated
- HEV has been transplanted with a liver in one instance
- Transfusions can be a source of infection
- Higher frequency of extra-hepatic manifestations
 - Cryoglobulinemia with membranoproliferative GN has been observed
 - CNS signs and symptoms
 - Can lead to liver or renal failure and graft loss

Viral hepatitis: Take Home Messages

- Major breakthroughs in understanding and treatment of Hepatitis C
- Hepatitis A, B and C are still with us:
 - Risks when/if patients are not identified
 - Hepatitis E may occur sporadically in the US
- Cirrhosis and its complications live on:
 - Particular reminder: ***the cured Hep C patient with cirrhosis still needs cancer surveillance lifelong!***