

## The ABC's (and D & E's) of the Viral Hepatitides Part 1

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### Objectives 2

1. Explain the various modes of transmission of each virus discussed.
2. Describe the mortality and morbidity associated with the viral hepatitides.
3. Give a basic description of the makeup and structure of each virus.
4. Be able to select the correct lab diagnostics for each virus discussed.



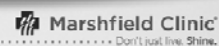
### Disclosures 3

- ❖ I have nothing relevant to this topic to disclose.
- ❖ All tables and graphs have been drawn from public domain websites.



### 4

## INTRODUCTION



### Terminology 5

- ❖ **Disease:** a deviation of a bodily process leading to signs and symptoms. A disease may be occult in that it is not readily detected by the observer.
- ❖ Conversely, **infection** is a biological process leading to viral replication but not necessarily clinically detectable disease.
- ❖ **Hepatitis** (pl. **Hepatitides**): an inflammation of the liver caused by non-infectious or infectious processes. Often used to describe the clinical presentation of liver disease, but also may require diagnostic studies to detect.
- ❖ Liver **cirrhosis** results from long-term insult, leading to fibrosis and nodules, and ultimately loss of function.



### Terminology 6

- ❖ **Prevalence:** the number of cases of a disease (or other marker e.g. antibody) at a given time in a population.
- ❖ **Incidence:** the rate of infection (or other occurrence e.g. sero-conversion) over a given time period in a population.
- ❖ **Endemic:** an infection that is maintained in a population irrespective of disease burden. A descriptive or numerical level of **endemicity** is often given.



**VH Group Viruses (HAV, HBV, HCV, HDV, & HEV) 7**

- ❖ All cause hepatitis, but their epidemiology and natural history of disease differs.
- ❖ HBV, HCV and HCV cause acute and chronic infection; HAV and HEV acute only.
- ❖ HAV and HEV are spread by oral-fecal route, causing 'infectious' or 'enteral' hepatitis.
- ❖ B, C, D do not survive intestinal bile acids and are only spread through blood or other body fluids (i.e. parenteral transmission).

**The Viruses 8**

Name	Genome	Capsid
Hepatitis A virus (HAV)	Single strand RNA, 7.5kB	Non-enveloped, icosahedral
Hepatitis B virus (HBV)	Partial double strand circular DNA, 3.2kB	Enveloped spheroid (non-infectious spherical and filamentous forms also)
Hepatitis C virus (HCV)	Single strand RNA, 9.6kB	Enveloped, spheroid
Hepatitis D virus (HDV)	Single strand, self hybridizing RNA, 1.7kB	Enveloped, spheroid
Hepatitis E virus (HEV)	Single stranded RNA, 7.2kB	Non-enveloped, icosahedral

**The Viruses Beyond A – E 9**

- ❖ Hepatitis F: postulated in 1990's, never substantiated.
- ❖ Hepatitis G: now called GB virus C, since although it infects the liver does not cause overt hepatitis. (Other disease?)
- ❖ Many other viruses (e.g. CMV, EBV, yellow fever) also have minor or significant hepatic components.

**Hepatitis 10**

- ❖ Viral hepatitis (VH) can run a rapid and sometimes fulminant course, or may be clinically unapparent and persist for years and decades before reactivating.
- ❖ Untreated chronic VH often leads to cirrhosis and hepatocellular carcinoma (HCC).
- ❖ Liver and spleen are primarily afflicted, but other systems can be affected too.

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**EPIDEMIOLOGY****HV Worldwide: A global problem 12**

An ancient disease (e.g. Hippocrates recognized infectious jaundice in 4000BCE).

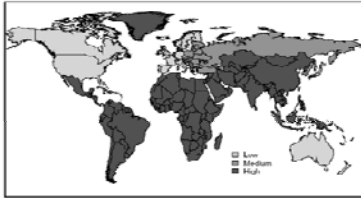
Approximately:

- ❖ 500mil people chronically infected with HBV & HCV
- ❖ 1mil deaths/yr (~2.7% of all deaths) from VH-related complications (cirrhosis, cancer)
- ❖ 57% of liver cirrhosis and 78% of primary liver cancers due to HBV & HCV
- ❖ 4.5mil cases of acute hepatitis due to HAV & HEV/yr

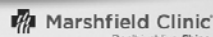
(WHO [http://who.int/csr/disease/hepatitis/GHP\\_framework.pdf](http://who.int/csr/disease/hepatitis/GHP_framework.pdf). Accessed 02/05/2013)

**HAV-Worldwide 13**

Hepatitis A Relative Endemicity



CDC 2005. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5507a1.htm>  
(Accessed 02/05/2013)



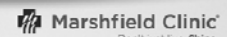
Don't just live. Shine.

**HBV-Worldwide 14**

Relative Prevalence of Chronic Hepatitis B (HDV similar)



CDC 2006. <http://www.cdc.gov/hepatitis/WorldHepDay.htm>  
(Accessed 02/05/2013)



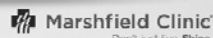
Don't just live. Shine.

**HCV-Worldwide 15**

Prevalence of Chronic Hepatitis C



CDC 2012. <http://wwwnc.cdc.gov/travel/pdf/yellowbook-2012-map-03-05-prevalence-chronic-hepatitis-c.pdf> (Accessed 02/05/2013)



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**HEV-Worldwide 16**

Hepatitis E Relative Endemicity



CDC 2013. <http://www.cdc.gov/hepatitis/HEV/HEVfaq.htm#section1>  
(Accessed 02/05/2013)

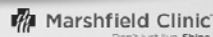


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**HV in the USA 17**

	Est. Acute Clinical Cases in 2010	Est. No. New Infections in 2010	Est. # Persons with Chronic Infections
HAV *	19,000	42,000	Never chronic
HBV *	15,000	53,000	800k-1.4mil
HCV *	2,800	17,000	2.7-2.9mil
HDV	NA	NA	NA
HEV	NA	NA	Never chronic

\* Nationally notifiable; NA, not available  
CDC 2013. <http://www.cdc.gov/hepatitis/Statistics/index.htm> (accessed 02/05/2013)



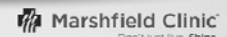
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**HV in the USA 18**

## ❖ Data for HDV, HEV less abundant:

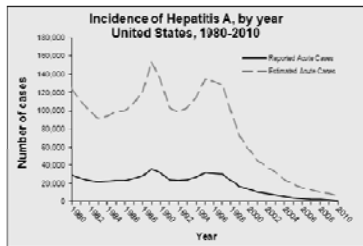
- ❖ HEV sero-prevalence in the USA found to be 66/10,000 persons(1)
- ❖ HDV? Infects 15,000,000 worldwide, but prevalence varies widely geographically(2).
- ❖ Using 5% HBV/HDV worldwide co-infection rate, USA may have ~10k chronically infected individuals.

(1) MF Faramawi et al 2011 Epidemiol Infect 139:1145  
(2) M Rizzetto et al 1990 Vaccine 8:S10



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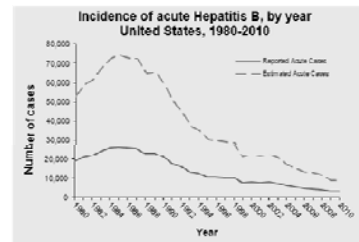
## HAV-USA by Year 19



CDC 2013. <http://www.cdc.gov/hepatitis/Statistics/index.htm>  
(Accessed 02/05/2013)

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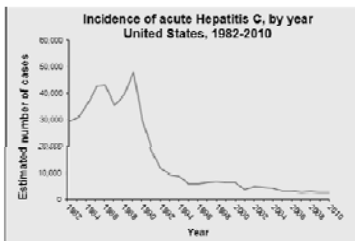
## HBV-USA by Year 20



CDC 2013. <http://www.cdc.gov/hepatitis/Statistics/index.htm>  
(accessed 02/05/2013)

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## HCV-USA by Year 21



CDC 2013. <http://www.cdc.gov/hepatitis/Statistics/index.htm>  
(accessed 02/05/2013)

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## HV in Wisconsin 22

## ❖ Acute cases in Wisconsin

	HAV		HBV		HCV		HDV		HEV	
	Rptd Cases	Cases /100k pop.	Rptd Cases	Cases /100k pop.	Rptd Cases	Cases /100k pop.	Rptd Cases	Cases /100k pop.	Rptd Cases	Cases /100k pop.
2007	32	0.57	36	0.64	0	0	0	0	1	0.02
2008	34	0.60	36	0.64	2	0.04	0	0	0	0
2009	33	0.58	46	0.81	3	0.05	0	0	1	0.02
2010	23	0.40	51	0.90	11	0.19	1	0.02	2	0.04
2011	8	0.14	18	0.32	15	0.26	0	0	3	0.05

❖ Courtesy of Dr. James Kazmierczak, WI DPH

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## HAV 23

- ❖ Virus is excreted in bile to the gut, in highest titer before symptom onset, and several weeks thereafter (Short period of viremia also).
- ❖ Degree of endemicity inversely related to level of sanitary/hygienic practices.
- ❖ Primary transmission is person to person by fecal/oral route.
- ❖ Viral particle is extremely hardy, so spreads also by fecally contaminated food and water.

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## HAV 24

- ❖ Incidence varies by level of endemicity
  - ❖ In highly endemic places nearly universal infection occurs during childhood.
  - ❖ Low endemicity areas see levels rise in adulthood.
- ❖ Children are usually asymptomatic reservoirs, so HAV is largely silent in high endemic areas.
- ❖ In contrast, HAV has a significant disease burden in low endemicity regions because adults usually become jaundiced and utilize medical services.

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## HAV 25

- ❖ In the USA, HAV incidence was much higher prior to the introduction of a vaccine.
- ❖ Highest in certain southwest and western states, and in Hispanic and Native American populations.
- ❖ Vaccine introduced here in the 1990's, now universally recommended for all children, led to a precipitous drop in incidence.



## HEV 26

- ❖ HEV, similar to HAV, is resistant to bile, so survives the lower GI tract.
- ❖ Virus travels via biliary tract to feces, where it is shed.
- ❖ Four genotypes
  - ❖ 1,2 infects humans, common in highly endemic 'developing' countries.
  - ❖ 3-4 found in humans, pigs other mammals, and is found worldwide, of low and high-endemicity regions.



## HEV 27

- ❖ In contrast to HAV, sero-prevalence of HEV is much lower in high-endemicity regions (~30-50% by middle age), suggesting less efficient spread.
- ❖ Epidemics thus do occur in high-endemicity locales.
- ❖ Adults present with clinical symptoms more than children, so disease burden is higher for HEV than HAV in these regions.



## HEV 28

- ❖ Of interest, 'developed' countries have been found to have a high sero-prevalence but disease is not observed. (In USA, incidence of HEV calculated to be 7/100k annually.[1]) Why?
- ❖ No IVD test for HEV antibodies-hepatitis cases not being diagnosed?
- ❖ Genotypes 3 and 4 predominate in developed countries, which may cause mild or asymptomatic infection.

(1) MF Faramawi et al 2011 Epidemiol Infect 139:1145



## HBV/HCV/HDV 29

- ❖ HBV, HCV & HDV are enveloped viruses that are inactivated by bile and *do not* survive in feces.
- ❖ In contrast to HAV and HEV, they cause long-lived viremia.
- ❖ Are thus spread parenterally by various routes:

Transfusion	Unprotected sex
Shared needle IVDU	Perinatal
Close household contact	Occupational exposure (e.g. HCW, EMS)



## HBV/HDV 30

- ❖ These two viruses are often considered together since HDV *requires* HBV to propagate.
- ❖ However, the prevalence of HDV is not always in sync with that of HBV in a given location.
- ❖ Blood as well as other body fluids all play prominent parts in HBV transmission.
- ❖ Like HAV, HBV has plummeted in many countries recently due to universal vaccination programmes.

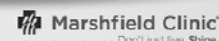


**HBV/HDV 31**

- ❖ Also like HAV, most HBV infection occurs early in high-endemicity regions, where it is usually silent, while in moderate and low-endemicity regions infection occurs later in life and causes clinical disease.
- ❖ And, ~90% of infant HBV infections become chronic, while only ~10% of adults progress to chronicity.
- ❖ Taken together, highly endemic regions have very high rates of chronic HBV infection and the sequelae of liver cirrhosis and HCC.

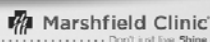
**HCV 32**

- ❖ HCV is most often transmitted through blood by various routes.
- ❖ In contrast to HBV, exposure to other body fluids is thought to play a lesser part.
- ❖ HCV was described in 1987 as the cause of non-A,B viral hepatitis, but is not new.
- ❖ HCV is found in all age groups including the elderly.

**HCV in the USA 33**

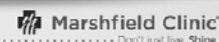
- ❖ HCV infects an estimated 2.7-3.9 mil persons, more than twice that of HBV.(1)
- ❖ The 48-68yo cohort has the highest prevalence (3.3% vs 1.6% overall) associated with IVUDU in the 1960's.(2,3)
- ❖ The incidence of infection has dropped in the USA in recent years due to blood screening and changes in IVUDU behaviors. But, with no effective vaccine on the horizon and the burden of existing chronic HCV, the huge impact on society will be felt for decades yet.

(1) CDC 2013 <http://www.cdc.gov/hepatitis/Statistics/index.htm> (Accessed 02/06/2013)  
 (2) BD Smith et al 2011 Hepatology 54:554A  
 (3) GL Armstrong et al 2000 Hepatology 31:777

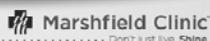
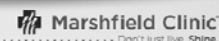
**HCC 34**

- ❖ HCC worldwide
- ❖ 5th most prevalent carcinoma in men; 7th in women
- ❖ ~50% of all HCC, and ~100% of childhood HCC is linked to chronic HBV; ~25% to chronic HCV.(1)(2)
- ❖ HCV or HDV co-infection, male sex, alcohol and tobacco abuse, familial HCC Hx, with chronic HBV increase HCC risk.(1)

(1) HB El-Serag 2011 N Engl J Med 365:1118  
 (2) JF Perz et al 2006 J Hepatol 45:529

**HCC - Women, 2008 35**

WHO 2008. <http://globocan.iarc.fr/factsheet.asp>  
 (Accessed 02/06/2013)

**36****CLINICAL FEATURES**

**Acute VH, General Features 37****Usual**

- ❖ Increased levels of liver transaminases
- ❖ Inflammation of liver tissues
- ❖ Swollen liver and spleen, palpable on exam

**Variably**

- ❖ Tissue build-up of bilirubin – **Jaundice**
- ❖ Urinary excretion of bilirubin – **Choluria**
- ❖ Fatigue, anorexia, malaise
- ❖ Pruritis
- ❖ Abdominal, muscular and/or joint pains
- ❖ Nausea and/or vomiting
- ❖ Fulminant progression

**Notes**

- Asymptomatic to symptomatic case ratio ~20:1.
- The younger the patient, the fewer the signs and symptoms.
- Fulminant cases are rare.

**Acute HAV, HEV 38**

- ❖ The disease of acute HAV and HEV is indistinguishable, and typical of acute VH.
- ❖ The incubation period of both ranges ~15-50 days, being on average 10 days longer for HEV.
- ❖ Recovery is typically complete in 2-3 months, but can be prolonged for up to a year in several rare forms.

**Acute HAV, HEV 39**

- ❖ Both occasionally (~1%) cause fulminant liver failure, but maternal HEV fulminant failure notably rises in pregnancy, as high as 25% in the 3<sup>rd</sup> trimester.
- ❖ This is not seen however in developed countries: genotype-related?

**Chronic VH, General Features 40**

- ❖ The liver damage of chronic VH is due to ongoing host cytotoxic T-cell attack of virally infected cells and not to cytopathic effects of the virus (which are minimal).
- ❖ Initial signs and symptoms are more insidious, but often ultimately leads to a number of symptoms, often beginning with malaise and fatigue. Meanwhile, liver damage continues as fibrosis develop.

**Chronic VH, General Features 41**

- ❖ As ongoing liver damage builds to cirrhosis, additional symptoms appear:
  - ❖ Weight loss
  - ❖ Bruising and bleeding occurs due to coagulopathies
  - ❖ Jaundice re-appears
  - ❖ **Peripheral edema** (edema of the legs) and **Ascites** (excessive abdominal fluid) develops
  - ❖ Various life threatening systemic failures occur
  - ❖ HCC often develops on top of the cirrhosis

**Chronic HBV/HDV 42**

- ❖ ~90% of infant, and ~10% of adult, acute HBV infections progress to chronicity.
- ❖ Effect of co-infection of HDV depends on timing of infection
  - ❖ Simultaneous infection with HBV: HDV has no effect on progression to chronicity or intensity of disease
  - ❖ Acute HDV infection on top of chronic HBV: HDV invariably becomes chronic, and existing liver disease usually greatly intensifies, sometimes fulminantly. Past this stage, HBV/HDV co-infection can subsequently stabilize.



**Chronic HBV/HDV 43**

Chronic infection has three main phases

Phase	Clinical Features
Immune Tolerance	<ul style="list-style-type: none"> <li>Viral replication high; liver damage minimal</li> <li>Usually seen in neonates, may persist for decades</li> </ul>
Immune Clearance	<ul style="list-style-type: none"> <li>Follows immune tolerance when present, OR initial phase of chronicity in older persons</li> <li>Viral replication high; liver inflammation ongoing</li> <li>Cirrhosis and HCC begins</li> </ul>
Inactive HBsAg Carrier State	<ul style="list-style-type: none"> <li>Viral replication is low</li> <li>Degree of inflammation and symptoms dependent on disease severity during Immune Clearance phase</li> </ul>
(Occult hepatitis B)	<ul style="list-style-type: none"> <li>Very low levels of viremia; all other indicators appear normal</li> <li>Not universally accepted, yet well-documented to occur in some individuals</li> <li>Consequences are unclear</li> </ul>

A Valsamakis 2007 Clin Microbiol Rev 20:426

**Chronic HCV 44**

- ❖ It is generally accepted that 75-85% of acute HCV infections become chronic, but may be as low as 55% in some cases.(1)
- ❖ Thought to be related to a high replication mutation rate generating multiple antigenically distinct quasispecies that eludes the immune system.(2)

(1) E Kenny-Walsh 1999 N Engl J Med 340:1228  
(2) P Farci et al 2000 Science 288:339

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**Chronic HCV 45**

- ❖ While phases of chronic HCV similar to HBV don't yet exist, chronic disease states are well-defined.
- ❖ Many patients demonstrate little more than fluctuations in liver aminotransferases for years. There may however be subjective symptoms i.e. fatigue and malaise that leads to a diagnosis.
- ❖ Fibrosis and cirrhosis typically develop slowly in 5-20% of cases within the first 20 years of infection, while HCC usually manifests after 20 years.(1,2)
- ❖ There is a strong association with various autoimmune diseases as well.(1)

(1) SC Ray, DL Thomas, Ch 154, Hepatitis C. In Principles and Practices of Infectious Diseases, GL Mandell eds  
2010 Churchill Livingstone, Philadelphia  
(2) AS Lok et al 2009 Gastroenterology 136:138

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**QUESTIONS?**

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