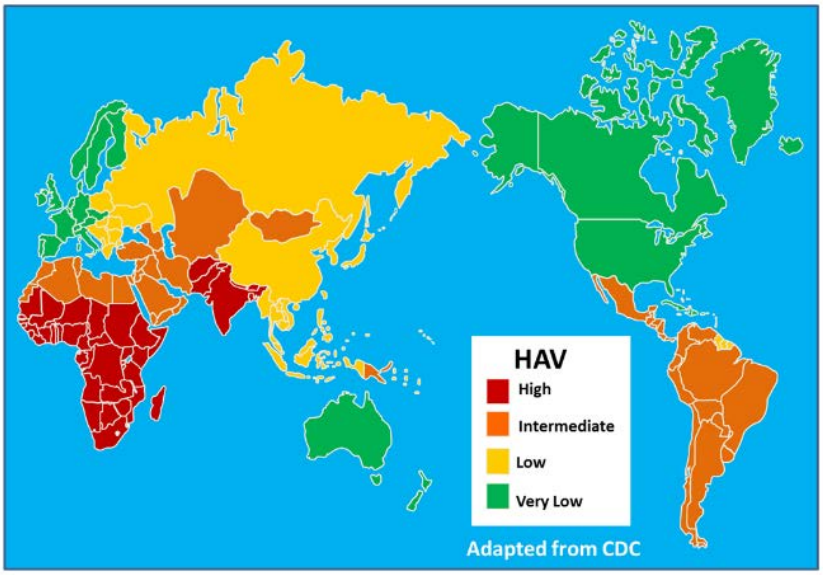
Chapter 6. Viral Hepatitis

6.1 Hepatitis A Virus (HAV)

Virology & Epidemiology

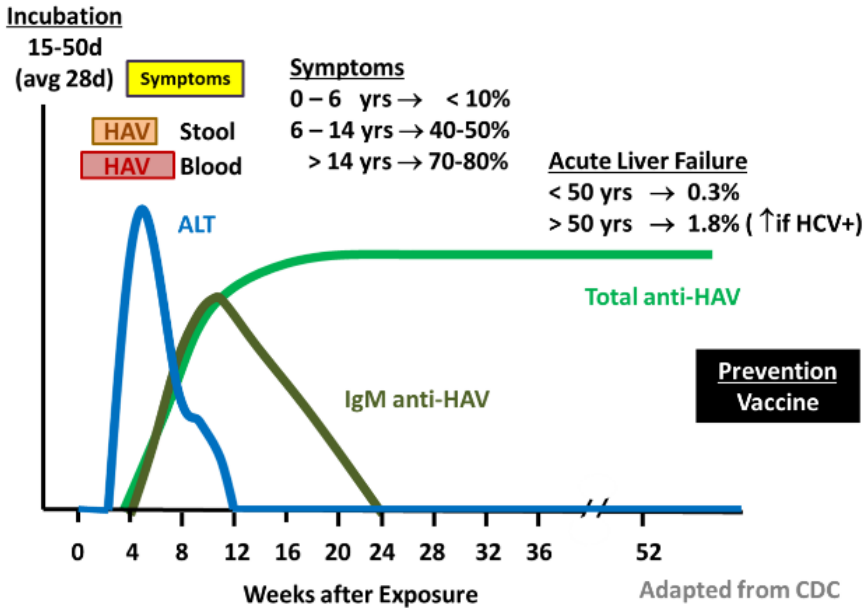
- **Hepatitis A virus (HAV)** is a single stranded RNA virus and is one of the most common viruses to infect humans (1.5 million infections worldwide each year)
- **Transmission** is primarily **fecal-oral**, but it can also be seen in IV drug users
  - Contaminated foods (e.g. raw seafood) often consumed by travelers to endemic countries
  - Outbreaks can occur if infected food handlers don't properly wash hands
  - Anilingus (mouth to anus contact)



Natural History & Diagnosis

- After an incubation period of approximately 28 days (range 15-50 days) symptoms of a flu-like illness may appear (with or without jaundice)

- HAV will cause an elevation of hepatocellular liver tests (ALT and AST) which can be severe (>1000) and this may be accompanied by jaundice and an elevated bilirubin
- The age of infection determines the likelihood of developing jaundice
  - <10% if age 0 – 6 years
  - 40-50% if age 6 – 12 years
  - 70-80% if age > 14 years
- Most patients with acute hepatitis will recover and develop life-long immunity
  - During the resolution of infection the pattern of liver tests may become more cholestatic (ALT falls and ALP rises)
  - There is **no chronic phase** to HAV infection
- If the INR is elevated it may indicate pending **acute liver failure (ALF)**, so you must watch for the development of encephalopathy *[see Chapter 10]*
  - ALF 0.3% if age <50
  - ALF 2% if age >50 and may be higher if chronically infected with hepatitis C virus (HCV)
- **Diagnosis** of acute HAV infection is made by testing antibodies to the virus
- **Total anti-HAV antibody** will measure both IgM and IgG antibodies to the virus
  - Positive test could indicate immunity from a past infection or vaccination (IgG antibodies)
  - Positive test could also indicate an **acute infection**, which must be confirmed by having a positive **IgM anti-HAV antibody**



Prevention & Treatment

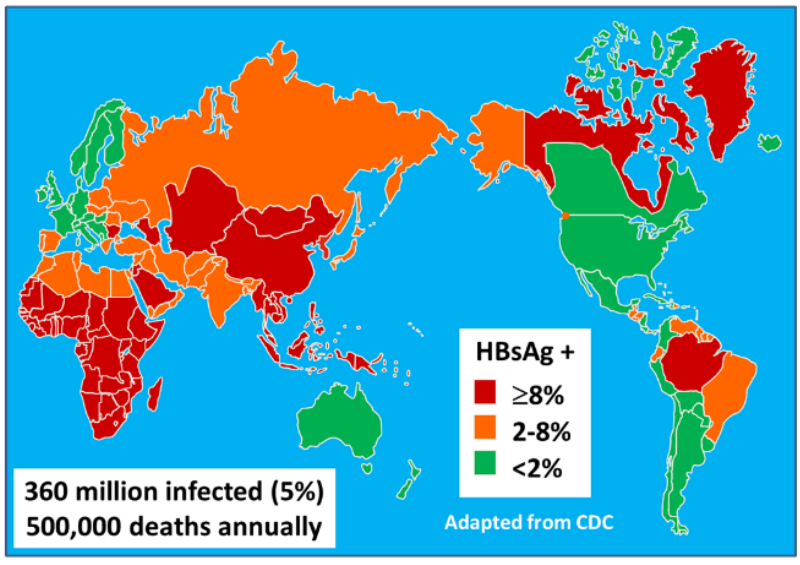
- HAV is preventable with **vaccination** and there are two forms of the vaccine
  - HAV vaccine (e.g. Havrix®) with two doses given at 0 and 6 months
  - Combined HAV / HBV vaccine (e.g. Twinrix®) with three doses given at 0, 1, and 6 months
- About 3 weeks after the first dose of the HAV vaccine, 99% will have immunity for one year and the booster dose should provide immunity for 20-25 years
- **Who should get the vaccine?**
  - Persons travelling to endemic areas
  - Men who have sex with men (MSM)
  - Persons Who Inject Drugs (PWID)
  - Persons with chronic liver disease
  - Persons receiving clotting factors (e.g. Hemophilia)

- There is **no specific therapy** for HAV infection other than supportive care, while following the liver function tests and watching for the development of hepatic encephalopathy (HE)
- Close personal contacts of infected persons can receive **post-exposure prophylaxis** with immunoglobulin (IG) and vaccination to prevent outbreaks

6.2 Hepatitis B Virus (HBV)

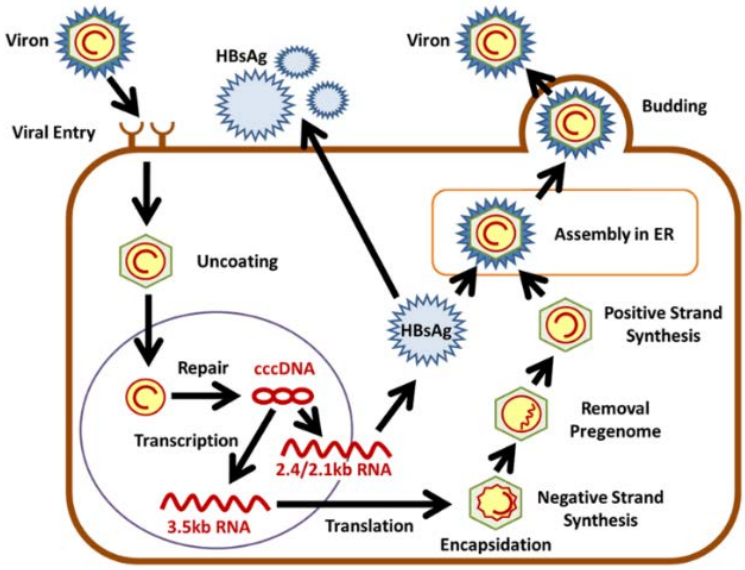
Virology & Epidemiology

- **Hepatitis B virus (HBV)** is a double stranded DNA virus which chronically infects approximately 360 million people world-wide (5% of the population) and is responsible for 500,000 death each year
- HBV is the leading cause of **hepatocellular carcinoma** (primary liver cancer) world-wide, which is the second leading cause of cancer related deaths globally



- **Transmission** can be **vertical** (from mother to child at birth), **horizontal** (between infected children), **parenteral** (through exposure to infected blood, e.g. in PWID) or **sexual**

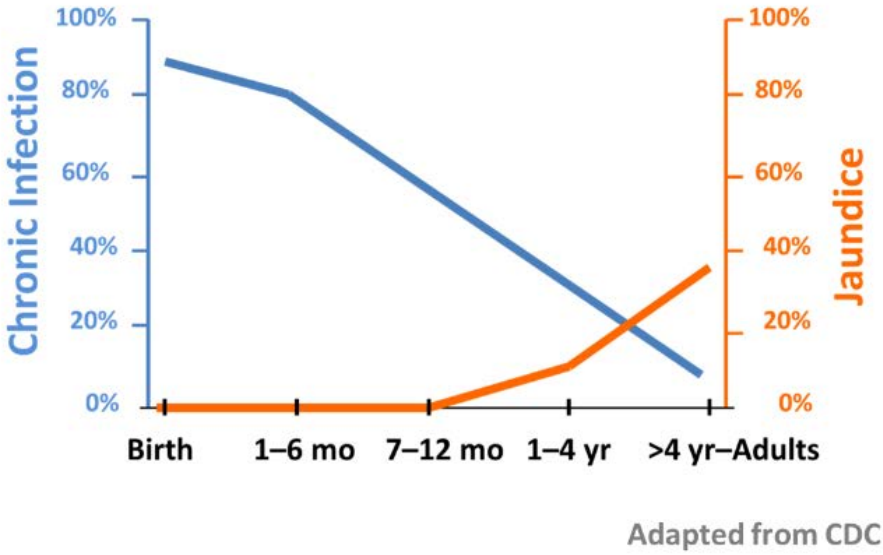
- The **life cycle** of HBV is complex
  - Once the viral particle attaches to the hepatocyte it uncoats and the virus enters the nucleus where it incorporates into covalently closed circular (ccc) DNA
  - This is separately transcribed to form RNA responsible for producing 1) hepatitis B surface antigen (HBsAg) and 2) the remainder of the viral structures
  - These come together in the endoplasmic reticulum and are assembled into mature virions which are released into the circulation only to infect other hepatocytes



Natural History & Diagnosis

- After an incubation period of approximately 120 days (range 45-160 days) symptoms of a viral illness may appear (with or without jaundice)
- The age at exposure, and maturity of the immune system, determine if an individual will develop symptoms of jaundice and acute hepatitis (usually with clearance of the virus) or a sub-clinical illness that becomes a chronic infection
  - Babies infected at birth or before their first birthday rarely develop symptoms but frequently develop chronicity (90-95%)

- Older children and adult patients may develop jaundice with acute hepatitis but most will recover with life-long immunity (chronicity develops in < 5%)

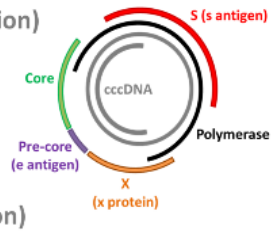


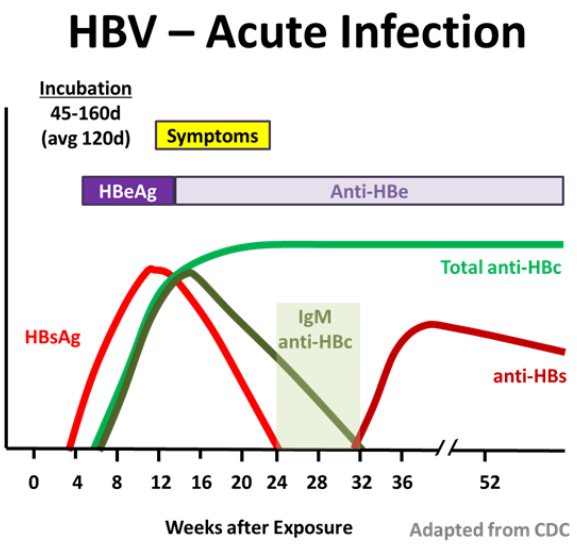
- Acute HBV in adults can cause an elevation of hepatocellular liver tests (ALT and AST) which can be severe (>1000) and this may be accompanied by jaundice and an elevated bilirubin
- If the INR is elevated it may indicate pending **acute liver failure (ALF)**, so you must watch for the development of encephalopathy
  - Approximately 0.5% of adult patients with acute HBV will develop **ALF**, which may result in the need for liver transplant
- **Diagnosis of HBV** infection is made by testing **antigens** (parts of the virus) or the **antibodies** to these antigens, with active viral replication being confirmed by measuring **HBV DNA** by polymerase chain reaction (PCR)
- **Hepatitis B surface antigen (HBsAg)** is a marker of infection, which could be acute or chronic

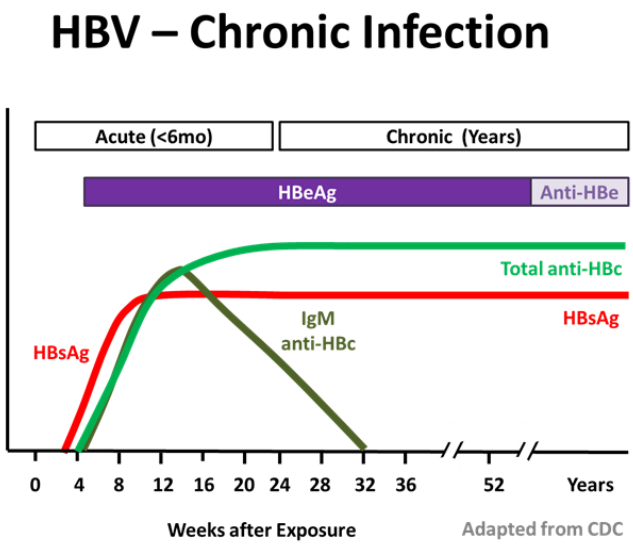
- **Anti-HBs antibody** (total) indicates the development of immunity, which could be from clearing the infection (natural immunity) or by receiving vaccination
- **Total anti-HBc (core) antibody** will measure both IgM and IgG antibodies to the core antigen and a positive test indicates exposure to the virus (active or past infection)
  - Natural immunity from a past infection (IgG antibodies) → will be HBsAg negative
  - Ongoing infection → will be HBsAg positive
  - **Acute infection** (or recent reactivation) → must be confirmed by having a **positive IgM anti-HBc antibody**, and might be the only test positive in the "window" between a positive HBsAg and a positive anti-HBs (see green box in figure below)
- **Hepatitis Be antigen** is from the pre-core region of the genome and is often associated with high levels of viral replication of the virus **(wild type)**
- **Anti-HBe antibodies** develop when a person clears the HBe antigen, indicating the virus is entering a lower level of viral replication
  - However, some individuals with a mutation in the pre-core or core promotor region of the virus can have active viral replication (HBV DNA detected) but are HBeAg negative and anti-HBe antibody positive **(pre-core mutants)**

HBV Genome and Tests

- anti-HBc positive = exposure to HBV
  - IgM = acute infection (or reactivation)
  - Total = active or cleared infection
- HBsAg positive = infection
  - acute or chronic
- anti-HBs positive = immunity
  - vaccine or natural (cleared infection)
- HBVDNA detectable = viral replication
  - HBeAg positive (anti-HBe negative) = wild type
  - HBeAg negative (anti-HBe positive) = pre-core mutant







- There are **five phases** to **chronic HBV** (see graph below)
- **Phase 1 (HBeAg positive chronic infection)**
  - This phase only occurs in children infected at birth (vertical infection) or in early childhood (horizontal infection). It DOES NOT occur if adults acquire the infection parenterally or sexually (adult chronic infection starts as phase 2).
  - Typically lasts for the first 20-30 years of life
  - HBV DNA levels are very high but the immune system is ignoring the virus (previously called "immune tolerant" phase, but this description is not completely accurate)
  - Therefore, the liver enzymes (ALT or AST) are normal, as is the liver histology (but biopsy usually not indicated)
  - Treatment is not indicated in this phase, unless the patient is pregnant where tenofovir can be given during the 3rd trimester of pregnancy to decrease the chance of vertical transmission from the mother to the baby

- **Phase 2 (HBeAg positive chronic hepatitis)**
  - If unvaccinated persons are exposed to HBV in adulthood, only approximately 5% will fail to spontaneously clear the infection, and they develop chronic hepatitis starting with Phase 2
  - In perinatal acquired HBV, the immune system will attempt to clear infected hepatocytes starting in young adulthood (previously called the "immune clearance" or "immune intolerant" phase)
  - This leads to liver inflammation, elevated liver enzymes (ALT or AST) and subsequent fibrosis (scarring) within the liver
  - HBV DNA levels eventually will drop with some patients undergoing **HBeAg loss** with development of **anti-HBe antibody** (HBe seroconversion), which happens at a spontaneous rate of approximately 10% per year
  - Therapy is indicated in this phase to suppress HBVDNA, normalize ALT, improve liver inflammation and prevent fibrosis progression
  - Oral agents will double the chance of **HBeAg seroconversion** and these drugs can be stopped one year after HBe seroconversion happens (although some patients will relapse)
- **Phase 3 (HBeAg negative chronic infection)**
  - In this phase, patients have low (usually < 2000 IU/mL) or undetectable HBV DNA with normal liver enzymes (ALT or AST) and minimal activity on the liver biopsy (although there may be fibrosis acquired during the chronic hepatitis in phase 2)
  - They will be HBeAg negative, anti-HBe positive and usually **HBV DNA negative**

- There is approximately a 1% chance per year that these patients will lose HBsAg (clear the infection and develop seroconversion (previously known as “natural immunity”)
- Treatment is not indicated, unless the patient has underlying cirrhosis, or is undergoing suppression of their immune system with immunosuppression or cancer chemotherapy
- Although they patients were previously labelled as “health carriers” or being in the “inactive residual” phase, these patients require regular surveillance to follow their liver tests and HBV DNA, and should (depending on their age) have surveillance for hepatocellular carcinoma (HCC) with ultrasound ± alpha-fetoprotein (AFP) every six months

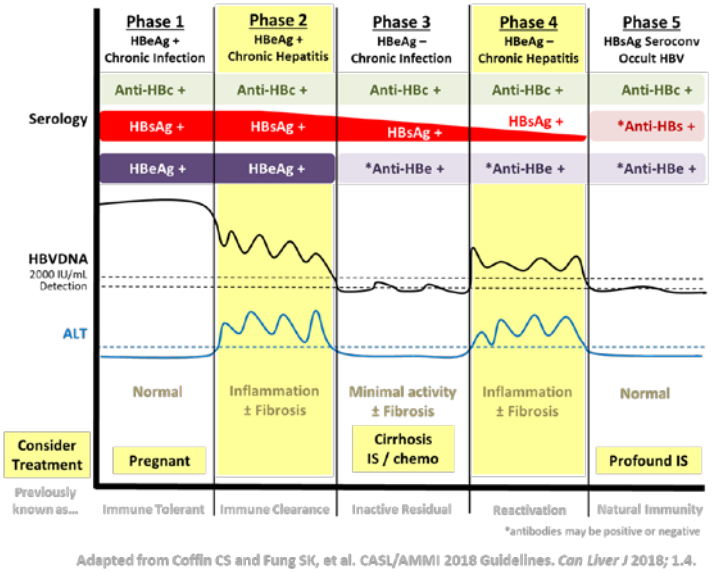
- **Phase 4 (HBeAg negative chronic <u>hepatitis</u>)**
  - As we age, and the immune system weakens and there can be a reactivation of the virus later in life, with some patients reverting to HBeAg positive (phase 2) and others reactivate replication the virus with a mutation in the pre-core or core promotor region, so that they can no longer make HBeAg **(precore mutants)** and they enter phase 4 chronic hepatitis
  - They will be HBeAg negative, anti-HBe positive but have **detectable HBV DNA,** although it is often lower than in phase 2 as the precore mutants replicate at a lower level
  - They can be considered for therapy if the liver tests are elevated or there is liver inflammation and/or fibrosis, but oral agents may need to be given life-long as you can’t use HBeAg seroconversion to determine when to stop treatment (already HBeAg negative)

- Quantitative levels of HBsAg can be followed, and if low (<100) you can consider stopping oral agents (although some patients will relapse)

- **Phase 5 (HBsAg seroconversion / occult HBV)**
  - Persons who clear the HBsAg and develop anti-HBs antibodies, have undergone a HBsAg seroconversion and have "cleared" the infection and developed "natural immunity"
  - However, due to the incorporation of the cccDNA into the host genome, these anti-HBc positive patients are at risk of the development of reactivation of their virus with potent immunosuppression (e.g. anti-CD20 monoclonal antibodies, or immunosuppression for solid organ transplantation), where they can again become HBsAg positive again with active hepatitis (often several flare of hepatitis with a very high ALT)
  - Therefore, this phase is also known as occult hepatitis B virus infection

- Figure below follows a single patient through the five phases of HBV during their lifetime from birth until death
  - Treatment is indicated in phase 2 and phase 4 (highlighted) when there is detectable HBV DNA (> 2,000 IU/mL) and active inflammation (on biopsy or indicated by an elevated ALT)
  - There are other specific indications for treatment including:
    - Phase 1 = pregnant patients, especially those with high HBV DNA (>200,000) can be considered for treatment with tenofovir to prevent vertical transmission to the baby
    - Phase 3 = if the patient is cirrhotic and has detectible HBVDNA (even if <2,000 IU/mL) or before starting immunosuppression (IS) / chemotherapy (chemo)

- Phase 5 = before starting profound immunosuppression (IS) like anti-CD20 antibodies



Adapted from Coffin CS and Fung SK, et al. CASL/AMMI 2018 Guidelines. *Can Liver J* 2018; 1.4.

Prevention & Treatment

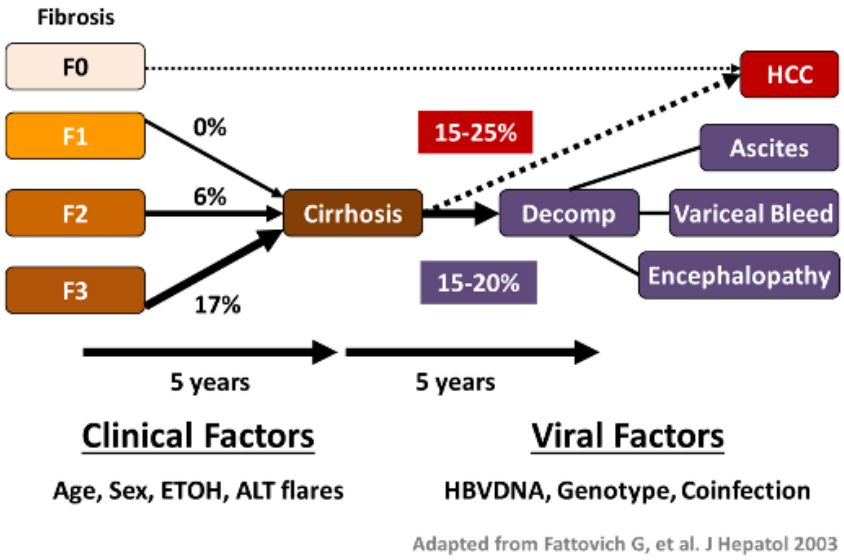
- HBV is preventable with vaccination and there are two forms of the vaccine
  - HBV vaccine (e.g. Engerix-B® or Recombivax HB®)
  - Combined HAV / HBV vaccine (Twinrix®)
  - Three doses are given at 0, 1, and 6 months
- Pre-exposure HBV vaccine is 95-100% effective in adults who complete the vaccine series and it is thought to provide protection for life
- Post-exposure HBV vaccine, given with one dose of hepatitis B immunoglobulin (HBIG), is 85-95% effective in preventing vertical transmission in neonates born to HBsAg+ mothers
- **Who should get the vaccine?**
  - Infants born to infected (HBsAg+) mothers → given with one dose of HBIG at birth

- Routine vaccination of all neonates or adolescents (**NOTE**: timing varies by province)
- Persons who have sex with an infected (HBsAg+) person
- Persons with multiple sexual partners (MSP)
- Men who have sex with men (MSM)
- Persons who inject drugs (PWID)
- Persons with chronic liver disease
- Persons with chronic kidney disease, including those on dialysis
- Persons with diabetes (age <60)
- Persons with HIV
- Residents and staff of institutions for developmentally disabled
- Persons with jobs that expose them to human blood or fluids (e.g. health care workers)
- Household contacts of an infected (HBsAg+) person
- Persons who travel to countries where HBV is endemic

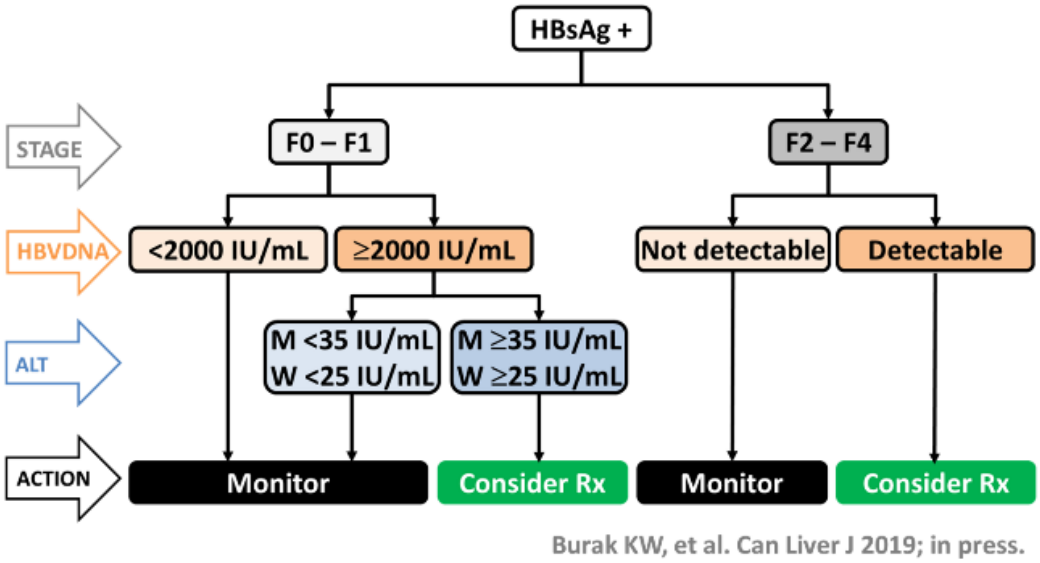
- **Who should get the screened for HBV with HBsAg testing?**
  - Immigrants and individuals whose parents are from endemic countries
  - Household and sexual contacts of HBV carriers
  - MSP or MSM
  - PWID
  - Inmates
  - Dialysis patients
  - Patients with chronic liver disease (elevated ALT or AST)

- All pregnant women
- If starting immunosuppression or chemotherapy (check both HBsAg & anti-HBc)

- **Goals of therapy for HBV**
  - **Biochemical response** = normalization of ALT
  - **Virologic response** = undetectable HBVDNA, which can be followed by HBeAg seroconversion (in wild type virus) and subsequently HBsAg seroconversion
  - **Histologic response** = reduction in liver inflammation and fibrosis
  - **Clinical response** = decrease in liver failure, liver cancer, need for liver transplant and death
- **Natural history of chronic HBV** infection should be considered when deciding who to treat
  - Cirrhosis will develop in approximately 25-30% of chronically infected individuals and once cirrhosis develops 15-25% of patients may develop decompensation with ascites (fluid in abdomen), variceal bleeding, encephalopathy (confusion) and/or hepatocellular carcinoma (HCC)
  - HBV can also result in HCC in non-cirrhotic patients
  - Natural history can be influenced by various factors that can hasten the development of cirrhosis or HCC
    - Clinical factors = older age, male sex, regular use of alcohol and frequent flares of ALT (during the immune clearance phase)
    - Virologic factors = high HBV DNA, certain genotypes, and co-infection with other viruses e.g. hepatitis C virus (HCV), hepatitis D virus (HDV), human immunodeficiency virus (HIV)



- **Indications for treatment** of chronic HBV infection (HBsAg+):
  - Active viral infection (HBV DNA detectable)
    - HBV DNA >2,000 IU/mL
    - If cirrhosis → any detectable virus
  - Significant hepatic injury
    - Moderate to severe fibrosis (stage F2-F4)
    - Increased ALT (>35 for men, >25 for women)
  - Special indications
    - 3rd trimester of pregnancy with high viral load
    - Pre-emptive to prevents flares with chemotherapy or immunosuppression

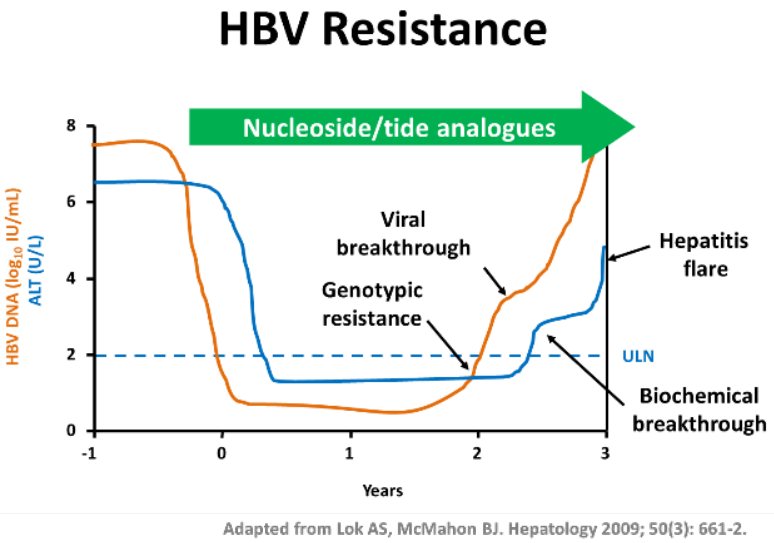


Treatment of HBV

- **Interferon**
  - Given by subcutaneous (s.c.) injections
  - Standard interferon (IFN) is given daily or 3 times per week (T.I.W.) for 4-6 months
  - **Pegylated interferon** (PEG-IFN) is longer acting, as the polyethylene glycol slows its elimination, and is given once weekly for 6 or 12 months (advantage = fixed duration)
  - IFN works by stimulating the immune system to fight the virus (immunomodulatory)
  - There are no issues with resistance
  - Side-effects include flu-like illness, weight loss, mood disturbances, hair loss, stimulation of immune conditions (e.g. autoimmune thyroid disease)
  - It must be avoided in pregnancy and can cause cirrhotic patients to decompensate
- **Oral agents**
  - Nucleoside or nucleotide analogues (nucs) are given as pills once daily
  - Nucs work by interfering directly with viral replication

- HBeAg positive patients can stop one year after seroconversion
- HBeAg negative patients usually take the drug long-term (perhaps lifelong)
- Minimal side-effects and can be given to cirrhotic patients (even with decompensation)
- Monitoring is required to watch for resistance and to confirm compliance with therapy
- Hepatitis can flare if drugs are discontinued and this can be fatal in cirrhotic patients
- **Nucleoside analogues**
  - **Lamivudine (LAM**) – first HBV agent available and is the least expensive; however, there are problems with resistance (70% after 4 years), so it is not first choice, but can be used to prevent HBV flares when giving chemotherapy / immunosuppression to HBV carriers
  - **Telbivudine (TBV)** – no longer used because also has problems with resistance
  - **Entecavir (ETV)** – potent drug with low chance of resistance (unless given to patients with LAM resistance), almost no side-effects (can use in renal disease)
- **Nucleotide analogues**
  - **Adefovir (ADF)** – first drug available for LAM-resistant patients, but no longer used because it also has resistance issues, renal toxicity, and is expensive
  - **Tenofovir disoproxil fumarate (TDF)** – potent drug with no resistance and well tolerated, but should be avoided in renal failure and can cause hypophosphatemia and metabolic bone disease (monitoring required with creatinine, PO4 and DEXA scan)
  - **Tenofovir alafenamide (TAF)** – new prodrug of TDF with fewer side-effects

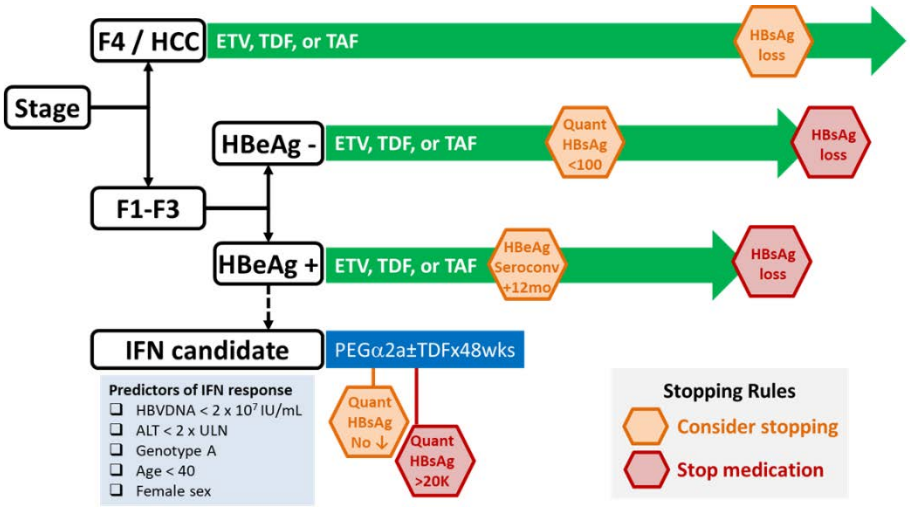
- **Monitoring** is required for patients on therapy
  - ALT and HBV DNA should be checked at least every 6-12 months
  - Return of detectable virus should prompt a check for compliance (or the development of resistance) and therapy should be altered before a hepatitis flare occurs



Adapted from Lok AS, McMahon BJ. Hepatology 2009; 50(3): 661-2.

- **Monitoring** is also required for patients not on treatment (phase 1 and phase 4) with ALT (every 3-6 months) and HBV DNA (every 1-2 years)
- **Hepatocellular carcinoma surveillance** with ultrasound of the liver ± alpha-fetoprotein (AFP) every six months is recommend for the following groups *[see Chapter 13.1]*
  - Cirrhotics (regardless of age)
  - Africans who are ≥ 20 years old
  - Asian males who are ≥ 40 years old
  - Asian females who are ≥ 50 years old
  - Persons with a family history of HCC (start earlier)

- **Summary of Treatment and Stopping Rules**



Burak KW, et al. Can Liver J 2019; in press.

Abbreviations: ALT = aminoalanine transferase; HBeAg = hepatitis B e antigen; HBVDNA = hepatitis b virus deoxyribonucleic acid; HCC = hepatocellular carcinoma; ETV = entecavir; F = fibrosis stage (Metavir scoring system); IFN = interferon; K = thousand; mo = months; PEGα2a = pegylated interferon alpha 2 a; Quant HBsAg = quantitative hepatitis B surface antigen; Seroconv = seroconversion; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil

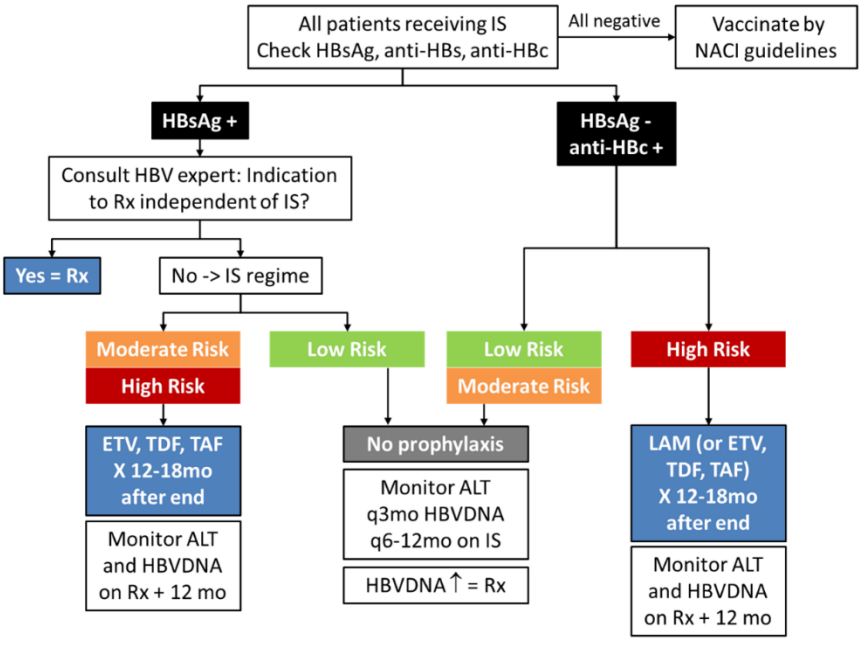
- **Management of HBV in patient receiving immunosuppression (IS)**

Risk of HBV Reactivation with IS

	HBsAg +	HBsAg - / anti-HBc +
High Risk (>10%)	B-cell depleting agents	B-cell depleting agents
	IS for BMT or organ transplant	IS for BMT or organ transplant
	Anthracycline derivatives	
	Prednisone ≥ 10mg ≥ 4wks	
Moderate Risk* (1-10%)	TNFα inhibitors	TNFα inhibitors
	Cytokine/integrin/TK inhibitors	Cytokine/integrin/TK inhibitors
	Prednisone < 10mg ≥ 4wks	Prednisone ≥ 10mg ≥ 4wks
		Anthracycline derivatives
Low Risk* (<1%)	AZA, 6MP, MTX	AZA, 6MP, MTX
	Intra-articular steroids	Intra-articular steroids
	Corticosteroids ≤1wk	Corticosteroids ≤1wk
		Prednisone < 10mg ≥ 4wks

*HBsAg - / anti-HBc + may be lower risk if anti-HBs titre > 100 IU/mL

Adapted from Coffin CS, et al. Can Liver J 2018; 1(4): https://doi.org/10.3138/canlivj.2018-0008



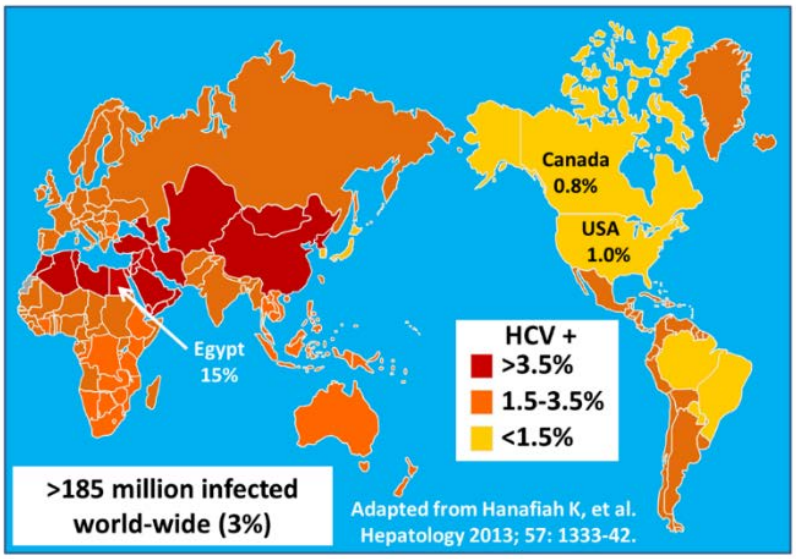
Adapted from Coffin CS, et al. Can Liver J 2018; 1(4): https://doi.org/10.3138/canlivj.2018-0008

Abbreviations: 6-MP = 6-mercaptopurine; AZA = azathioprine; BMT = bone marrow transplant; ETV = entecavir; IS = immunosuppression; LAM = lamivudine; NACI = national advisory committee on vaccination; Rx = treatment; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil; TNF = tumour necrosis factor

6.3 Hepatitis C Virus (HCV)

Virology & Epidemiology

- **Hepatitis C virus (HCV)** is a single stranded RNA virus and chronically infects approximately 3% of the world's population (185 million globally) and approximately 0.8% of Canadians (240,000)
  - More than 75% of infections in North America occur in baby-boomer and most aren't aware that they are infected
  - Therefore, some groups recommend screening for HCV (with anti-HCV antibodies) in all persons born between 1945 – 1965



- There are **6 genotypes** (sub-types of the virus) which have a geographical distribution and respond differently to some specific therapies (new drugs are pan-genotypic)
- **Transmission** is primarily **parenteral,** but rarely can be spread sexually or vertically
  - Intravenous drug use (IDU) is most common risk factor (~60% of infections in Canada)
  - Persons who received clotting factors prior to 1987 and those who received blood or organ transplants prior to 1992

- Iatrogenic (unsafe injections)
  - At least 15% of Egyptians are infected from mass injection programs for schistosomiasis during which needles were reused
- Traditional medicine practices (e.g. cupping)
- Tattoos and piercings (especially if done in prison)
- Sexual transmission can occur if MSPs
  - Uncommon in monogamous couples (2% after 20 years unprotected sex)
- Vertical transmission typically <5% (but 20% if co-infected with HIV)

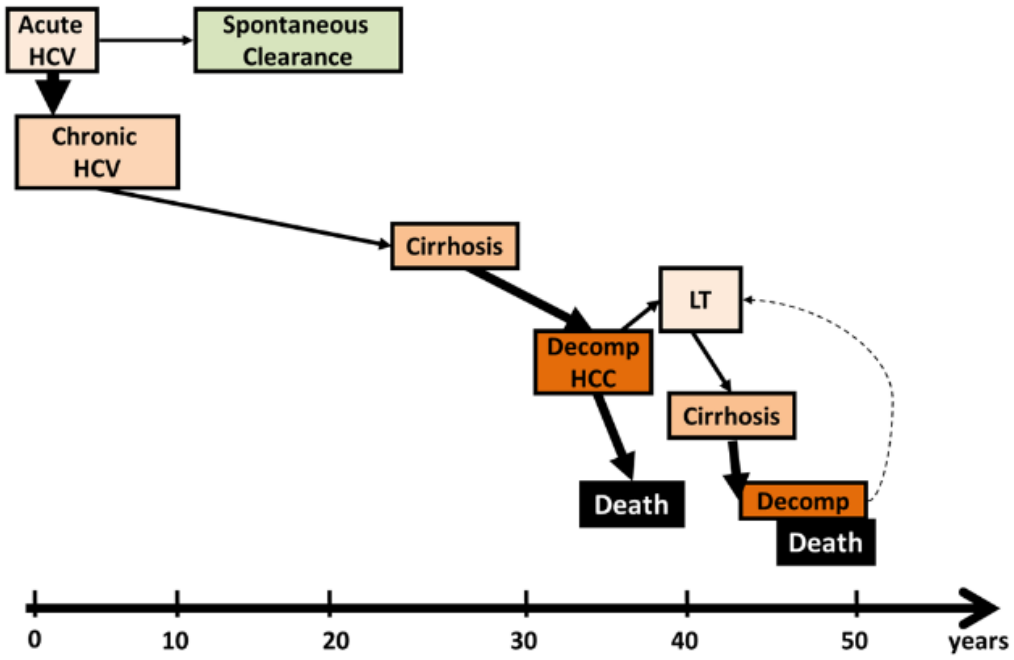
Risk Group	Size of Popn	HCV Prev in Popn	# of HCV Cases	% of HCV Cases
IDU	268 K	52%	140 K	58%
Current IDU	84 K	62%	53 K	22%
Previous IDU	184 K	48%	88 K	36%
Transfusion	3.3 M	0.8%	26 K	11%
Hemophilia	2.2 K	40%	900	0.4%
Other	27.6 M	0.27%	76 K	31%
Total	31.2 M	0.8%	243 K	100%

Adapted from Myers RP, et al. Can J Gastroenterol 2012;26(6):359-75.

Natural History & Diagnosis

- HCV has an incubation of approximately 45 days (range 14-180 days) but rarely causes symptoms of acute hepatitis (sometimes seen in active injection drug users) and usually does not cause acute liver failure
- Spontaneous clearance of the virus occurs in only 15% of acute infections and 85% will become chronically infected

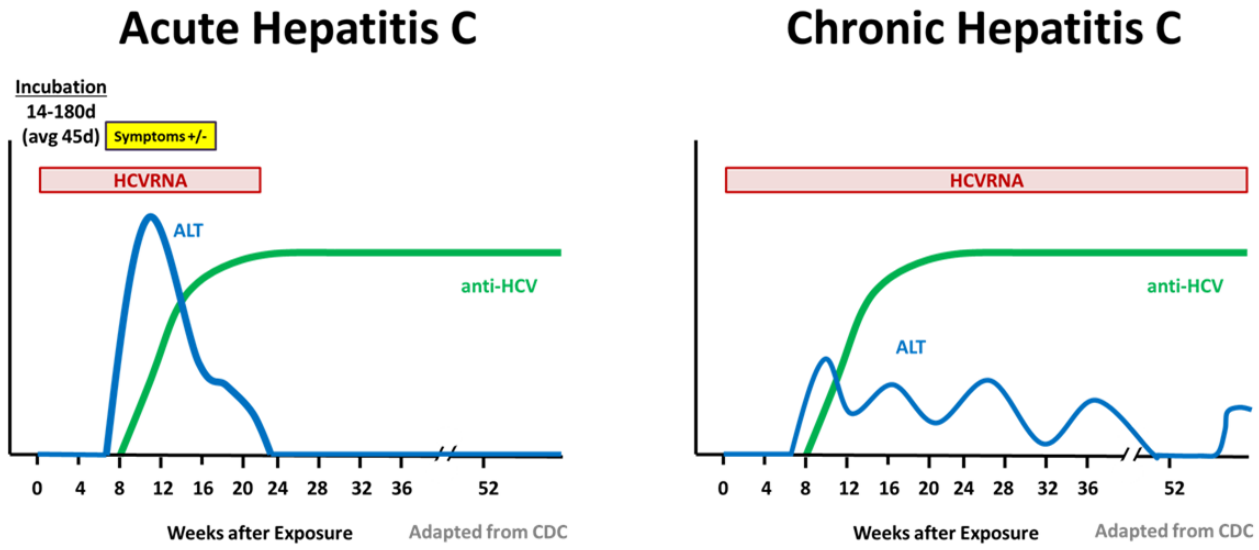
- HCV will cause an elevation of hepatocellular liver tests (ALT and AST) which can fluctuate and it is not uncommon to have an ALT in the “normal” laboratory range
- Patients usually do not have symptoms unless they develop cirrhosis
- HCV is a common cause of cirrhosis and has been the leading indication for liver transplantation world-wide, and the most common cause of hepatocellular carcinoma (HCC) in North America
- Cirrhosis may develop in approximately 20-30% of individuals after 20-30 years of infection
    - **Natural history** can be accelerated by regular consumption of alcohol, presence of non-alcoholic fatty liver disease (NAFLD), older age at infection, co-infection with HBV or HIV
- Cirrhotics have approximately a 5% chance per year of developing HCC and have a 50% chance of developing decompensation over the next 10 years (ascites, variceal bleeding, encephalopathy)
- Once decompensated, there is median survival of approximately 2 years and this is an indication for liver transplantation (LT)
- Unfortunately, recurrence of the virus after LT is universal with 80% developing recurrent hepatitis in the LT allograft
- The natural history after LT can be accelerated by immunosuppression (anti-rejection drugs) and 20% may have cirrhosis within 5 years
- **Treatment can be given to alter this natural history**



- Some patients can also develop **extra-hepatic manifestations** of HCV
  - Hematologic = essential mixed cryoglobulinemia, non-Hodgkin's lymphoma (NHL), idiopathic thrombocytopenia purpura (ITP)
  - Renal = membranoproliferative glomerulonephritis (MPGN), membranous nephropathy
  - Dermatologic = porphyria cutanea tarda (PCT), leukocytoclastic vasculitis, lichen planus
  - Metabolic = type 2 diabetes mellitus (DM)
- **Diagnosis** of HCV infection is made by testing positive for **anti-HCV antibodies** and must be confirmed by detecting the **HCV RNA** by qualitative PCR
  - Treatment decisions can be facilitated by knowing the **genotype** (1 – 6) and in the past the **viral load** (quantitative HCV RNA) was also important
  - However, viral load should not be repeated outside of the setting of anti-viral therapy *(Choosing Wisely Canada™ Recommendation)*

- It is also important to note, that after spontaneous clearance of the virus or successful treatment with anti-viral drugs (sustained virologic response), the anti-HCV antibody will remain positive for life and the test should not be repeated

  NOTE: these antibodies are NOT protective against future infection and persons with ongoing high-risk behavior can become re-infected (confirmed by repeat HCV RNA)



Prevention & Treatment

- There is **no vaccine** available for HCV
- Safe injection practices / needle exchange programs can reduce transmission amongst PWID
- **Goals of Therapy**
  - Eradication of the virus (**sustained virologic response**) is a **cure**, and is defined as HCVRNA being negative 12 weeks after stopping therapy (SVR12)
  - This can prevent progression to cirrhosis
  - In cirrhotics, this may eliminate the need for liver transplant and it reduces but does not completely eliminate the risk of HCC

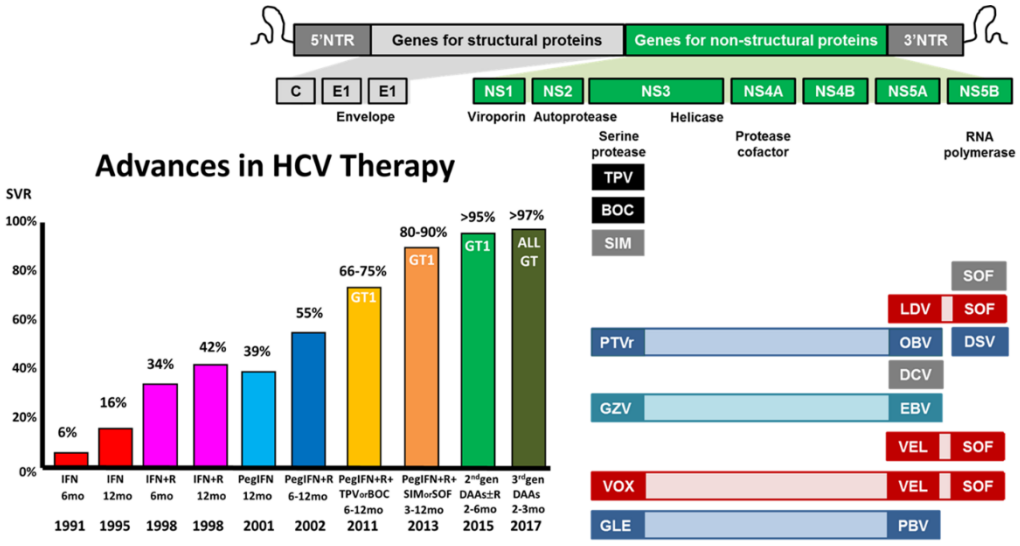
- Therapy may also improve extra-hepatic manifestations of HCV
- Therapy is offered to patients with positive HCV RNA who have evidence of fibrosis (with or without elevated ALT)

- **Advances in HCV Treatments**
  - Early treatments for HCV with standard **interferon (IFN)** given by subcutaneous injection three times per week resulted in low SVR rates and the addition of **ribavirin (R)** only slightly increased response rates
  - Polyethylene glycol (PEG) increased the half-life of interferon allowing for once weekly injections and **PEG-IFN** combined with ribavirin resulted in SVR in ~50%
  - Treatment had many significant side-effects
    - PEG-IFN causes flu-like symptoms, nausea, anorexia, weight loss, depression, anxiety, insomnia, irritability, thrombocytopenia (bruising), neutropenia (infection risk), anemia (fatigue), stimulation of immune conditions (thyroid disease), rashes, reactions at injection site and could lead to decompensation in cirrhotics
    - Ribavirin causes hemolytic anemia, rash, cough, insomnia and is teratogenic (causes birth defects)
  - First generation of direct acting anti-virals (DAAs) were released in 2011 and were protease inhibitors developed specifically for genotype 1 infection (GT1)
  - Addition of **boceprevir (BOC)** or **telaprevir (TPV)** to PEG-IFN + R (triple therapy) increased SVRs but also increased side-effects and there were drug-drug interactions with other medications metabolized by cytochrome P450 (CYP) 3A4
    - Boceprevir (BOC) worsened anemia and caused dysgeusia (abnormal taste)
    - Telaprevir (TPV) caused anemia, significant rashes and anorectal burning

- The second generation DAAs, **simeprevir (SIM)** and **sofosbuvir (SOF)**, were released in 2013
  - These drugs when combined with PEG-IFN + R resulted in higher SVRs for genotype 1 with fewer side-effects (than the 1st generation DAAs) and allowed for a shorter treatment duration
- For the first time ever we were also able to eliminate the need for interferon by combining two DAAs that worked at different parts of the HCV genome, thereby preventing the development of resistance (see below)
  - SOF could be combined with ribavirin for an all oral therapy for genotype 2 and 3
  - SOF could be combined with SIM for an all oral therapy for genotype 1
- Beginning in 2015, new all oral combination products were released (mainly for genotype 1) with treatment duration of 8-12 weeks achieving SVR in >95%
  - They have minimal side-effects, although some groups still require ribavirin
  - Access to these drugs was limited due to their expense (~$50,000 for 8-12 weeks)
  - **Harvoni®** is a once daily combination pill of two DAAs, **sofosbuvir (SOF)** and ledipasvir (LDV)
  - **Holkira PAK®** is a combination of 3 DAAs (given as four pills daily) = **paritaprevir** with a **ritonavir** booster **(PTVr)** combined with **ombitasvir (OBV)** along with **dasabuvir (DSV)**
  - **Daclinza®** or **daclatasvir** was given with SOF
  - **Zepatier®** is a once daily combination pill of two DAAs, **grazoprevir (GZV)** and **elbasvir (EBV)**

- In 2017, new DAA combination pills were approved which were pan-genotypic (worked equally well in all genotypes) and/or were shown to cure patients who had previously failed previous DAA therapy (cure in >97%)
  - **Epclusa®** is a once daily combination pill of two DAAs, **velpatasvir (VEL)**, which is pan-genotypic, and **sofosbuvir (SOF)**
  - **Maviret®** is a pan-genotypic single pill combination of **glecaprevir (GLE)** with **pibrentasvir (PIB)**
  - **Vosevi®** is a once daily combination pill of three DAAs, **voxilaprevir (VOX)** with **velpatasvir (VEL)** and **sofosbuvir (SOF)**, and is indicated for DAA failures

- **Summary of Sustained Virologic Response (SVR) for HCV Treatments and Mechanism of Action of DAAs in HCV genome**

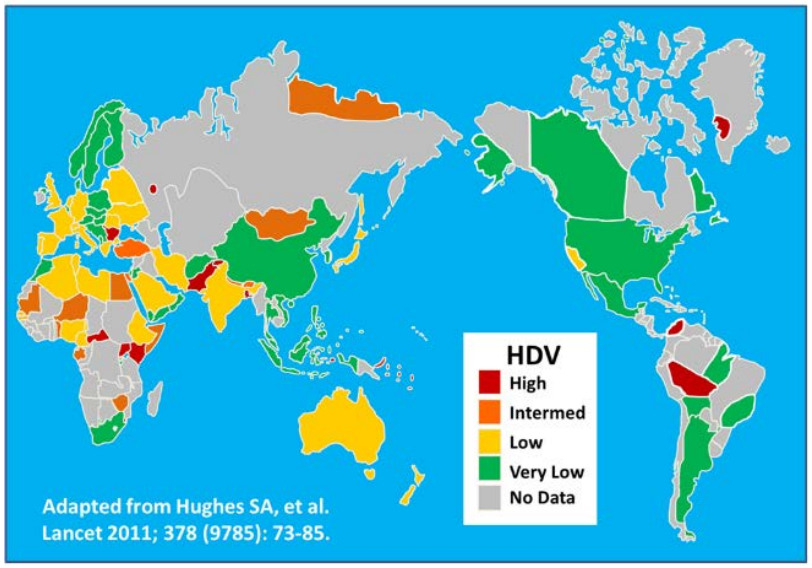


Adapted from Myers RP, et al. Can J Gastroenterol Hepatol 2015; 29(1): 19-35.
and Shah H, et al. CMAJ 2018 Jun 4; 190(22):E677-E687.

6.4 Other Cause of Viral Hepatitis

Hepatitis D Virus (HDV)

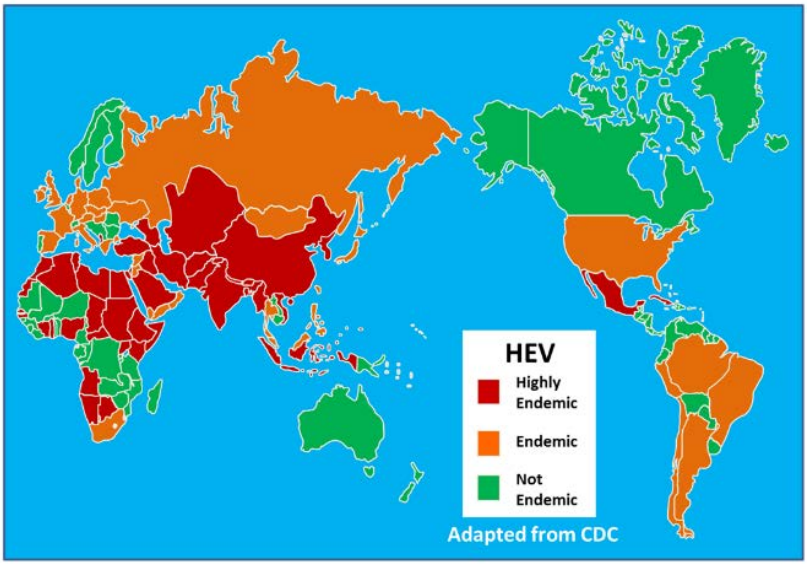
- HDV (also called **delta virus**) is a defective single stranded RNA virus that can only replicate in the presence of HBsAg
- Transmission is parenteral or sexual
- Prevalence is > 15 million worldwide



- It can be a co-infection, acquired along with HBV, or it can cause a super-infection in a chronic HBsAg carrier
- It will lead to more rapid progression of HBV with increased chance of progression to cirrhosis and its complication
- Testing is by **anti-HDV antibodies** and confirmation is with **HDV RNA** by PCR
- There is **no vaccine** for HDV, although vaccination for HBV will prevent both infections
- Treatment is with PEG-IFN, although responses are poor and it requires prolonged therapy

Hepatitis E (HEV)

- HEV is a single stranded RNA virus
- Transmission is fecal-oral or via zoonosis (contact with infected animals)
- HEV is endemic in the developing world (Africa, Asia) and also Mexico



- It can cause an acute hepatitis (similar to HAV) resulting in **acute liver failure (ALF)** in 2%
  - If infection occurs during the 3rd trimester of pregnancy, ALF has a mortality of 20%
- Chronicity of the virus has been described in immunosuppressed individuals (e.g. liver or kidney transplant recipients)
- There is a vaccine for HEV (available in China)
- Treatment is supportive for acute HEV and ribavirin has been used for chronically infected individuals

Non A - E Viral Hepatitis

- Many other viruses can cause a non-specific hepatitis
- **Epstein Barr Virus (EBV)** causes infectious mononucleosis, which typically presents with mild to moderate ALT elevation (with or without self-limited jaundice) and associated lymphadenopathy and splenomegaly
  - Diagnosis is supported by atypical lymphocytes on blood smear and is made with a positive Monospot or EBV serology
  - In an immunocompromised host (ICH) the viral load can be followed by PCR
  - Treatment is supportive
- **Cytomegalovirus (CMV)** is a beta herpes virus and the largest virus to infect humans
  - Acute infection may cause a mild flu-like illness
  - It can reactivate in an immunocompromised host (e.g. bone marrow or solid organ transplants and those with HIV)

    NOTE: CMV can cause more of a cholestatic hepatitis (ALP > ALT)
  - Testing is with serology or viral load by PCR
  - CMV inclusions can be seen on the liver biopsy and immunohistochemistry can confirm the presence of CMV within the liver
- **Herpes simplex virus (HSV)** – hepatitis is rare and typically seen in ICH or pregnant women
- **Other viruses** (e.g. adenovirus) can cause non-specific hepatitis
  - Acute viral infection of the liver may be associated with flu-like symptoms or a “viral prodrome” with fever, malaise (fatigue), muscle aches, etc.

- They typically present with elevation of ALT, which can be severe, and occasionally these non A-E viruses cause **acute liver failure**
- Hepatitis “F” has been reserved for the yet to be discovered virus that causes the majority of non A–E acute liver failure

Abbreviations

ADF – adefovir

anti-HBc antibody – antibody to hepatitis B core antigen

anti-HBe antibody – antibody to hepatitis B e antigen

anti-HBs antibody – antibody to hepatitis B surface antigen

BOC – boceprevir

cccDNA – covalently closed circular DNA

CYP – cytochrome P450

DAA – direct-acting antivirals

DCV – daclatasvir

DSV – dasabuvir

EBV – elbasvir

EBV – Epstein Barr virus

ENT –entecavir

GT1 – genotype 1

GLE – glecaprevir

GZV – grazoprevir

HAV – hepatitis A virus

HBeAg – hepatitis B e antigen

HBIG – hepatitis B immunoglobulin

HDV – hepatitis D virus

HEV – hepatitis e virus

HIV – human immunodeficiency virus

HSV – herpes simplex virus

ICH – immunocompromised host

IDU – intravenous drug use

IFN – interferon

IL2-8B – interleukin 28B

ITP – idiopathic thrombocytopenia purpura

LAM – lamivudine

LDV – ledipasvir

MPGN – membranoproliferative glomerulonephritis

NHL – Non-Hodgkin's lymphoma

Nucs – nucleoside/nucleotide analogues

OBV – ombitasvir

PCT – porphyria cutanea tarda

PEG – polyethylene glycol

PEG-IFN – Pegylated interferon

PIB – pibrentasvir

PO4 – phosphate

PTVr – paritaprevir with a ritonavir booster

PWID – persons who inject drugs

R – ribavirin

s.c. – subcutaneous

SIM – simeprevir

SOF –sofosbuvir

SVR – sustained virologic response

TBV – telbivudine

TAF – tenofovir alafenamide

TDF – tenofovir disoproxil fumarate

TPV – telaprevir

VEL – velpatasvir

VOX – voxilaprevir

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Natural History of Chronic HBV. Adapted from Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol* 2008; 48(2): 335-52.

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NOTE: Several figures have been adapted from figures and statistics available from the Centers for Disease Control and Prevention (retrieved over past 15 years). For more information, please visit https://www.cdc.gov/hepatitis/index.htm

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