New infections per year: HBV 35k, HAV 30k, HCV 10k
Chronic Infections: HCV 4m w/ 12k/yr deaths, HBC 2m w/ 3k/yr deaths, HEV (very rare occurring in solid-organ Tx, immunosuppressed pts, cirrhotic pts)

- Bacteria
  - **GNR (abscess), Staph/Strep, Clostridium, Actinomyces, Listeria, Shigella, Salmonella, Yersinia, Gonorrhea/Chlamydia (Fitz-Hugh Curtis), Legionella, Burkoholderia, Brucella, Coxiella, Bartonella (Peliosis Hepatitis), RMSF, Ehrlichia, Leptospirosis (Weil's Syndrome), Tertiary Syphilis (Gumma), Lyme, TB, Cryptosporidiosis (AIDS Cholangiopathy)**
  - **Sepsis (exo/endotoxins thru cytokines inhibit bile acid transport across hepatic sinusoids leading to intrahepatic cholestasis)**
- Parasite
  - **Schistosomiasis (pre-sinusoidal portal hypertension), Babesiosis, Malaria, Toxo, Leishmaniasis, Echinococcus spp (Hydatid Cyst), Amebiasis (Abscess), *Strongyloidiasis, Fascioliasis, Trichinosis***
  - **Liver Flukes: *Clonorchis sinensis, Opisthorchis viverrini, Fasciola hepatica/gigantica* (refer to physiology notes)**
- Fungal
  - **Candida & Histoplasmosis (immunocompromised)**
- Virus
  - Non-Hepatotropic
    - **EBV** (ranges from subclinical abnl LFTs (immunocompetent) to ALF (immunocompromised, neonates, pregnancy), always exclude hemolytic anemia as a cause of hyperbilirubinemia, rarely chronic infection, Bx (non-specific), Tx (none))
    - **CMV** (ranges from subclinical abnl LFTs (immunocompetent) to ALF (immunocompromised, neonates, pregnancy), occasionally granulomatous cholestasis can occur, important cause of neonatal hepatitis, can cause AIDS cholangiopathy, should always be considered in the DDx of post-transplant hepatitis, Bx (multinucleated giant hepatocyte with large nuclear inclusions ("owl's eyes") along w/ mononuclear portal and pareynchemal inflammatory infiltrates w/ cholestasis), Tx (gancyclovir))
    - **HSV** (ranges from subclinical abnl LFTs (immunocompetent) to ALF w/ interestingly only mildly elevated bilirubin (immunocompromised, neonates, pregnancy), Bx (Cowdry A intranuclear inclusions in multinucleated hepatocytes at the margins of hemorrhagic/coagulative necrosis), Tx (acyclovir))
    - **Other: VZV, HIV, SARS, P-B19, Reovirus, Mumps, Yellow Fever, Coxsackie, Echo, Adeno, Rubella**
  - Hepatotropic Viruses (viral replication occurs in hepatocytes, viremia leads to elevations in serum aminotransferases)
    - Most infectious serious virus (risk from a needle stick: 30% HBV, 3% HCV, 0.3% HIV)

History

- HAV: Krugman (1956) discovered HAV after investigating an epidemic of hepatitis in a state school for mentally disabled children in New York City
- HBV: Blumberg (1963) discovered HBV after identifying an antibody in hemophilics which reacted with an antigen in the serum of an Australian with hepatitis ("s-Ag"). Testing widely became available in 1970. Vaccine widely became available in 1980
- HCV: Houghton (1989) discovered HCV after it became evident that most cases of post-transfusion hepatitis were caused neither by HAV nor HBV and was referred to as non-A, non-B hepatitis. Testing became widely available in 1992
- HDV: Rizzetto (1977) discovered HDV when he identified a unique nuclear antigen
- HEV: Krawczynski (1993) discovered HEV as a cause of non-HAV hepatitis in an epidemic of hepatitis in fecal contaminated drinking water in New Delhi
- HFV: A so-called HFV originally described in the 1990s was later debunked ("F = False")
- HGV: Simons (1995) discovered HVG as a cause of transfusion associated non-A-E hepatitis after analyzing the serum of a pt w/ the initials "GB" who developed hepatitis in 1967

HAV/HEV

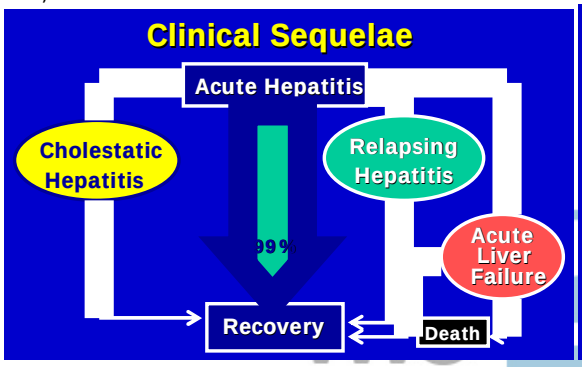
Transmission

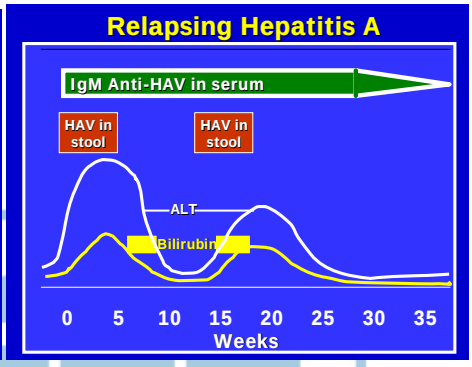
- Human liver is the reservoir, excreted thru bile into feces, survives in env for 1mo, transmitted fecal to oral route
- Industrialized Countries: unknown (65%), recent travel from a developing country b/c of poor sanitation (15%), homosexual sex, day care / institutions b/c kids / MR put anything in their mouth, raw shell fish <5d b/c they are able to concentrate HAV within them when they are living in water infected with human sewage, food or water born outbreak (eg. recently there was an outbreak in raw green onions at Taco Bell)
- [High to Low] Stool – Serum – Saliva (NB virtually none in urine/semen)
- Very resistant to chemicals/heat
- NB it was believed that HEV was very rare in industrialized countries such that the only RF is recent travel from a developing country but new data suggests that HEV does occur in US citizens who have not travelled!!!
- Virus is absorbed thru the SI and reaches the liver via the portal vein where it infects hepatocytes and subsequently is released into bile and then into feces
- Genome: single stranded linear RNA virus w/ various genotypes but they are not clinically significant
- b/c of brief viremia sexual, parenteral, vertical transmission can occur but it is rare (<5%)
- Incubation Period 4-6wks

- 30/5% of Americans have + convalescent serology HA/EV but only fraction recall every having acute symptomatic illness

S/S (incubation 4wks)

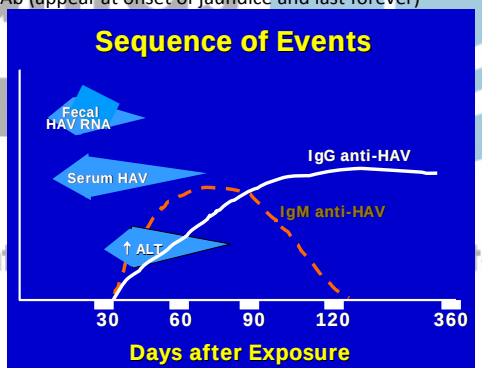
- Subclinical (children)
- Acute (adults) rapid onset w/ a prodrome of hepatitis symptoms and constitutional symptoms lasting 4-6wks (ab pain, fatigue, anorexia, N/V, HA, myalgia/arthralgia, pruritus, peripheral rash (rare: cutaneous vasculitis, mononeuritis multiplex, aplastic anemia)) w/ jaundice, HM, RUQ pain, et al developing when these constitutional symptoms start improving
- Fulminant (elderly, ~3%)
- NB similar for HEV but higher incidence of FHF (~20%) in pregnant women esp the later the pregnancy
- NB HA/EV is NOT cytopathic such that liver injury is 2/2 host immune response such that highest viremia and fecal shedding begins just before onset of clinical illness and lasts to 1-2 weeks after onset of jaundice
- "Prolonged Cholestatis" (months of jaundice, pruritus, diarrhea, anorexia but no increase in transaminases, resolves on own but some have used steroids but trials are conflicting)
- "Relapsing Infection" (<20% risk, recurrent bouts ~4wks apart, more common in children, accompanied by extra-hepatic manifestations: rash (15%), arthritis/arthralgias (10%), leukocytoclastic vasculitis (rare), cryoglobulinemia (rare), resolves on own)





Acute Dx

- Acute: IgM HA/EV Ab (appear at onset of jaundice and last 4 months) w/ Transaminasemia >1000s, Bili <10, RNA PCR (not clinically available)
- Convalescence: IgG HA/EV Ab (appear at onset of jaundice and last forever)



Acute Tx

- No evidence that antivirals work therefore just supportive care
- Liver Transplant if Fulminant Hepatic Failure (FHF)

Prevention

- Food/Hand Washing
- Active Vaccine: HepA-Ag (given as 2 doses: 0mo and 6mo w/ booster Q10yrs, take effect after 2-4wks, 85% immunity)
  - Became available in 1995
  - Who? all school children >1yo (1999 CDC recommendation), homosexual, IVDU, sewage workers, HIV, HBV/HCV chronic liver dz, travelers to high risk countries at least 2wks in advance, residents of prisons and institutions for the mentally retarded and physically handicapped, military
  - NB IgG of vaccinated pts is NOT detected by hospital assays
  - A combined HAV/HBV vaccine exists (TWINRIX)
- Passive Vaccine: Immune Serum Globulin (lasts only 4-6mo)
  - Who? travelers who are leaving in 2wks b/c the active vaccine cannot take full effect
  - Can be given concurrently w/ active vaccine

Post Exposure Tx

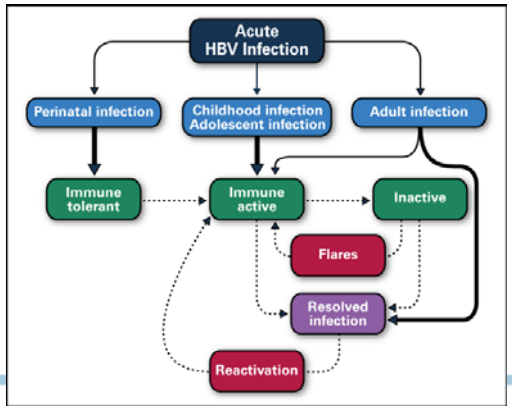
- Active and Passive Vaccine (given w/in 2wks of exposure)

HBV (only common DNA virus)

- Transmission (highest to lowest: blood – GU fluids – saliva – breast milk – urine – CSF – tears)
    - Industrialized Countries: Sexual, Percutaneous, Immigrants (50%)
    - Developing Countries: Vertical (400million people affected world-wide, 75% in Southeast Asia, Western Pacific, Africa representing 8% of the population!!!)
        - Acute: as the infection is acquired later in pregnancy the risk of transmission increases from 10% during 1st trimester to 90% during 3rd trimester
        - Chronic: e-Ag+ 90% vs e-Ag- and e-Ab- 40% vs e-Ag- and e-Ab+ 5% (w/o Px)
        - Pregnancy
            - Pre-Pregnancy
                - Mandate contraception b/c if pregnancy occurs and Tx has to be stopped there is a risk of flare
            - Pre-Partum
                - **DNA >200,000 IU/L OR e-Ag+:** tenofovir or telbivudine or lamivudine during 3rd trimester (controversial b/c teratogenic effects, IFN clearly contraindicated b/c of its anti-proliferative effects)
                - **DNA <200,000 IU/L AND e-Ag-:** just do peri-partum Tx below
            - Peri-Partum (some evidence that CS may reduce risk of transmission)
                - **S-Ag+ OR Unknown:** neonate gets first vaccine dose AND HBIG 0.5mL IM at delivery w/in 12hrs (transmission rate: giving nothing ~100%, giving either HBIG or vaccine ~30%, giving both HBIG and vaccine ~2%, NB these numbers are much lower if e-Ag is negative and DNA <200,000 IU/L)
                - **S-Ag-:** neonate gets first vaccine dose only
            - Post-Partum
                - HBV+ mothers can breastfeed if baby got HBIG and is getting vaccinated AND mother is not on Tx
    - Screening: immigrants from countries whose incidence is >2% which is essentially any developing country, blood/tissue donors/receivers, HD pts, pregnant, infant of HBV sAg+ mother, undergoing chemo/immunosuppressants Tx (VERY IMPORTANT), HIV, IVDU, health care workers, close contacts, inmates, travelers, homosexuals and heterosexuals w/ more than one partner, chronic liver dz
        - Approach: **HBsAg HBsAb, HBcAb** and if + then proceed w/ further w/u w/ **HBeAg, HBeAb, DNA, Genotype, HAV/HCV/HDV labs**
- Mechanism
    - Pathogenesis
        - Not only hepatotropic but also infects adrenal gland, testis, colon, nerve ganglia, skin
        - Not cytopathic rather injury is 2/2 host immunologic response
    - Virology
        - DNA virus
        - Genotypes (A-H): vary in geographic location (A/D = US/Europe, B/C = Asia, E = Africa, F = Central American, G = ?, H = Mexico) and clinical outcome (cirrhosis/cancer potential, remission rate, treatment response, etc) D/C most aggressive and least responsive to meds compared to A/B
    - Main Proteins
        - Polymerase
            - **"YMDD Mutation"**
                - suspect in pts who initially respond to nucleosides w/ absent DNA but then get a rise in DNA
                - decreased response to nucleosides esp lamivudine (~20/70% at 1/5yrs), adefovir (0/30% at 1/5yrs)
                - higher r/o progressive dz and acute hepatitis
        - S-Ag = protein indicating the presence of virus
            - NB anytime you have both Ag AND Ab that means you have two different viruses!
            - Mutations exist but are rare
        - C-Ag
            - NB C is an antigen bound to the surface of infected hepatocytes hence never able to detect the Ag but Ab are able to be detected as soon as your body mounts an immune response b/c they are floating until they hit an Ag unlike S/E Ab where the Ab likely immediately binds Ag b/c the Ag are floating around
            - Mutations exist but are rare
        - E-Ag = protein indicating the presence of actively replicating virus
            - NB S and E are soluble antigens and thus are found in serum hence if there is an antibody to these antigens you will not pick them up b/c the ab is binding them therefore you either have Ag or Ab (never both at the same time b/c one is always in excess) thus the transition from Ag to Ab signals that the body is fighting, while vice versa the transition from Ab to Ag signals that a chronic infection is developing (if just s then low infectivity while if both s and e then high infectivity)
            - **"Precore Mutation"**

- pre-core gene codes for e-Ag
- suspect a mutation in pts who have dz w/ high DNA levels but e-Ag/Ab are NOT positive
- important b/c this virus tends to have decreased response to IFN requiring lifelong therapy and there is a higher r/o cirrhosis, HCC and acute liver failure

- Bx
  - **Ground Glass Hepatocytes (most specific finding)**
  - Periportal and Interface Hepatitis



- Risk of developing chronic infection: higher the younger the age (85% newborn, 50% infants, 25% children, <5% adults), male, impaired immunity
- Risk of developing chronic complications once chronic: HIV coinfection, genotype C

	HBsAg	anti-HBs	HBcAg	anti-HBc	HBeAg	anti-HBe	DNA (1 IU/mL = 5 copies/mL)	LFTs/Bx (acute flare = ALT >10xULN)	Tx
"HBV Vaccinated"	-	+	-	-	-	-	-	Normal	
"At Risk"	-	-	-	-	-	-	-	Normal	
Active									
"Acute HBV"	+	-	-	+M	+	-	Detectable	Abnl	
"Window Period"	-	-	-	+M	-	-	Detectable	Abnl	
Chronic									
"Immunotolerant"	+	-	-	+M	+	-	>$2x10^7$ IU/mL	Normal	Unclear just follow
"Immunoactive E-Ag +"	+	-	-	+M	+	-	$2x10^{5-7}$ (<20M)	Abnl	Consider Tx
"Immunoactive E-Ag –"	+	-	-	+M	-	+	$2x10^{4-5}$ (<200k)	Very Abnl	Lifelong Tx
"Immunoinactive/Carrier"	+	-	-	+G	-	+	<$2x10^4$ IU/mL (<20k)	Normal	Unclear just follow
"Resolved HBV"	-	+	-	+G	-	+	Undetectable	Normal	

- Risk in Immunoactive E-Ag+ Pts: Cirrhosis (5%/yr), Decompensation if Cirrhotic (5%/yr), HCC if Cirrhotic (2.5%/yr)
- Other causes of only + anti-HBc: false +, HBsAg is actually present but at levels below detection, HCDV infection actually suppresses sAg production, after HBV has resolved for several years sometimes the HBs-Ab is lost
- Prevention
  - Passive Vaccine (HBIG) of s-Ab
    - neonatal and high risk groups
    - can be given concurrently w/ active vaccine
    - marginal r/o anaphylaxis, arthralgia/myalgia, rash
  - Active Vaccine (Recombivax, Engerix-B) of s-Ag
    - Given to all infants
    - 3 doses (0,1,6mo, HD pts need 4 doses) IM into deltoid
    - s-Ab develops after 2wks, >100mIU/mL is considered 100% protective, even though s-Ab drops over time (50% of adults are undetectable) it is NOT recommended to measure titers post-vaccination EXCEPT in dialysis pts, infants born to HBsAg+ mothers, immunodeficient pts, sex partners of persons w/ chronic HBV, healthcare!!!, test at 1-2 months after third dose, titers <10mIU/mL is below the critical protective level (HOWEVER data suggests that even at these levels b/c of "immunologic memory") and if present then repeat series and if still non-responder then discuss use of HBIC for at risk exposures
    - Factors that impede Ab response: >40yo, immunocompromised, any chronic dz, advanced liver dz, smoking, obesity, injection into the buttock, certain HLA haplotypes, on Infliximab
    - 5-8% of pts do not develop adequate levels

- Exposure

Source	HBsAg+	HBsAg-	Unknown
Unvaccinated	HBIG + Vaccine	Vaccine	Test Source
Vaccinated	Check anti-HBs titer and if >10 then no Tx vs if <10 then 1 dose of vaccine + HBIG	No Tx	Check anti-HBs titer and if >10 then no Tx vs if <10 then 1 dose of vaccine + HBIG

- Acute
  - Incubation: Sx/ALT develop after 2-24wks, s-Ag becomes + after 10wks
  - 10% Subclinical (seen in children, these pts enter into a chronic stage beginning w/ immunotolerant phase) vs 90% Acute Hepatitis w/ Serum Sickness 2/2 IC circulation w/ rash, GN, arthritis, vasculitis (seen in adults, these pts begin to resolve the infection beginning w/ window phase, hepatitis indicates that an intact immune system is present and is fighting the virus, NB if really bad consider HDV co-infection, rarely fulminant)
  - Tx: supportive as most recover w/in 3-6mo therefore no Tx unless still +e-Ag after 6mo (some Tx for acute fulminant HBV w/ Lamivudine but no good studies)
- Recovered
  - Window Period: it takes ~1mo for Ab to develop after loss of Ag, in 25% of cases you have both +S-Ag and S-Ab but in these cases the titers of S-Ab are low, heterotopic and non-neutralizing therefore pt has not likely recovered
  - Recovered: sometimes after several yrs titers of S-Ab fall and all you have is a +C-Ab, isolated C-Ab can also be seen in coinfection w/ HCV
- Chronic (defined as the persistence of s-Ag for >3-6mo, usually asymptomatic, detected on routine labs until they decompensate into cirrhosis or cancer, only occasionally do pts present with an acute flare, progresses thru three phases)
  - (1) Immunotolerant Phase: the body is "tolerating" the virus in that the body is not mounting an attack against the hepatocytes to remove the virus hence very high DNA levels and nl histology/LFTs (this phase can last anywhere from days in adults to decades in children)
  - (2) Active Phase: T-lymphocytes attack and kill hepatocytes infected w/ virus resulting in flares of hepatitis = when this is recurrent or prolonged there is progression to cirrhosis and r/o HCC
    - E-Ag+: the body is "waking up" and the body is mounting an attack against the hepatocytes to remove the virus hence the drop in DNA level and abnl histology/LFTs (can last from weeks to decades)
    - E-Ag-: the body is now able to begin clearing the virus hence the continue drop in DNA level and eventual loss of E-Ag and still abnl histology/LFTs
  - (3) Inactive/Carrier Phase: the body has effectively cleared all active virus therefore there is no more attack on the liver and thus hepatitis and pts generally do well (some actually get S-Ag seroconversion aka "Resolved HBV") unless the prior active phase resulted in cirrhosis OR the virus reactivates
  - Other
    - if only c-Ab + then (1) false + if pt has no RFs for acquiring HBV, (2) pt has cleared infection but for some reason has not generated Abs, (3) window period
  - Complications
    - Cirrhosis: RFs (**DNA (most important)**, e-Ag negative (interesting!!!), male, older age, viremia, higher ALT, HDV/HCV/HIV coinfection)
    - HCC: RFs (**DNA (most important**, NOT e-Ag status or LFTs)
    - **VERY IMPORTANT** Flares/Reactivation
      - **Setting: during immunosuppressive Tx even Rituximab, chemotherapy Tx, BMTx, pre-HARRT, etc HBV replication increases and then after sudden withdrawal of Tx there is immune reconstitution followed by rapid destruction of infected hepatocytes causing a flare**
      - **Px for s-Ag+: start antivirals 4-6wks b/f starting Tx and continue for 6-12mo after stopping Tx**
      - **Tx: giving antivirals is not helpful when Sx occur b/c it's too late**
    - Extrahepatic Manifestations (Tx w/ plasma exchange and antivirals)
      - Arthritis
      - Polyarteritis Nodosa (most serious one, 30% of PAN have HBV but only 1% of HBV develop PAN, 35% mortality, unclear if HBV Tx along w/ immunosuppressive therapy is best)
      - Glomerulopathy (1° MPGN, 2° MGN, IgA Nephropathy, MCD, etc, Bx + for IC and HBV Ag)
      - Gianotti-Crosti Syndrome (erythematous papulo-nodular dermatitis of face and limbs in pediatric population)
      - Type II Cryo (rare, more common in HCV)
  - Chronic Tx
    - First decide if pt has good social, comorbid, etc factors for good outcome
      - Non-Cirrhotics w/ Immunoactive HBV
        - DNA >20k IU/mL
          - ALT >2xULN = Tx
          - ALT <2xULN = Discordance b/t DNA and LFTs therefore check histology
            - Abnl Bx = Tx
            - Normal Bx = monitor DNA & ALT Q3-6mo

        - DNA <20k IU/mL = monitor DNA & ALT Q3-6mo
        - NB
            - +eAg (NB these pts are very responsive to therapy)
            - -eAg (NB it used to be that only +eAg pts were Tx b/c eAg reflected active virus but now research indicates that –eAg pts can still have high viremia due to mutation of virus to not produce e-Ag thus the only way to identify these pts is to find high DNA levels in associated w/ elevated LFTs or inflammation on Bx, NB these pts are less responsive to therapy often requiring lifelong Tx)
    - Cirrhotics w/ Immunoactive HBV (b/c Tx reverses fibrosis, use NS/T not INF b/c can precipitate decompensation)
        - Compensated
            - DNA >2K IU/mL = Tx & transplant eval if decompensating
            - DNA <2K IU/mL = monitor DNA & ALT Q3-6mo & transplant eval if decompensating
        - Decompensated: Tx regardless of DNA
- Factors associated w/ Favorable Tx: higher ALT, lower DNA, perinatal acquisition, female, no HIV/HCV/HDV, flares during Tx, genotype A (not B/C/D), no immunosuppressive therapy
- Types (new studies are suggesting that combination therapy w/ NT/IFN may be beneficial but at moment tenofovir > entacavir > IFN)
    - First Line: Nucleos(t)ide Analogues 1° tenofovir (Viread) and entacavir (Baraclude), 2° lamivudine (Epivir), adefovir (Hepsera), telbirudine (Tyzeka)
        - The Good: less SEs, less expensive, very effective vs The Bad: resistance, long or indefinite duration, low rate of s-Ag seroconversion
        - Mech: nucleotide analogues that competitively inhibit viral polymerase
        - Goals: 1st conversion to inactive status (e-seroconversion, DNA $<10^4$ aka <10 IU/mL, LFTs nl) which can take ~1-3yrs and once you achieve these goals (seen in 80% of pts) then Tx for 6-12mo more and then stop or consider secondary goal → 2nd DNA undetectable, improved liver histology, s-seroconversion (only occurs in 3% of pts)
            - NB Viral Breakthrough = increase in DNA by 1log10 after undetectable
            - NB Viral Rebound = increase in DNA to $>2x10^4$ after undetectable
            - NB Biochemical Breakthrough = increase in ALT >ULN after nolrmal
            - NB 25% will relapse after Tx especially in e-Ag negative pts at baseline therefore most give life-long Tx!!!
            - NB cure is impossible
            - NB some pts will not reach these goals and thus you have to Tx forever
            - NB Tx forever in cirrhotic pts
        - SEs: hemolytic anemia, teratogenic, mouth ulcers, nephrotoxicity, fanconi's syndrome, osteoporosis
        - Resistance: in Tx naïve pts resistance is minimal (<1%) if the pt is compliant and you are suppressing the virus to undetectable levels, follow DNA Q3mo, if there is not 10 fold decrease after the month switch to another drug, if DNA does not become undetectable at 24wks then switch to another drug, if there is a 10 fold increase above the previous nadir then check resistance profile w/ genetic testing, Viread/Baraclude have limited resistance (~1% at 5yrs) hence first line, Tx: instead of switching just add a second agent b/c sequential monotherapy can result in multi-drug resistance
            - If LAM resistance (65% at 4yrs) then add TEN
            - If ADV resistance (15% at 4yrs) then add LAM or TEL or ENT (not TEN)
            - If TEL resistance (10% at 4yrs) then add TEN
            - If ENT resistance (1.2% at 4yrs) then switch to TEN
            - If TEN resistance (0% NO REPORTED CAESES!!!) then no one knows what to do
            - Other options for all of these is to add emtricitabine
    - Second Line: 1° IFN-alpha-2a (Roferon-A, pegylated version called Pegasys) 2° IFN-alpha-2b (Intron-A, pegylated version called PEG-Intron)
        - Goal: you just Tx for 1yr and then stop
            - NB only use on +e-Ag pts
            - NB seems to work better in genotype A pts (50% seroconversion vs <30% in all other genotypes)
            - NB never use in cirrhotic pts
            - NB seroconversion can occur up to 6mo after stopping Tx
            - NB flares commonly occur at 4-8wks of Tx, if mild continue but if severe then reduce dose or discontinue (this is why you don't give IFN to pts w/ cirrhosis)

        - NB lots of SEs (for some reason generally less then seen in HCV!!!), must be injected, expensive
    - Transplant
        - Recurrence is near universal w/ 20% developing cirrhosis at 5yr

HCV

- Transmission
    - Epidemiology
        - Prevalence: 1.3% of the US Population (~4 million people) vs highest in Egypt (~15%)
        - Incidence: peak in 1980s w/ 200,000 cases/yr to 16,000 cases/yr in 2006
        - Industrialized Countries: 1° Percutaneous (transfusion esp in hemophiliacs were the main but after screening blood became effective now IVDU is the primary mode of transmission representing ~70% of HCV now, it is said that 75% of IVDU are +HCV, 25% are coinfected w/ HIV, w/ transfusion screening risk had decreased from 1/20 to 1/2,000,000, hemodialysis esp in the middle east, healthcare worker exposure from known needle sticks, piercings/tattoos) and 2° Sexual (actually studies show very rare unless anal or sex while menstruating) and Perinatal Exposure
            - r/o vertical transmission is 2% w/ -RNA and 5-50% w/ +RNA depending on # of copies (higher risk if coinfected w/ HIV) and there is no data on the use of antiviral therapy and "HCIG" does not exist
            - +Ab in baby 15months or +RNA in baby 2months after delivery from a mother with HCV = perinatal transmission (any earlier is transplacental transfer)
            - mode of delivery does not affect transmission rate
            - HCV+ mothers can breastfeed
            - Most children that acquire HCV clear it unlike HBV in which most stop trying to fight it
        - Screening: was originally based on RFs profile but now the recommendation is that all adults born b/t 1945-1965 ("baby boomer") should be screened
        - More people now die of HCV (15k/yr) than HIV (13k/yr) and HCV death is expected to increase to 35k/yr
    - Virology
        - Genome: SS RNA
            - NB Genotype: 1 (a/b 55/15%, seen in USA/Europe), 2 (15%, seen in USA/Europe), 3 (5%, seen in USA/Europe, causes steatosis, also seen in Middle East and North Africa b/c of contaminated needles used for country wide vaccination against Schistosomiasis during the 1960s), 4 (rare, seen in Middle East), 5 (rare, seen South Africa), 6 (rare, seen in Asia)
                - NB70 subgenotypes (lower case letter) used to not matter but now it appears that Genotype 1b develops less resistance to PI than Genotype 1a
        - Physiology: not direct viral hepatoxicity but sequela from the immune response
            - NB steroids increase uptake of HCV by hepatocytes increasing their virulence
- Disease
    - (1) Subclinical 70%, Acute 30%, Fulminant <1%
        - Sx: refer above (incubation period of 2-26wks usually ~8wks)
        - Dx: +/-RNA, +/-Ab
            - RNA can be detected after 2wks of exposure (1-5 copies/mL = 1 IU/mL hence not an exact conversion)
                - Viral Load correlates w/ ALT and Inflammation
            - Ab can be detected after 8wks of exposure
                - False Negative: hemodialysis pts and immunocompromised (therefore if you suspect HCV infection then check RNA)
            - NB no useful test to distinguish b/t acute versus chronic b/c it is a chronic infection that has acute bouts
        - Vaccination: high mutation rate b/c RNA polymerase has poor proofreading ability → great heterogeneity and thus the inability to create a mass applied vaccination (NB interestingly a vaccine (GI-5005) is actually being developed based on T-cell fxn)
        - Post-Exposure Px: not effective
        - Tx: no Tx unless pt has not spontaneously cleared virus after 3-4mo after presentation then give PEG-IFN 3-6mos
            - NB 80% SVR for Genotype 1!!!
            - NB adding Ribavirin does not improve SVR
            - NB the problem is that most pts are asymptomatic thus doctors never see them (hence screening high risk groups is advocated)
        - What determines if pt will go into remission or develop chronic HCV and subsequent cirrhosis?
            - Increased Risk: initially asymptomatic (the more symptomatic the LESS likely pt will develop chronic infection!!!), older age, male gender, White ethnicity, immunodeficient, IL-28B TT genotype, alcohol use, HBV/HIV coinfection, tobacco/MJ use, Metabolic Syndrome, Severe Hepatitis, Smoking
                - NOT Genotype

        - NOT Viral Load
- (2a) Resolved/Remission 30%
    - Sx: none
    - Dx: -RNA, +Ab
        - NB some pts might have –RNA intermittently therefore to confirm true remission you need to repeat RNA at 3mo intervals to make a dx of remission or could be false negative
        - Ab test is an ELISA test, if you think remission b/c RNA is negative and Ab is positive then confirm w/ RIBA aka Recombinant ImmunoBlot Assay
            - Ab Test (ELISA) vs RIBA (Western Blot) therefore it's kind of like the HIV confirmatory test b/c there can be false positives with the ELISA test including ESRD, high Ig, +RF, +ANA
    - Tx: none
- (2b) Chronic 70% (75% of these pts are undx!!!, unlike in HBV the risk is increased the older you get but only slightly)
    - RFs for Progressive Dz: fibrosis, duration of infection, older age at acquisition, obesity, DM, steatosis, male, alcohol, HBV/HIV coinfection, immunosuppressed
    - Sx: chronic pts are usually asymptomatic until they develop cirrhosis (25% of chronic pts)
        - Cirrhosis: 20% at 20yrs
        - Decompensation: 3%/yr
        - HCC (refer)
    - Dx: +RNA and +Ab for >6mo
        - remember PCR is on a log scale so 1million to 2million is not a big jump at all
        - ALT fluctuates and at any one time only 60% will have abnormal LFTS!!!
        - Sometimes Ab is negative in immunosuppressed pts
    - Extrahepatic Symptoms
        - Mechanism: unknown but in some cases due to deposition of IC and/or T-lymphocytes in organs and the production of autoantiboidies
        - Types
            - Endo: Thyroiditis esp Hashimoto's (most common extra-hepatic dz), T2DM
            - Heme: Lymphoma, MGUS, Thrombocytopenia
            - Rheum: Sjogren's, Arthritis, +ANA, +ASMA, +ALKM (NEVER MAKE A DIAGNOSIS OF AN AUTOIMMUNE CONDITION BASED ON ANTIBODIES ALONE IN A PATIENT WITH HCV)
            - Renal: Glomerulonephritis asp MPGN/MN or 2/2 Cryo
            - Pulmonary: IPF ?
            - Derm: Mixed Cryoglobulinemia (80%) w/ Organ Damage (15%, leukocytoclastic vasculitis, renal dz, etc), Porphyria Cutanea Tarda, Lichen Planus, Vitiligo, Canities (Graying of Hair), Hyde's Prurigo Nodularis, Mooren's Corneal Ulcer, Necrolytic Acral Erythema
    - Tx
        - Other
            - Big Question: treat now (Stage 4, naïve, no complicating features, Genotype 1b) or treat later (all others)
            - Lambda interferon will be coming out soon and is nice b/c it acts in the liver only and thus has minimal systemic SEs but in the future we will have IFN free Tx and thus will not be an issue
        - Goals: 1° permanently eradicate HCV 2° Sx, LFTs, histology, r/o cancer but this takes awhile therefore keep monitoring these pts for several years
        - Indications: Chronic Dz (+RNA/+Ab)
            - Extrahepatic HCV
                - NB pts can get exacerbations of other non-extrahepatic auto-immune dermatologic diseases classically psoriasis
                - NB symptomatic cryo responds to HCV Tx but if fails then consider rituximab, steroids, plasma exchange
            - Stage 3/4 Fibrosis
                - NB Stage 0/1/2 is generally not Tx b/c if pt doesn't have bad damage at that point then pt probably will not develop damage in the future
                - NB Stage 4 is Tx b/c there is a lower r/o complications including cirrhotic decompensation and HCC b/c there is evidence of fibrosis regression
                - NB if genotype 2/3 then don't do Bx b/c you know Tx will work
                - When to Bx?
            - ??? does grade of inflammation matter ???
        - Contraindications
            - decompensated liver dz
            - pregnancy

- psych illness
- active substance abuse
- severe cardiac/pulm/renal/DM dz
- seizure disorder
- active autoimmune dz
- severe cytopenias

- Coinfections
  - HIV
    - First HAART then HCV-Tx
    - Ribavirin can interfere w/ HAART therapy and can exacerbate lactic acidosis therefore follow pts closely
    - NB always Tx HBV for HIV-HBV coinfected pts but if pt is not needing HAART then use NT that have NO anti-HIV effects (eg. adefovir or IFN) otherwise if pt is needing HAART then give tenofovir or lamivudine
  - HBV (controversial)
    - Pts tend to have more severe liver injury w/ higher rates of cirrhosis
    - One virus predominates and it is often HCV
    - Tx concurrently using IFN and Ribavirin and NT
- Poor Predictors of Response
  - Virus: Genotype 1>4/5/6>2/3 (unfortunately 75% of US population is 1, genotypes do not affect severity only response to Tx), Viral Load >600,000IU/mL
  - Pt: Old, AA>H>W, Male, Metabolic Syndrome, HIV/HBV Coinfection
  - Liver: fibrosis, fatty liver, iron level in liver
  - NEW: IL-28 Gene Polymorphisms (CC is good while TT is bad, results in variable production of IFN-lamba3 leading to variable spontaneous viral clearance and variable response to IFN Tx)
- Transplant (refer)
- History (new studies are suggesting that therapy can be effective w/o IFN which is good b/c of all of its SEs)
  - Early 1990s: INF-alpha-2a x24wks
  - Mid 1990s: INF-alpha-2a x48wks
  - Late 1990s: INF-alpha-2a + Ribavirin x48wks
  - Early 2000s: Pegylated INF-alpha-2a + Ribavirin x48wks = 50/80% SVR for Genotype 1/2 (NB monotherapy w/ ribavirin is not effective)
  - Late 2000s: Triple Therapy w/ Pegylated INF-alpha-2a + Ribavirin + Direct Acting Antivirals (DAA) x48wks
    - SVR using T: 75% naïve, 55% prior partial, 85% relapser, 15% prior null
    - SVR using B: 65% naïve, 50% prior partial, 70% relapser, ?% prior null
    - NB relapse rate after triple therapy is 9% for both T and B
- Strategy
  - General
    - timing of checking labs is imperative
    - make sure pharmacy/shipments are in order
    - have them sign a contract understanding R/B/L/A, SEs, that they have been given the opportunity to ask questions
    - adjust meds for renal disease
  - Pre: Check CBC, CMP, RNA, beta-HCG, TSH
    - Anemia
      - No Heart Dz
        - If Hgb <10 then dose reduce RBV to 600mg and if not adequate then consider Procrit and/or discontinue TVR
        - If Hgb <8.5 then stop all therapy
      - Heart Dz
        - If Hgb drops by >2 then dose reduce RBV to 600mg and if not adequate then consider Procrit and/or discontinue TVR
        - If Hgb <12 despite 4wks of reduced dose then stop all therapy
    - Thrombocytopenia
      - If Plt <50 then reduce PEG-IFN to 90mcg
      - If Plt <25 then stop PEG-IFN
    - Leukopenia
      - If ANC <750 then reduce PEG-IFN to 135mcg and if not adequate then consider Neulasta

                - If ANC <500 then stop PEG-IFN until ANC >1000 then restart at 90mcg
        - Start Triple Therapy
        - Week 1
        - Week 2
        - Week 3
        - Week 4: Check RNA
            - If RNA undetectable (<10-50 IU/mL) then Rapid Virologic Response (RVR) which just tells you how sensitive the pt is to Tx w/ SVR >90% (it doesn't really change Tx)
            - If RNA 0-1000 then not RVR but still continue Tx
            - If RNA >1000 IU/mL then STOP Triple Therapy (TVR/PEG-IFN/RBV)
        - Week 12: **STOP TELAPREVIR** and Check RNA
            - If RNA >2log decline then Early Virologic Response (EVR) = continue Tx
                - Complete EVR (cEVR) = undetectable (<10-50 IU/mL)
                - Partial EVR (pEVR) = >2log decline but still detectable
            - If RNA <2log decline = STOP Triple Therapy (TVR/PEG-IFN/RBV) b/c pt will not achieve SVR in >98%
            - If RNA has increased from nadir by >1log10 then "virologic breakthrough" = STOP DUAL Therapy
        - Week 24: Check RNA
            - If RNA detectable then STOP Dual Therapy (PEG-IFN/RBV)
            - Stop IFN/RBV at 24wks if RNA was undetectable at weeks 4/12 otherwise continue to 48wks
                - NB always Tx for 48wks for cirrhotics, prior partial responders, prior null responders
                - NB can stop if Genotype 2/3
            - If RNA has increased from nadir by >1log10 then "virologic breakthrough"
        - Week 36: Check RNA
            - If RNA has increased from nadir by >1log10 then "virologic breakthrough"
        - Week 48: Check RNA
            - If RNA has increased from nadir by >1log10 then "virologic breakthrough"
        - 6mo after stopping Tx: Check RNA to assess
            - If RNA undetectable then Sustained Virologic Response (SVR) = cure
            - Relapser = previously undetectable RNA now returns (0.1%/yr hence check RNA Qyr w/ most occurring during the first three months)
            - Partial Responder = decreased RNA from baseline but not undetectable
            - Null Responder = no decrease in RNA
- IFN-alpha-2a (Roferon-A, pegylated version called Pegasys) 2° IFN-alpha-2b (Intron-A, pegylated version called PEG-Intron)
        - Dosing: Pegasys = 180mcg SC Qwk vs PEG-Intron = 1.5mcg/kg SC Qwk
        - Mech: enhances markers on surface of infected hepatocytes allowing for increased immune system destruction
        - SEs
            - Liver (hepatitis flair b/c IFN is stimulating the immune system to kill infected hepatocytes)
            - General (Flu-Like Sx, Weight Loss)
            - Heme (Leukopenia/Thrombocytopenia)
            - Psych (Depression (consider prophylactic SSRI, assess at every visit w/ CES-D scale, if worsening then decrease PEG-IFN to 135mcg then to 90mcg if no improvement), Insomnia, Difficulty w/ Memory/Concentration, Psychosis, Suicidal, Seizures)
            - ID (Infection)
            - Derm (Reversible Alopecia, Pruritus, Injection Site Tenderness – rotate location and apply ice before and do at night)
            - GI (N/V/D, Loss of Appetite)
            - CNS (Nerve Palsy)
            - Endo (hypo/hyperthyroidism, diabetes)
            - CV (MI)
            - Renal (AIN)
        - NB Pegylated (increased half-life allowing for weekly dosing)
        - NB no risk of viral resistance

- NB IFN-alpha (HCV, HPV, Hairy Cell Leukemia, CML, Kaposi Sarcoma), beta (MS), gamma (Chronic Granulomatous Dz)

- Ribavirin (Copegus, Rebetol, Ribapak, Ribasphere)
  - Mech: purine analogue that upregulates anti-viral genes and enhances IFN action
  - Dosing: 500mg if <75kg or 600mg if >75kg PO BID x48wks or 400mg PO BID if Genotype 2/3
  - SEs
    - General (Teratogenic – two forms of contraception, not OCPs b/c PIs decrease effectiveness therefore usually condom + IUD and to continue up to 6mo after Tx)
    - Heme (Dose-Dependent hemolytic anemia)
    - Eye (Retinal Hemorrhage and Thrombosis)
    - Rheum (Autoimmune Flairs)
    - CNS (Dizziness, Insomnia)
    - General (Fatigue)
    - CV (MI)
    - Derm (Pruritus)
    - Pulm (SOB, Cough, Pharyngitis)
    - GI (N, Pancreatitis)
- Direct Acting Antivirals (DAA)
  - Protease Inhibitors (approved 05/2011, prevent the synthesis of enzymes needed for HCV replication)
    - New: Simeprevir
    - *** only approved for genotype 1 not effective in genotype 2 ***
    - Differences b/t T and B
      - T: no lead in phase and duration of 12wks
      - B: 4wk lead in phase and duration of 24-44wks
    - Telaprevir (Incivek)
      - Trials: ADVANCE (naïve pts), REALIZE (relapsers), etc
      - Dosing: 750mg PO TID and take w/ a fatty meal (~20g, eg. 2oz of cheese, whole avocado, 3tbs peanut butter) (NB will be approved for BID dosing soon)
      - SEs (only appear and last for the first few weeks unlike those seen w/ IFN and RBV)
        - Derm
          - Mild: localized pruritic rash = oral antihistamines and topical corticosteroids (NB not systemic)
          - Mod: generalized or w/ vesicles/bullae/ulcers = " " + discontinue TVR
          - Severe: SJS/DRESS or no improvement of moderate rash after 7d = " " + discontinue all meds
        - GI (N/V/D, dysgeusia, anorectal dz including hemorrhoids and anal itching/burning)
        - Heme (anemia)
        - Extensive Drug Interactions b/c inhibits CYP-3A4 and Aldo-Keto-Reductase Pathway therefore go through every med and tell pt that they cannot start a medicine w/o discussing w/ hepatologist (THE BIGGEST INTERACTION IS WITH STATINS)
    - Boceprevir (Victrelis) (not used b/c more complicated dosing regimen)
      - Trials: SPRINT-2 (naïve pts), RESPOND-2 (relapsers), etc
      - Dosing: very complex
      - SEs: same but anemia is more severe
    - NB pts can never miss a dose!!! If they miss >1d then stop therapy
    - NB resistance emerges quickly w/ monotherapy hence giving IFN and RBV is imperative
    - Contraindications: HIV or HBV coninfection (little data on how these agents affect HIV and HBV if coinfected and drug-drug interaction), no kidney dz, decompensated cirrhosis
  - Polymerase Inhibitors (statins!)
    - Sofosbuvir (Sovaldi)

- Drugs that are potent P-gp inhibitors may significant decrease sovaldi concentrations
    - AEDs: carbamazepine, phenytoin, phenobarbital
    - Abx: rifabutin, rifampin, rifapentine
    - Herbals: St. John's Wort
    - HIV: tipranavir, ritonavir
- Nucleotide Analogue Inhibitor
- Entry Inhibitors
- Replicase Inhibitors (NB Milk Thistle which is a herbal taken by many pts is proposed to work this way on the internet)
- Other IFNs like IL-23 (type 3 IFN, only targets liver hence less SEs)

HDV

- Epidemiology
    - Distribution: globally w/ highest prevalence in South America and South Europe, interestingly does not parallel HBV as there are areas endemic with HBV but no HDV, generally uncommon in the US predominantly confined to high risk groups
    - Prevalence: 5% of HBV carriers are infected w/ HDV = 15-20 million world-wide
    - Incidence: decreasing since its discovery likely b/c of HBV vaccination and blood product screening (however this decrease has plateaued in during the mid 1990s)
    - Acquisition: 1° IVDU, 2° sexual and vertical transmission
    - Genotypes: I (1°, most-severe, Europe/Africa/North-America), II (3°, least-severe, Asia), III (2°, mod-severe, South-America), IV-VIII (rare)
- Pathogenesis
    - Virology: HDV migrates into hepatocyte nucleus and utilizes host-RNA polymerase to create further genomic RNA and T&T RNA into HDV-Ag (HBV independent) → HBV infected hepatocytes create a lipoprotein envelope w/ HBV-s-Ag which surrounds HDV genome and HDV-Ag (HBV dependent) → immune response against HDV causes liver injury which is corroborated by the presence of various autoantibodies (eg. anti-liver-kidney microsomal type 3 aka anti-LKM-3) that emerge after HDV infection
        - NB degree of liver injury depends on the interplay of HDV/HBV genotypes (eg. most-severe: HBV-F and HDV-III) and host immune response
- S/S (Two Types)
    - **Co-infection:** infection of HBV and HDV occurs SIMULTANEOUSLY
        - Serology: **HBV-c-IgM +**
        - Presentation: acute hepatitis
            - NB characteristic double AT peak as HDV infection establishes a short period after HBV infection otherwise identical to acute hepatitis 2/2 HBV alone just more severe
        - Prognosis: it was originally believed that HDV aggravated the severity of HBV infection however recent studies indicate that this is NOT CONSISTENTLY the case therefore in general the same statistics for HBV infection in adult IVDU hold true…
            - Acute Infection: 80% subclinical, 20% acute hepatitis, <1% liver failure
            - Chronic Infection: <5% become chronic
    - **Super-infection**: infection of HDV is SUPERIMPOSED ON ESTABLISHED chronic HBV infection
        - Serology**: HBV-c-IgM –**
        - Presentation: pt w/ chronic hepatitis p/w acute hepatitis or pt w/ cirrhosis p/w decompensation
            - NB characteristic DROP in HBV DNA occurs b/c HDV replication inhibits HBV replication (usually seronegative for e-Ag w/ +e-Ab)
        - Prognosis: progression to cirrhosis and complications of ESRD and HCC is faster
- Dx
    - Acute (+Ag then +IgM w/ an intervening window period, never concurrent) vs Chronic (-Ag and +IgG/M, never concurrent, interesting that IgM in many cases persists)
        - Ag via tissue IHC (serum levels unreliable therefore rarely checked but generally they appear at the onset of infection but are short lived once Ig are produced forming undetectable IC)
        - IgM/G via serum ELISA
        - RNA via serum PCR (always check to confirm + serology, earliest marker, level correlates w/ severity of infection and efficacy of treatment)
- Tx
    - Prevention: HBV Vaccination
    - Post-Exposure Px: HBIG
    - Acute Tx: Supportive
    - Chronic Tx
        - HBV: Tx until complete seroconversion (loss of Ag and gain of Ab for s/e) and undetectable DNA level and then proceed with a 6mo taper BUT if pts were already seroconverted b/f Tx then Tx lifelong when using nucleos(t)ide analogues or 1yr therapy if using IFN-α

- HDV: goal is seroconversion w/ suppression of activity (- serum RNA, - tissue Ag), normalization of LFTs, and amelioration of necroinflammatory activity on Bx
    - IFN-α (9 MU 3x/wk x48wks)
        - Marginally effective (~50% clearance after 1yr of Tx)
        - High doses for long duration (significant SEs)
        - High relapse rate
    - NB nucleos(t)ide analogues and ribavirin are not effective
    - Future: post-translational modification of HDV-Ag can serve as targeted therapy
- Transplant: pts are given HBIG resulting in decreased HBV/HDV reinfection, 90% survival rate at 5yrs

Non-Liver Disease Causing Hepatotropic Viruses

- **HGV aka GB Virus**
    - Epidemiology: acquired thru percutaneous needle exposure, sexually, vertically, often coexisting w/ HCV (20% of HCV pts are viremic and 80% are seropositive), 5 genotypes (2 = US), world-wide geographic distribution, 14-38% of people w/ frequent exposures to blood are viremic and 50-70% are seropositive (anti-E2), 16% of healthy blood donors are seropositive, age of acquisition determines likelihood of chronicity (uniform in children vs rare in adults)
    - Virology: RNA virus, similar to HCV w/ 27% nucleotide homology but the proteins are quite different
    - S/S: although acute hepatitis developed in the first identified pt other studies indicate that this virus does not appear to cause liver disease or any extra-hepatic disease even in immunocompromised persons, nor does this virus appear to modulate the course of HCV/HBV coinfection
    - Dx: b/c no liver disease occurs diagnostic tests are not widely available and generally reserved for research purposes
    - Tx: b/c no liver disease occurs no Tx are necessary or established, in studies in pts coinfected w/ HGV-HIV-HCV IFN and ribavirin do lead to sustained virologic clearance of HGV in 1/3 of pts
    - Interesting: there has been little interest in HGV until 2001 when it was observed by Tillmann, et al that HGV delayed HIV progression, decreased vertical transmission and improvement HAART response w/ overall increase in survival in pts coinfected w/ HGV-HIV (why? HGV additionally replicates in CD4+ T-cells and the NS5A protein produced down-regulates expression of the CXCR4 receptor that HIV binds while the E2 protein interferes with the early steps in the HIV life cycle)
- **Others: TT Virus aka Transfusion-Transmitted Virus or Torque-Teno Virus, Sanban Virus, Yonban Virus, SEN Virus, TTV-Like Mini Virus**
    - History: discovered during the search for transfusion associated non-A-G hepatitis in a pt w/ the initials “TT” in 1977
    - Virology: DNA virus (first human single stranded circular DNA virus)
    - Epidemiology: acquired thru percutaneous needle exposure but can also be transmitted enterically, world-wide distribution, near universal infection in healthy blood donors
    - S/S/Dx/Tx: “ “