



Hepadnaviruses

Virion

Genome

Genes and proteins

Viruses and hosts

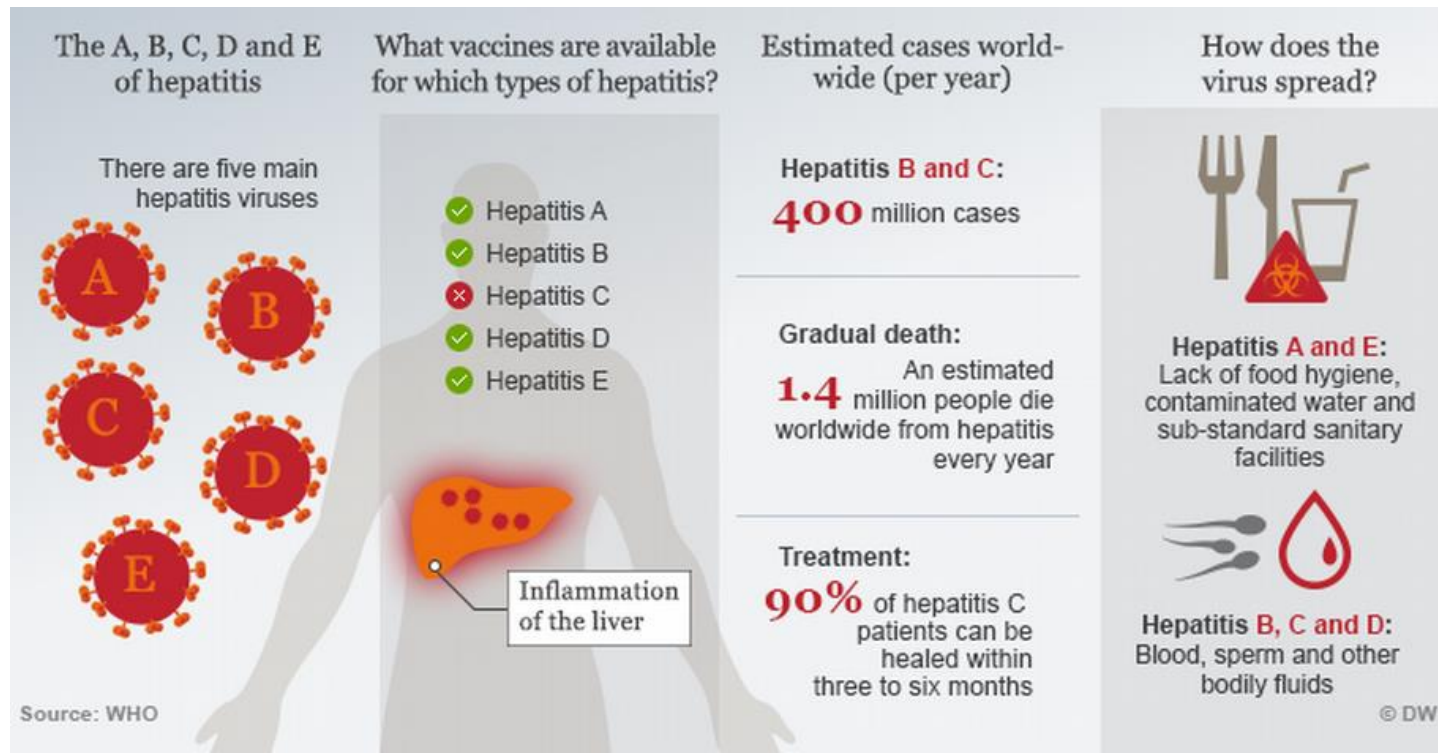
Diseases

Distinctive characteristics



Hepatitis viruses

- A group of unrelated pathogens termed “hepatitis viruses” cause the vast majority of virally induced hepatitis in humans.
- There are five main hepatitis viruses
 - HAV & HEV (enteric) is transmitted by fecal-oral routes
 - HBV, HCV & HDV (serum hepatitis) is transmitted primarily through blood contact





Viruses and hosts

- *Hepadnaviridae* from *hepatitis* and *DNA*
- Hepatitis = Greek, hepar (liver) + itis (inflammation)
- Hepatitis B viruses of human, chimpanzee, duck, gibbon, gorilla, ground squirrel, heron, orangutan, snow goose, woodchuck, woolly monkey



Diseases

- Transmission by blood and sexual contact
- Hepatitis: incubation period 30-180 days
 - Acute hepatitis can be mild to severe
 - Chronic hepatitis may lead to fibrosis, cirrhosis, and liver cancer
- Treatment: pegylated interferon, lamivudine, entecavir, telbivudine, tenofovir, adefovir
- Prevention:
 - Vaccination with recombinant hepatitis B surface antigens
 - Injection with anti-hepatitis B immunoglobulin after exposure to virus



Fever



Fatigue



Nausea



Loss of appetite



Jaundice
(yellowing of the
skin or eyes)



Stomach
pain



Vomiting



Dark urine,
pale stools, and
diarrhea

Symptoms of hepatitis B

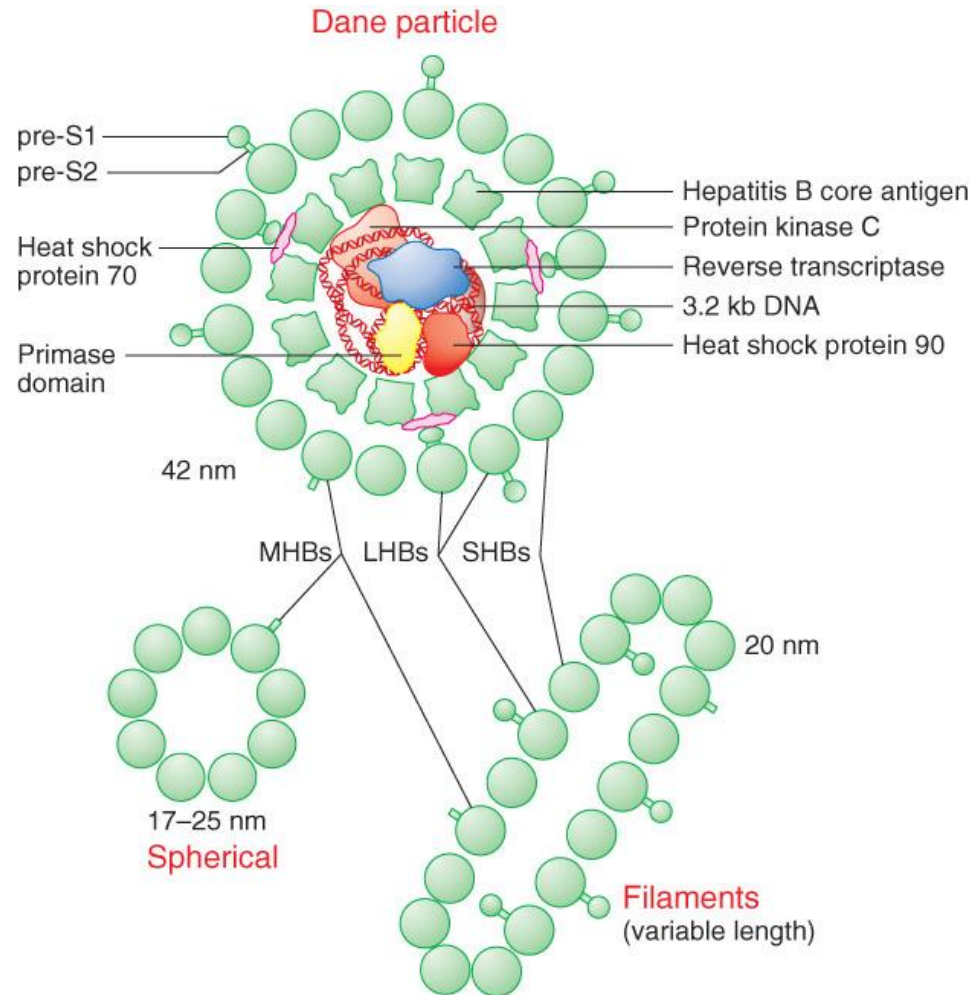
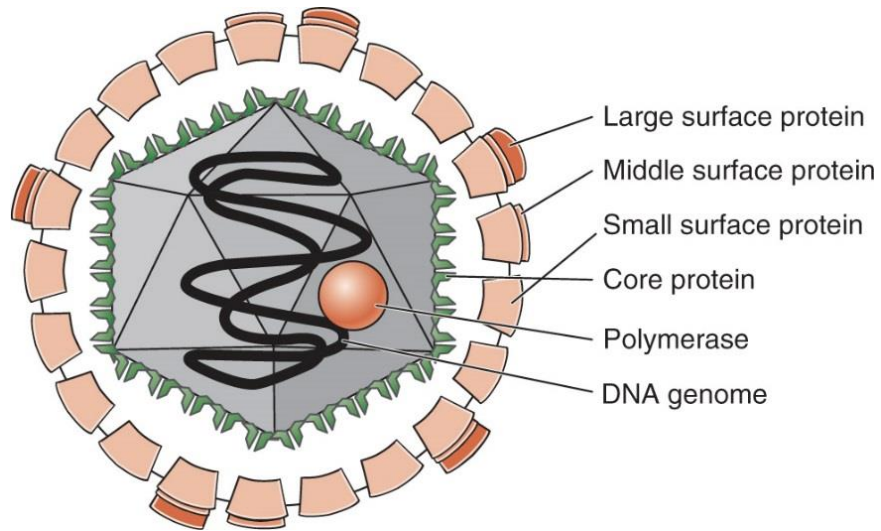


Virion

- Spherical enveloped particle; icosahedral capsid (T=4); diameter 42 nm
- Dane particles are infectious virions
- Abundant smaller spherical and filamentous forms lack nucleocapsid and are not infectious
 - Composed primarily of lipids and HBV surface proteins.
 - May divert the immune system by binding to antibodies and complement
- 8 major genotypes (A to H) exist which vary in disease severity and response to **interferon**
- 4 distinct serotypes contain two pairs of mutually exclusive epitopes present on small surface antigen
 - Common epitope: “a”
 - Two pairs of mutually exclusive epitopes: “d” or “y”; “w” or “r”



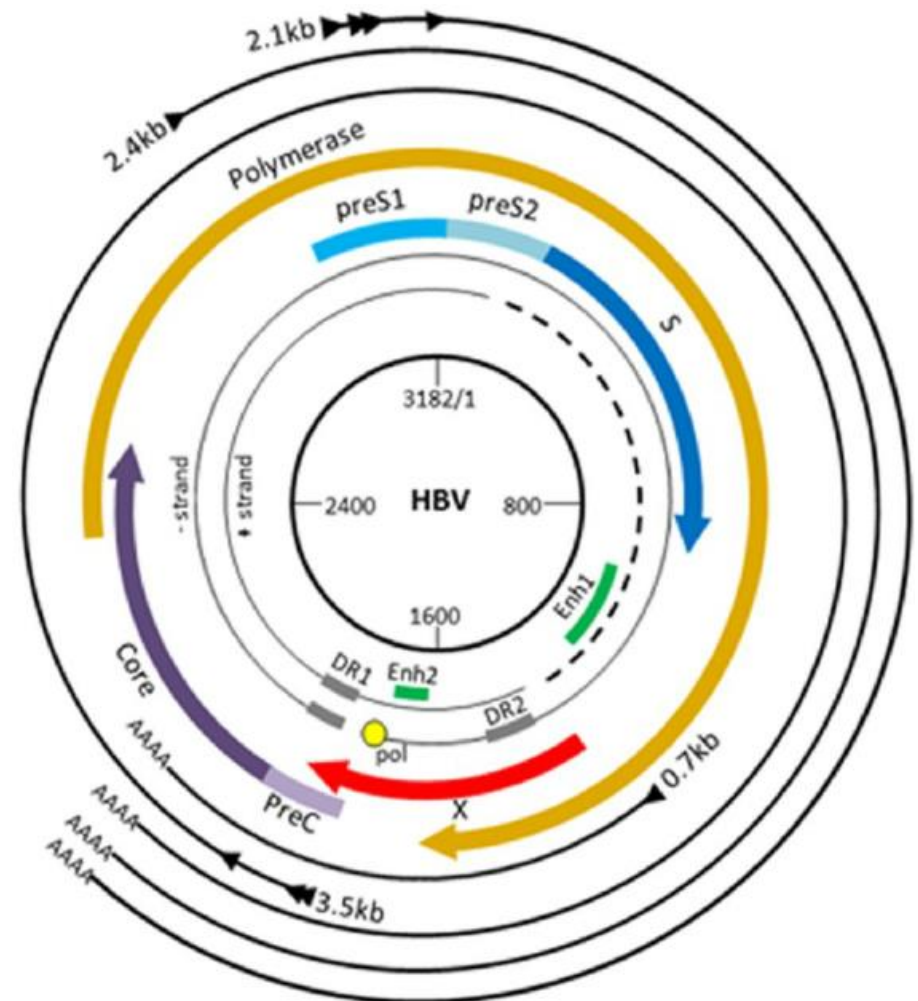
Virion





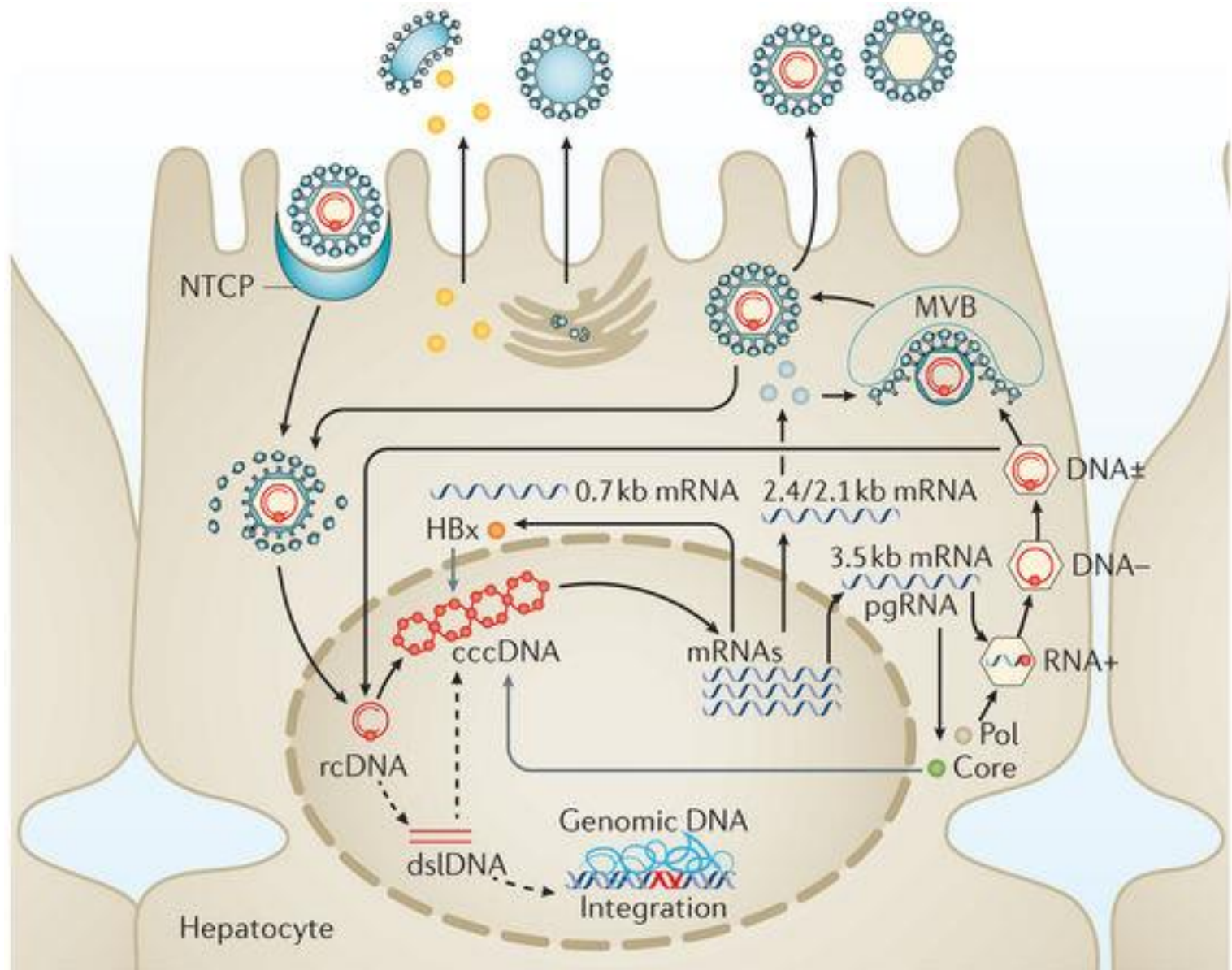
Genome

- Circular partially dsDNA with single stranded gap on one strand, 3.2 kb
 - Full length strand (- strand), 3.2 kb
 - Shorter strand (+ strand), 1.7 kb
- 4 ORFs (S, C, P, X) encodes 7 proteins





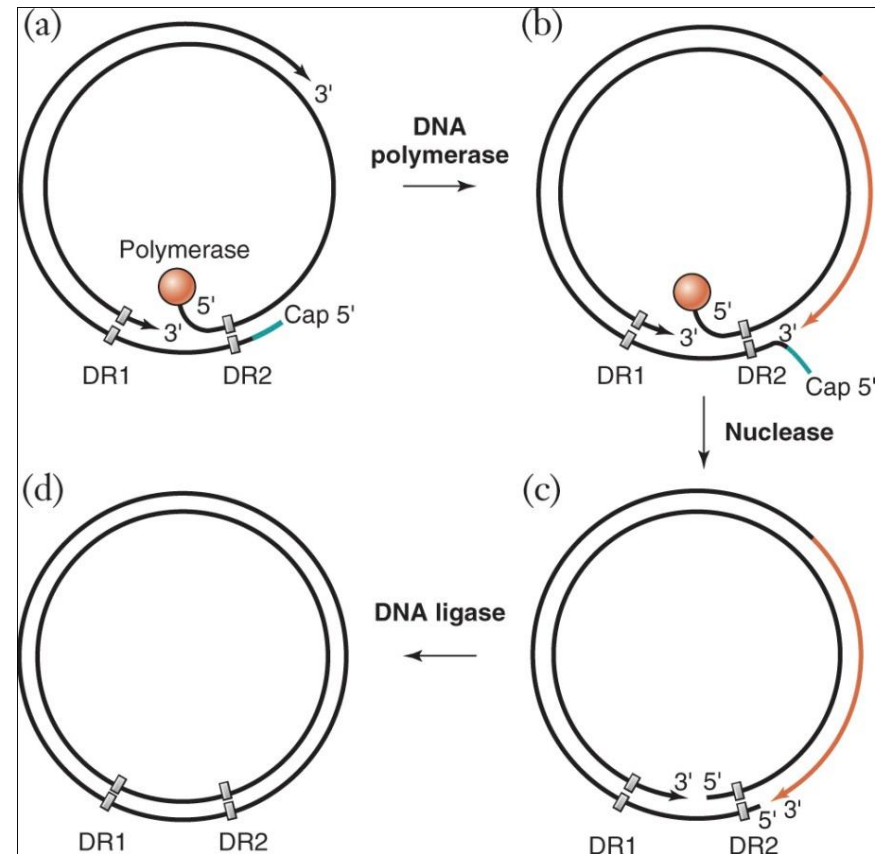
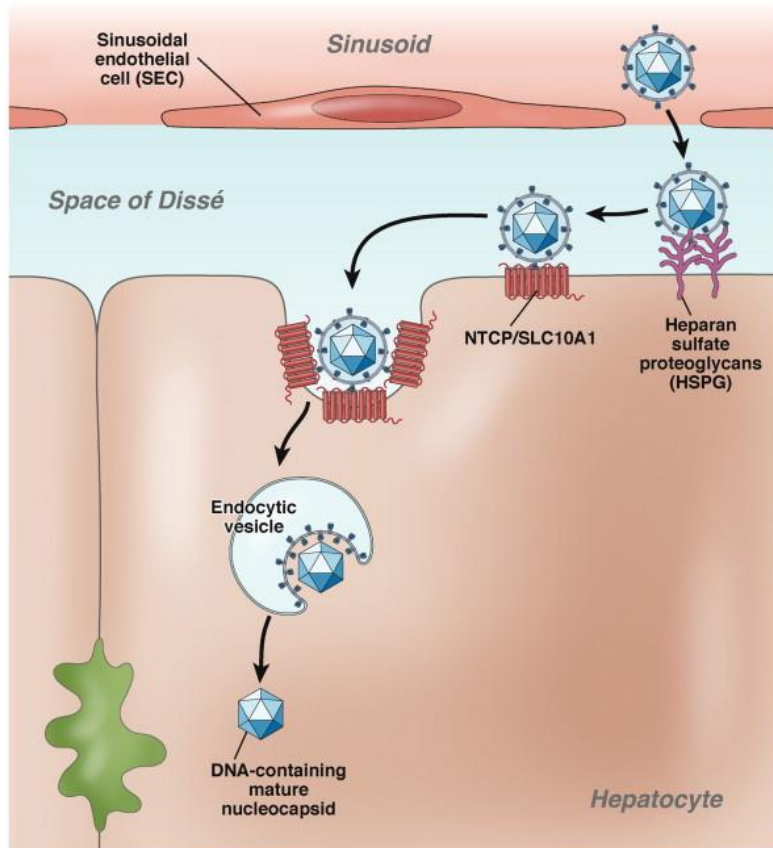
HBV Life cycle





Entry

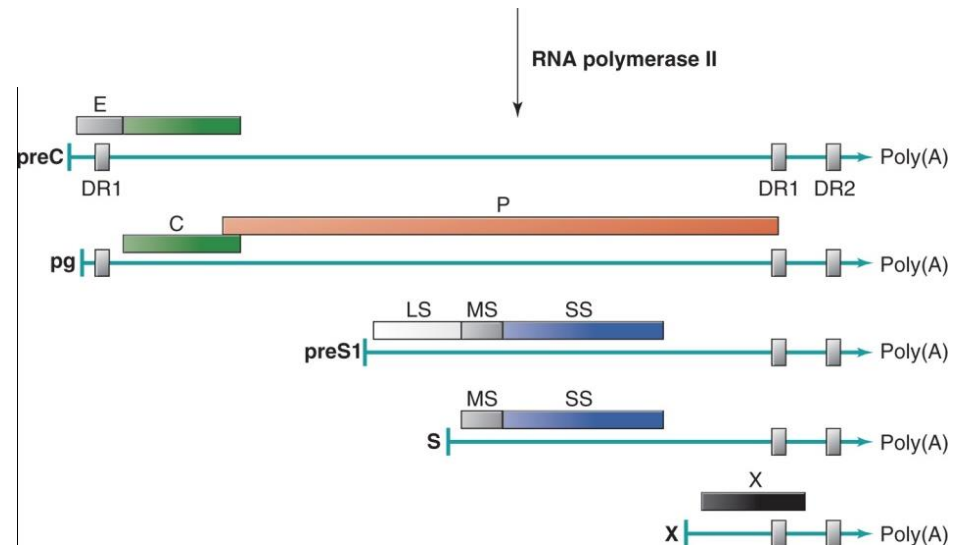
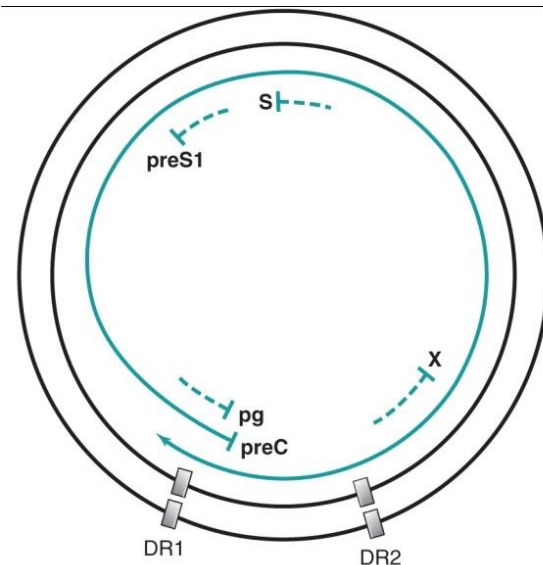
- Nucleocapsids enter the cytoplasm via receptor-mediated endocytosis and are transported to the nucleus
- Host repair enzymes extend the plus strand, sealing the gap





Transcription

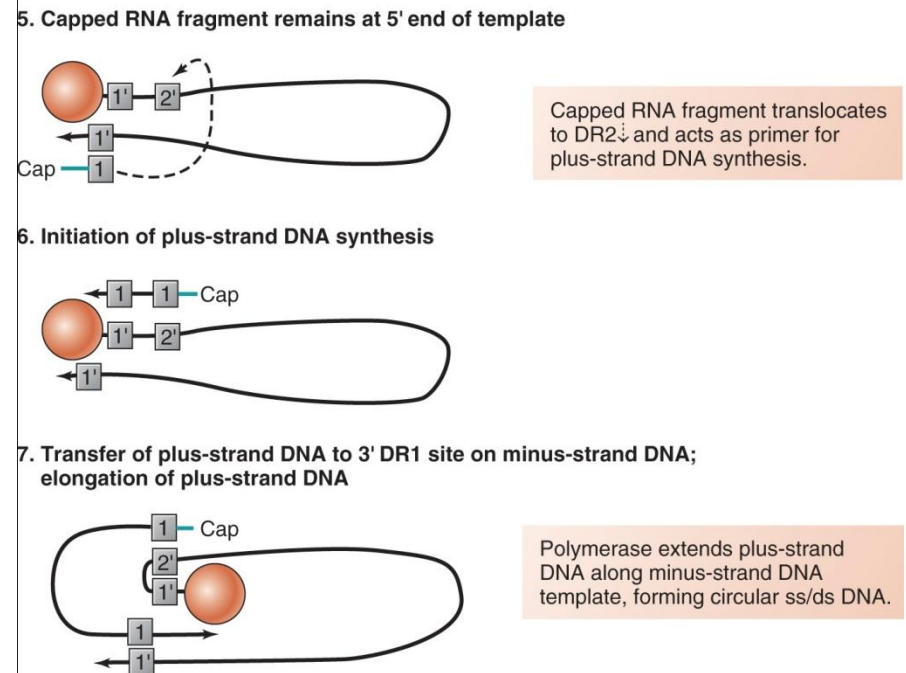
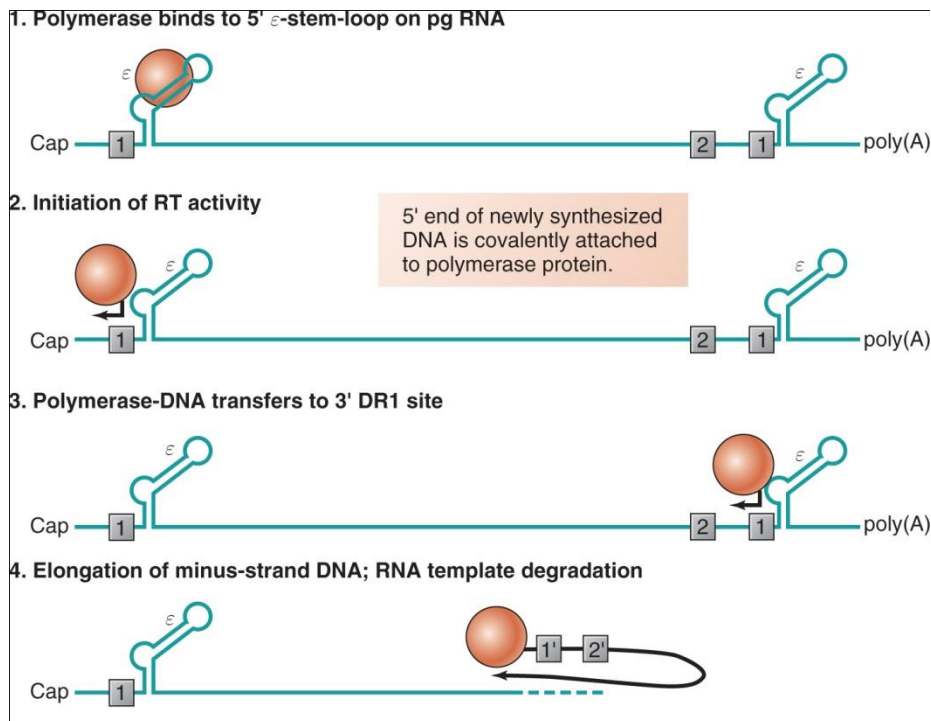
- Transcription by cellular RNA pol II yields 4 mRNAs and a pregenome RNA
 - S: Large, middle, and small hepatitis B surface (envelope) antigens (HBsAg)
 - C: Hepatitis B secreted precore antigen (HBeAg) and hepatitis B core (capsid) antigen (HBcAg)
 - P: Viral polymerase (DNA-dependent DNA polymerase, reverse transcriptase, with RNase H activity)
 - X: Regulatory protein HBx





Genome replication

- The pregenome RNA is packaged by interaction with polymerase and core proteins
- Genome replication occurs via reverse transcription of pregenome RNA

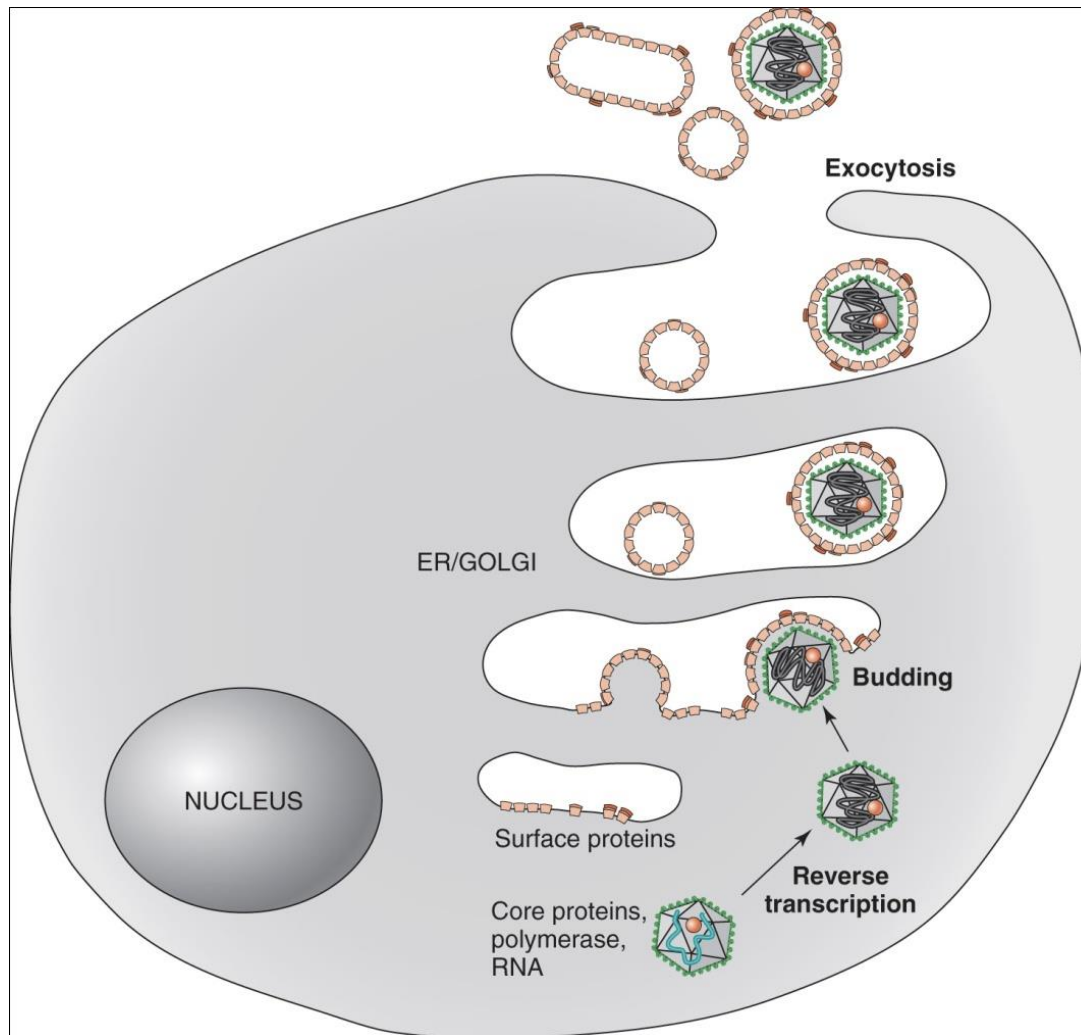


Reverse transcription of pregenome RNA to form HBV genome DNA



Assembly

- Virions are formed by budding in the endoplasmic reticulum





Retroviruses vs Hepadnaviruses

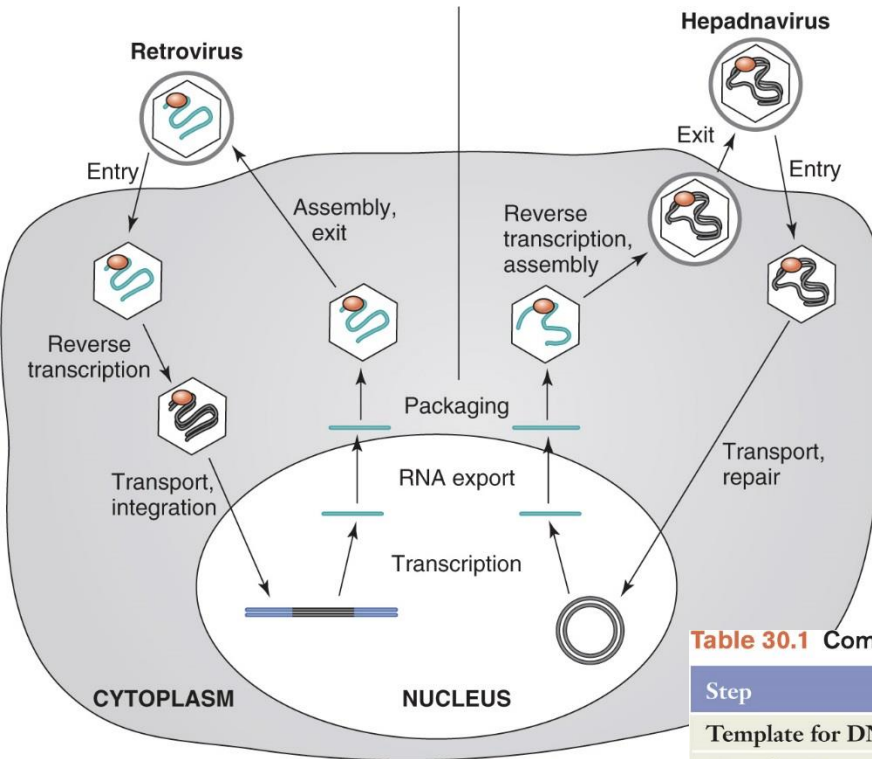


Table 30.1 Comparison of reverse transcription by retroviruses and hepadnaviruses

Step	Retroviruses	Hepadnaviruses
Template for DNA synthesis	Plus-strand virion RNA	Plus-strand pregenome RNA
Site of DNA synthesis	Residual capsid after virus entry (cytoplasm)	Newly assembled capsid before virion formation (cytoplasm)
Primer for initiation of minus-strand DNA synthesis	Cellular tRNA bound near 5' end of genome RNA	Polymerase protein bound near 5' end of pregenome RNA
First switch: to 3' end of RNA template	Via terminal repeat (R) sequence	Via subterminal DR1 sequence
RNA template degradation	RNase H activity in reverse transcriptase	RNase H activity in Polymerase
Initiation of plus-strand-DNA synthesis	RNase H-resistant polypyrimidine tract in genome RNA	RNase H-resistant capped 5' RNA fragment bound to DR2 sequence
Second switch: to 3' end of minus-strand DNA	Via primer-binding site	Via DR1 sequence
Final product	ds linear DNA with long terminal repeats	Partly ss/ds circular DNA
Fate of DNA	Integrated into cellular chromosomal DNA	Incorporated into virions



Diseases

- Hepatitis B virus can cause acute or chronic hepatitis, leading to cirrhosis, and liver cancer
 - Tissue damage is a result of host immune response
 - Symptoms range:
 - Asymptomatic to flu like, jaundice, elevated liver enzymes, serum sickness
 - About 1% suffer from fulminant hepatitis
 - Cirrhosis involves fibrous deposition on liver and production of ascites fluid
- Hepatitis B virus is transmitted by blood transfusions, contaminated needles, and unprotected sex
 - Passage of virus from mother to newborn can cause severe disease
- A recombinant vaccine is available
 - Anti-HBV immunoglobulins can also be used to prevent infection via immunoprophylaxis
- Antiviral drug treatment has real success
 - Pegylated interferon is an immune system modulator
 - Other drugs (Lamivudine etc.) interferes with the reverse transcription step



HBx and HCC

- X protein:
 - implicated in the development of hepatocellular carcinoma.
 - Up-regulates: c-src kinase, Ras/raf/MAPkinase, SAPK, protein kinase C, and Jak/Stat pathway, NF- κ B
 - Sequesters tumor suppressor protein p53
 - Inhibits apoptosis mediated by Fas, tumor necrosis factor, and others