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HIV and Hepatitis co-infection

Marsh Gelbart 2010





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Learning Outcomes

- To appreciate the growing scale of co-infection by HIV and the Hepatitides
- To understand that the rates of co-infection will continue to increase, as better treatments for HIV become available
- To examine treatment options in case of co-infection
- To be able to apply knowledge to clinical practice and patient care



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An increasing problem

- The incidence of viral hepatitis amongst people living with HIV is higher than the general population
- There is shared risk behaviour for transmission
- HIV progression is accelerated by co-infection by hepatitis, particularly hepatitis C virus (HCV)



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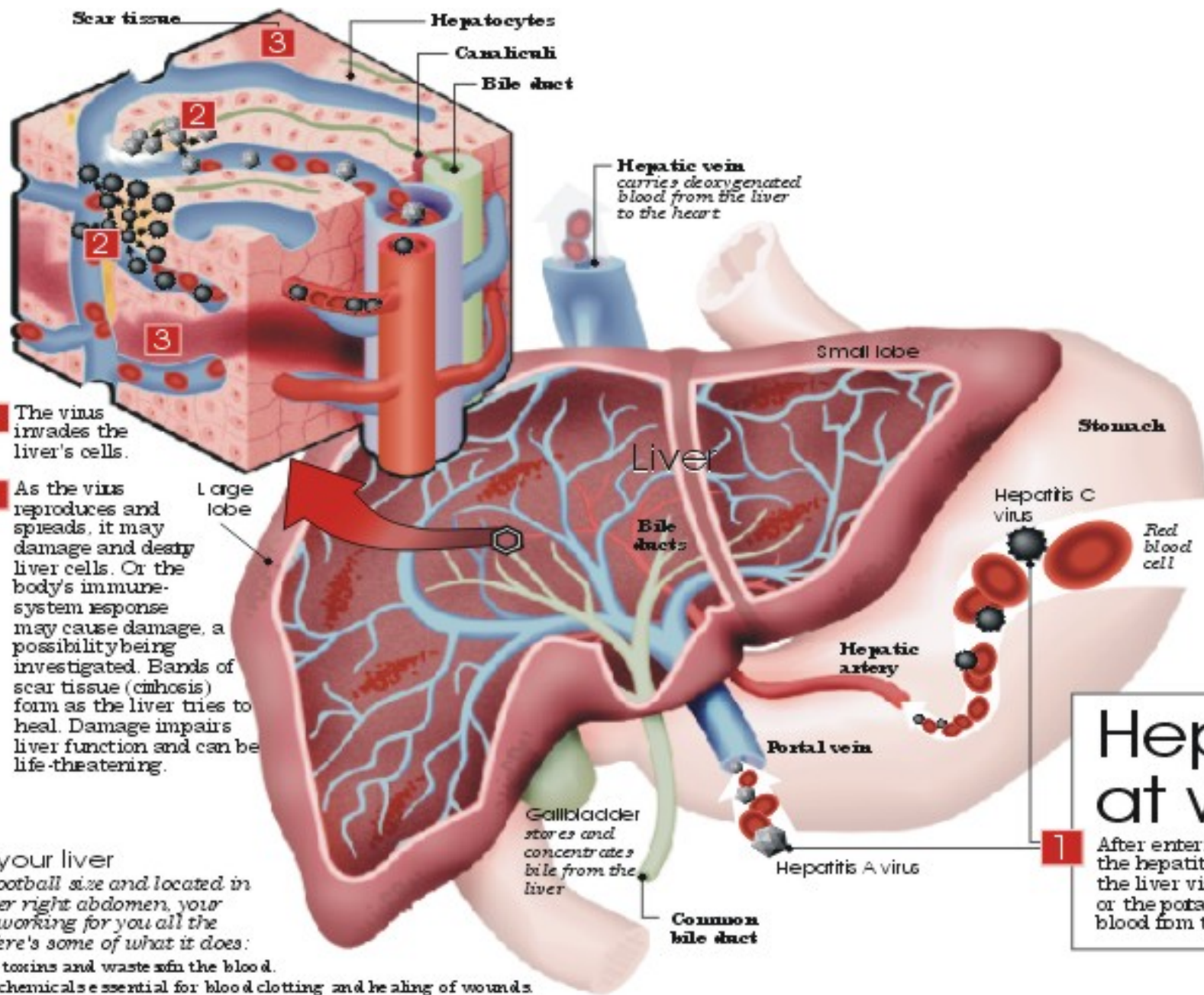
Longevity means a shift in emphasis

- In the past, people with HIV did not live long enough to suffer from problems associated with hepatitis.
- Highly active anti-retroviral therapy (HAART), means that more people with HIV are now living longer and more likely to suffer from the long term morbidity and mortality associated with hepatitis
- Vaccinating against, screening for and treating the hepatitises helps reduce the incidence of cirrhosis, liver failure and hepatic carcinoma



The hepatitisides

Hepatitis A	Short incubation & Enteric transmission
Hepatitis B	Long incubation & Parenteral transmission
Hepatitis C	Long incubation & Parenteral transmission
Hepatitis D	Co-infection with hepatitis B
<i>Hepatitis E</i>	<i>Similar to HAV</i>
<i>Hepatitis F</i>	<i>Unknown</i>
<i>Hepatitis G</i>	<i>Does not cause liver disease</i>



- 2 The virus invades the liver's cells.
- 3 As the virus reproduces and spreads, it may damage and destroy liver cells. Or the body's immune-system response may cause damage, a possibility being investigated. Bands of scar tissue (cirrhosis) form as the liver tries to heal. Damage impairs liver function and can be life-threatening.

Hepatitis at work

1 After entering the blood stream, the hepatitis virus is carried into the liver via the hepatic artery or the portal vein, which brings blood from the digestive tract.

Love your liver
 About football size and located in the upper right abdomen, your liver is working for you all the time. Here's some of what it does:

- Filters toxins and waste from the blood.
- Makes chemicals essential for blood clotting and healing of wounds.
- Converts protein absorbed from food into amino acids the body can use.
- Makes bile, a fluid that aids digestion.
- Stores iron.
- Processes and stores sugars needed for quick energy.

Source: *The Human Body* by Darling Kinderley; *BlackWorld Book Encyclopedia*; *Encyclopedia Americana*; *The American Medical Association Encyclopedia of Medicine*

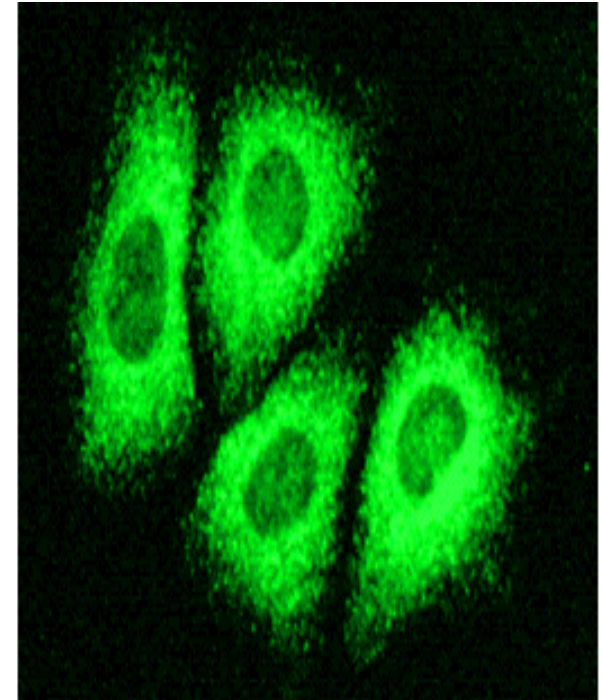


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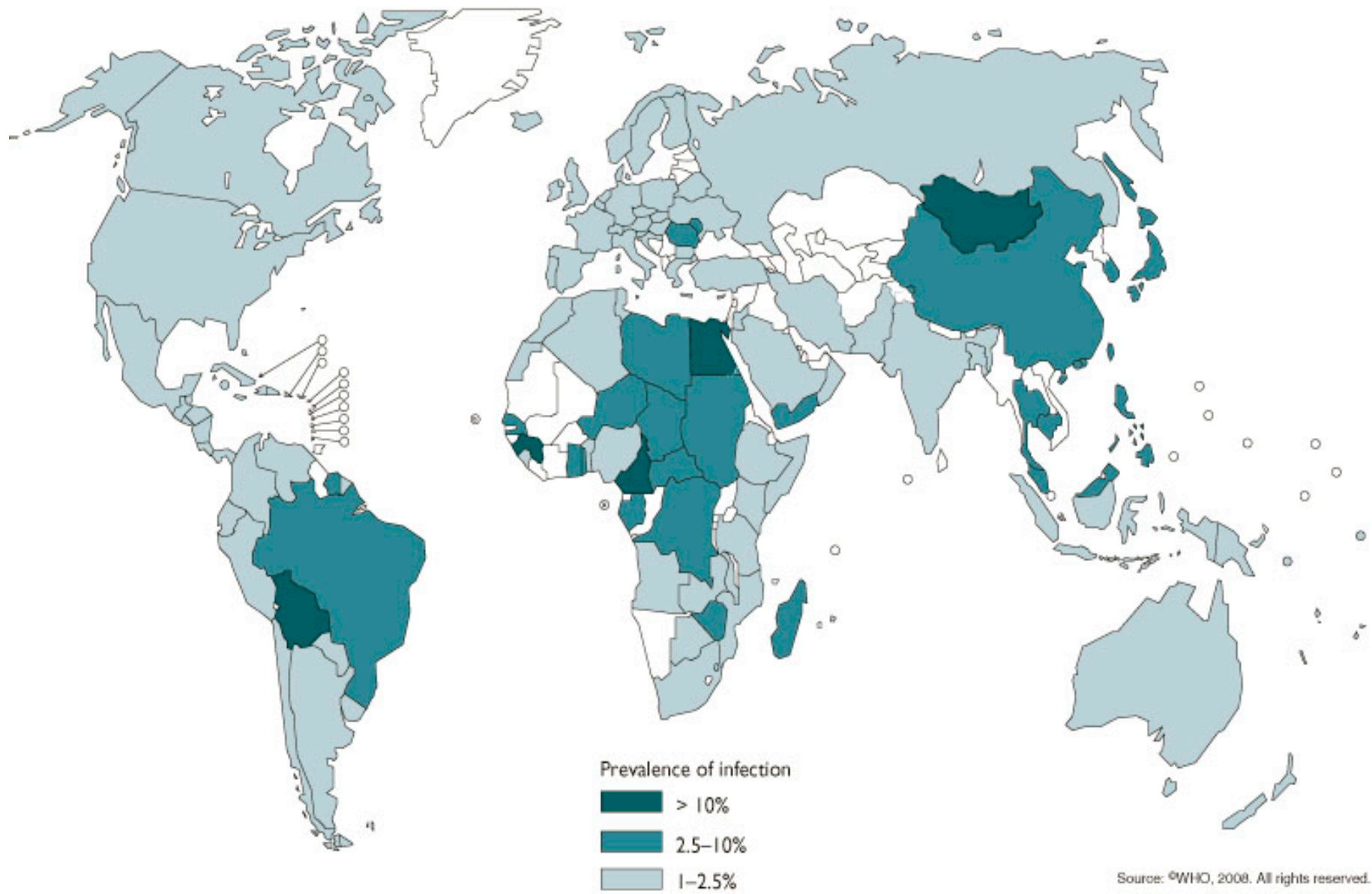
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Hepatitis C Epidemiology

- 170 million people worldwide
- In Europe, highest in Romania (4.5%), followed by Mediterranean countries and lowest in Scandinavia
- Worldwide, high in Egypt, Pakistan, Central Africa, other parts of Asia / Middle East
- 0.6% people in Britain (of whom, around 80% undiagnosed)



Hepatitis C, 2007





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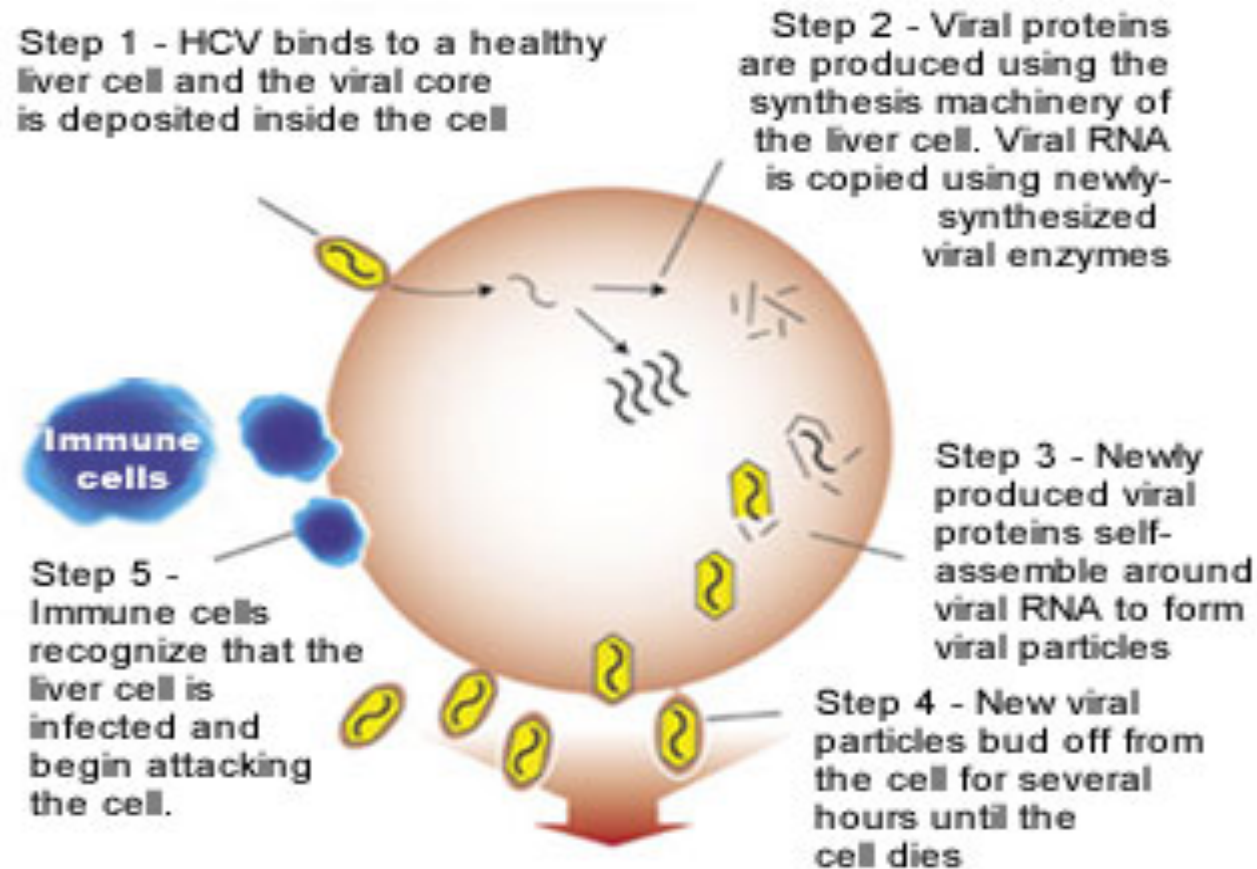
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Risk factors for Hepatitis C

- Highest risk groups are IVDUs (estimated between 50-90% positive),
- Prisoners, sex workers
- Sharing works used to snort cocaine
- Vertical transmission rates are around 3-8%
- The risk of sexual transmission is present but low
- Having had hospital treatment or blood transfusions abroad
- Needle stick injuries amongst healthcare workers



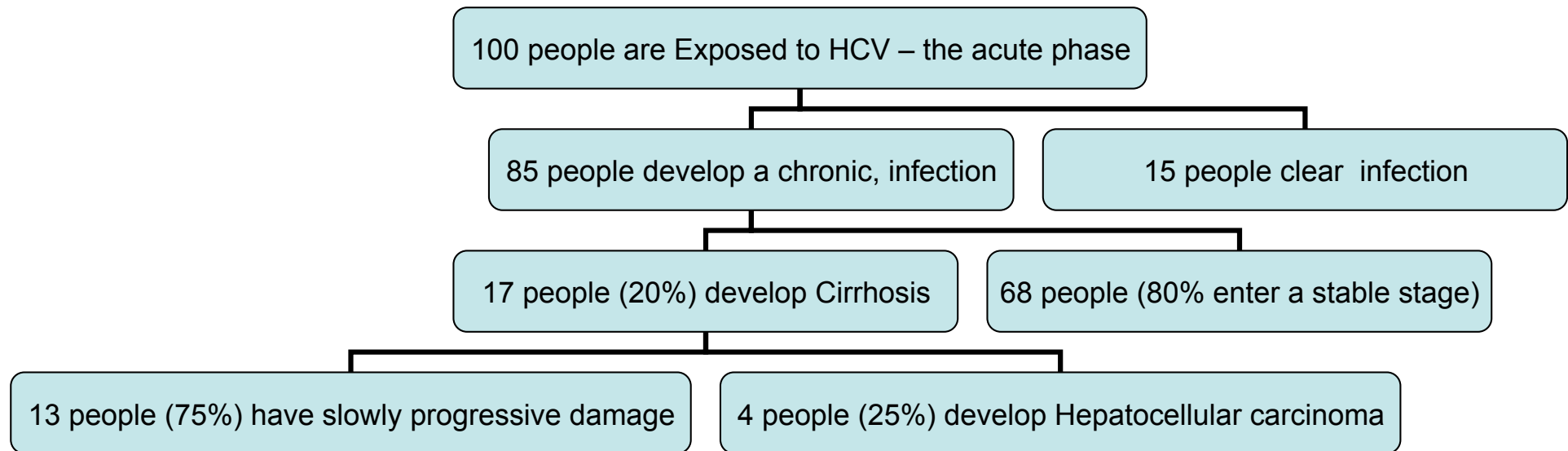
How Hepatitis C Virus (HCV) Infects and Kills Human Cells



Viral budding and the immune response result in massive cell death in the liver



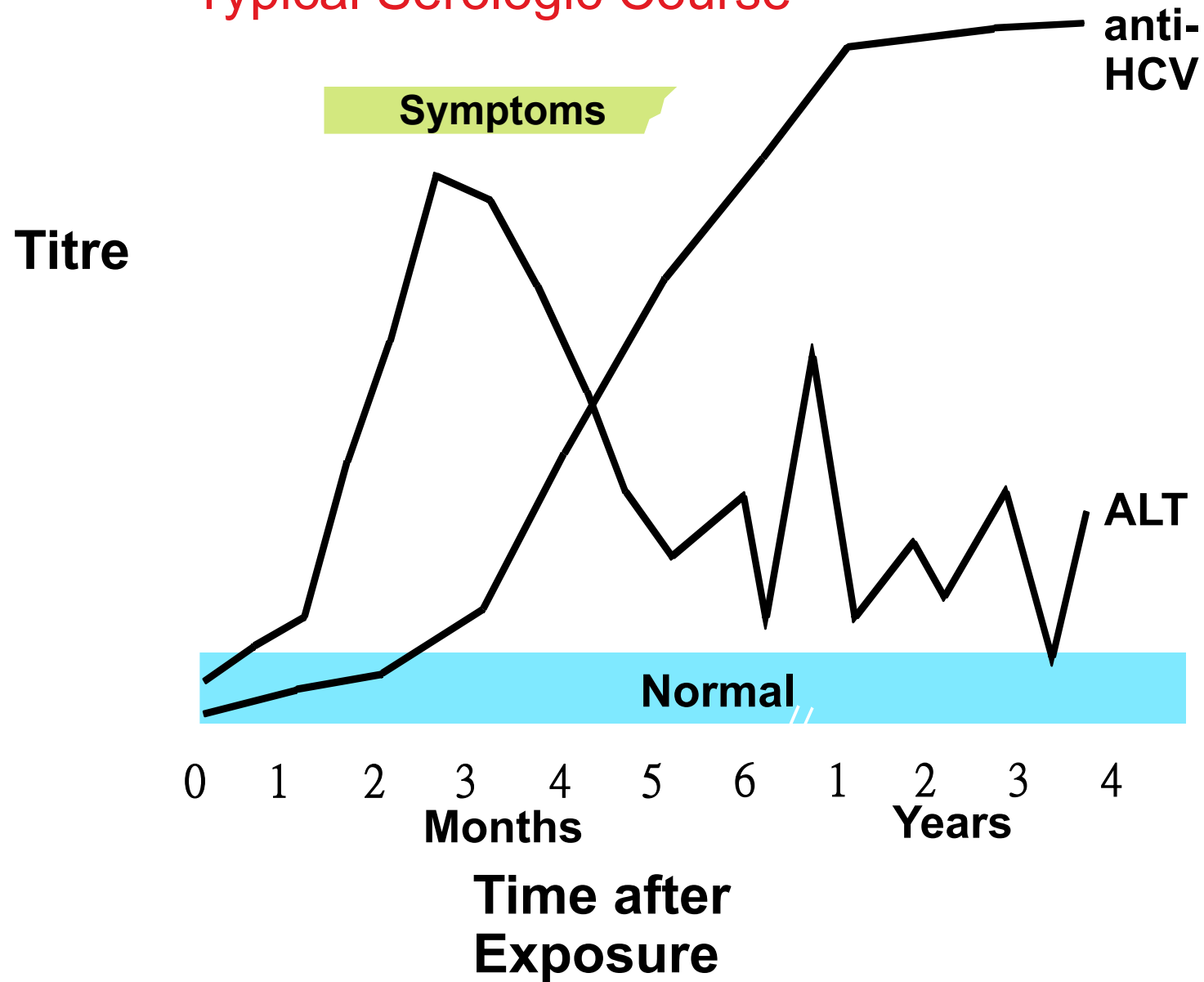
Hepatitis C the natural course





Hepatitis C Viral Infection

Typical Serologic Course





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Effect of HIV on HCV progression

- As cell mediated immunity declines with HIV progression, there are fewer effective cytokines able to control HCV replication
- Progression to cirrhosis in HIV positive people much more likely
- Raised HCV viraemia in HIV positive people is inversely correlated with CD4 count and immunosuppression
- Hepatocellular carcinoma (HCC) occurs quicker and at a younger age in HIV positive people



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Effects of HVC on HIV progression

- Some studies suggest that clinical deterioration is faster in cases of co-infection
- In particular, people co-infected with HCV genotype 1, may progress to AIDS and death somewhat faster



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Who gets treatment?

Drug therapy in Hepatitis C

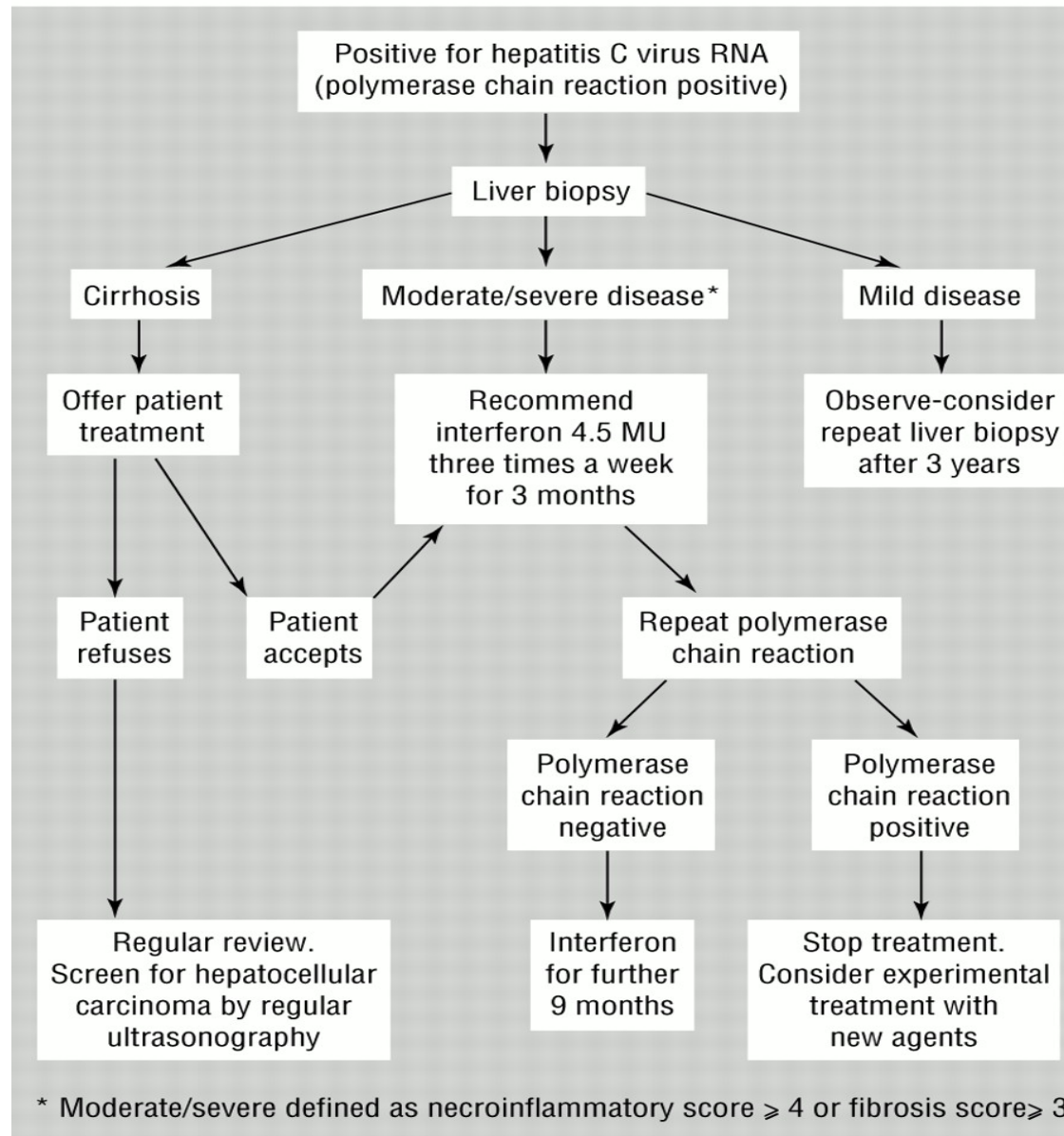
- Has to be rationed because of cost (both to the NHS and to the patient).
- Depends on **liver biopsy** findings.
- *More complex in HIV: less chance of success but potentially more to lose by not treating.*
- Decision may be influenced by genotype.

Monotherapy for HCV – typical management regime



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Liver function tests (LFTs)

- Most people with Hepatitis C infection have abnormal LFTs (but often mild).
- Raised ALT (alanine aminotransferase) levels.
- As progression to chronic liver disease occurs other LFTs may become raised.
- Abnormal LFTs are not a useful marker of disease stage and a liver biopsy is usually required.



HAART and Hepatotoxicity

- HCV co-infection increases risk of hepatotoxicity on HAART 2-3 fold
- However, the majority (88%) are able to take HAART with no problems and HCV should not prejudice decision to start HAART
- Nevarapine + Ritonovir in particular are associated with toxicity
- When immune function improves, there can be a flare up of liver disease in HCV as the immune system attacks infected liver cells
- Liver enzymes should be carefully monitored after HAART commencement. Mild - moderate changes can and should be managed without cessation.



General principles of HCV Therapy

- All patients ideally require CD4 ≥ 200 counts = poorer response -lower
- Abstain from alcohol - support
- Hep A+B Vaccination if required
- Similar criteria as mono-infection – influenced by the result of the liver biopsy's histology
- Primary goal of treatment is viral eradication (-ve PCR 6 months post therapy cessation)



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When do you start treatment? Which nemesis do you deal with first?

- Treat in relation to HCV and HIV status of individual patient
- HCV should be treated first if HIV stable
- If low CD4 then HIV to be treated first
- Mild HCV and advanced HIV will be managed differently to End Stage Liver Disease and CD4 \wedge 800
- Close liaison between HIV and hepatology teams



HCV treatment

- Non-pegylated interferon
- Early studies of interferon mono-therapy in co-infection shows results similar to mono-infection (providing there is a good CD4 count)
- Response rates vary (20-40%) and are influenced by HCV genotype - with type 2+3 being most favourable
- Genotype 1 should have at least 48 weeks Rx (genotypes 2+3 may be stopped at 24 weeks)



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Non-pegylated interferon and ribavirin

- Non-pegylated interferon can be given in conjunction with ribavirin, a nucleoside analogue
- Absence of cirrhosis, low HCV viral load and patient age influence outcome
- IFN/RBN costly and toxic so important to predict likelihood of treatment success at earliest time point
- Recent evidence suggests this should be done after 12 weeks therapy
- If necessary to discontinue treatment, cessation decisions to be made with the patient



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Possible problems with HCV treatment

- Pre-morbid depression common - Psychiatric assessment needed
- Anaemia common - especially in HIV co-infection when HB can drop 2-3g - RBV to be maintained at full dose if possible
- Support HB - ? Erythropoietin (expensive but effective)
- Rashes can cause Rx failure
- Ribavirin is teratogenic



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Pegylated Interferon and Ribavirin

- Studies in co-infection still in progress
- By week 48, more pts achieve undetectable HCV on PEG-IFN than standard
- BUT sustained viral response lower and study discontinuations high
- PEG-IFN also has anti HIV effect with a drop in viral load. Thus should be used alongside HAART regime in cases of co-infection



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PEG-IFN vs Standard

- Peg-IFN has improved success in patients with genotype 1 infection
- effective in those with Advanced Liver Disease and Cirrhosis
- PEG-IFN under review by NICE
- Co-infection is an evolving field - all patients should be offered chance to take part in clinical trials



Interactions of HCV treatments and HAART

- Ribavirin inhibits effectiveness of AZT/D4T
- Ribavirin enhances the effects of DDI but also *increases* its toxicity
- Avoid Ribavirin and DDI in combination it can lead to severe lactic acidosis syndromes

MANAGEMENT ALGORITHM FOR HIV POSITIVE PATIENTS WITH HCV INFECTION

Anti-HCV positive

HCV RNA negative

Annual check of HCV RNA

HCV RNA positive

HCV genotype
HCV load (if test available)
Check immune status for HBV and HAV
and vaccinate if required

HIV therapy not yet required

Requires / is on HIV therapy

Optimise HIV treatment

Consider liver biopsy to stage disease

Mild
≤3/18
and
≤2/6

Moderate
≥4/18
and/or
≥3/6

Cirrhosis
=6/6

Consider treatment if:
Extrahepatic disease or
Transmission risk
or
Healthy and high CD4
count

Pegylated* Interferon and ribavirin
6 months for genotype 2 or 3
12 months for genotype 1 or 4

* Non-pegylated interferon is an
option for genotypes 2/3

Liaise with local hepatology team
Screen for varices
Consider screening for HCC
Antiviral therapy on individual basis

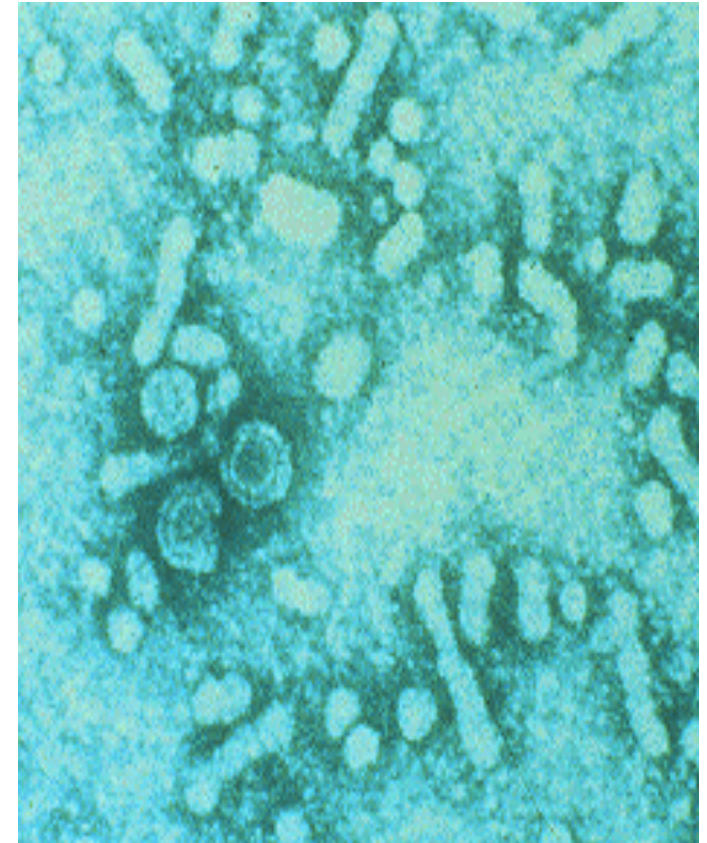


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Hepatitis B Co-infection

- Co-infection with HIV and Hepatitis B virus (HBV is common)
- 75% of HIV infected patients have markers of previous HBV infection
- In co-infection, Hepatitis B surface antigen (HBsAG) carriage after an acute infection of HBV, increases from 10% to 20-25%
- Thus a greater chance of becoming a chronic carrier of HBV

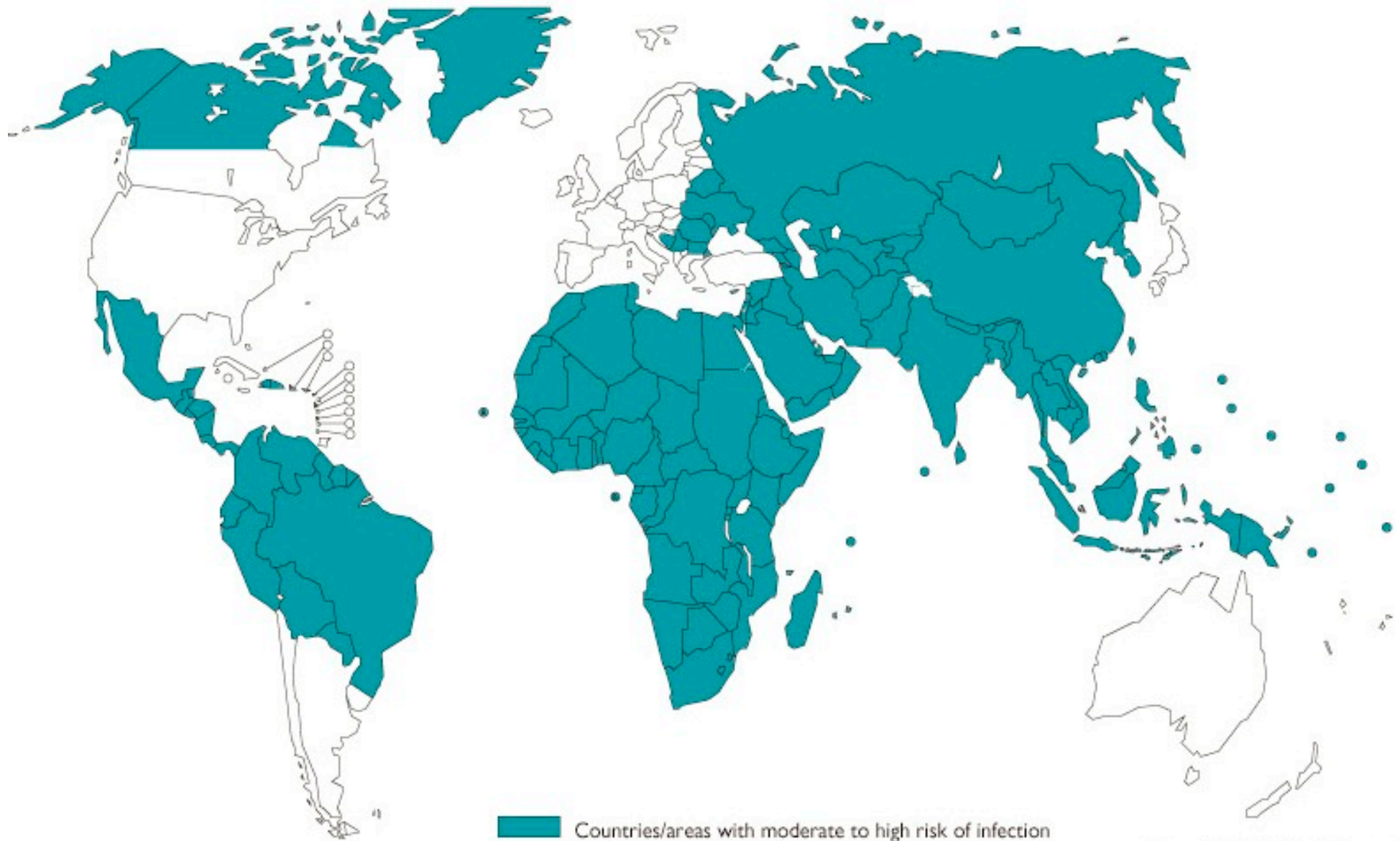




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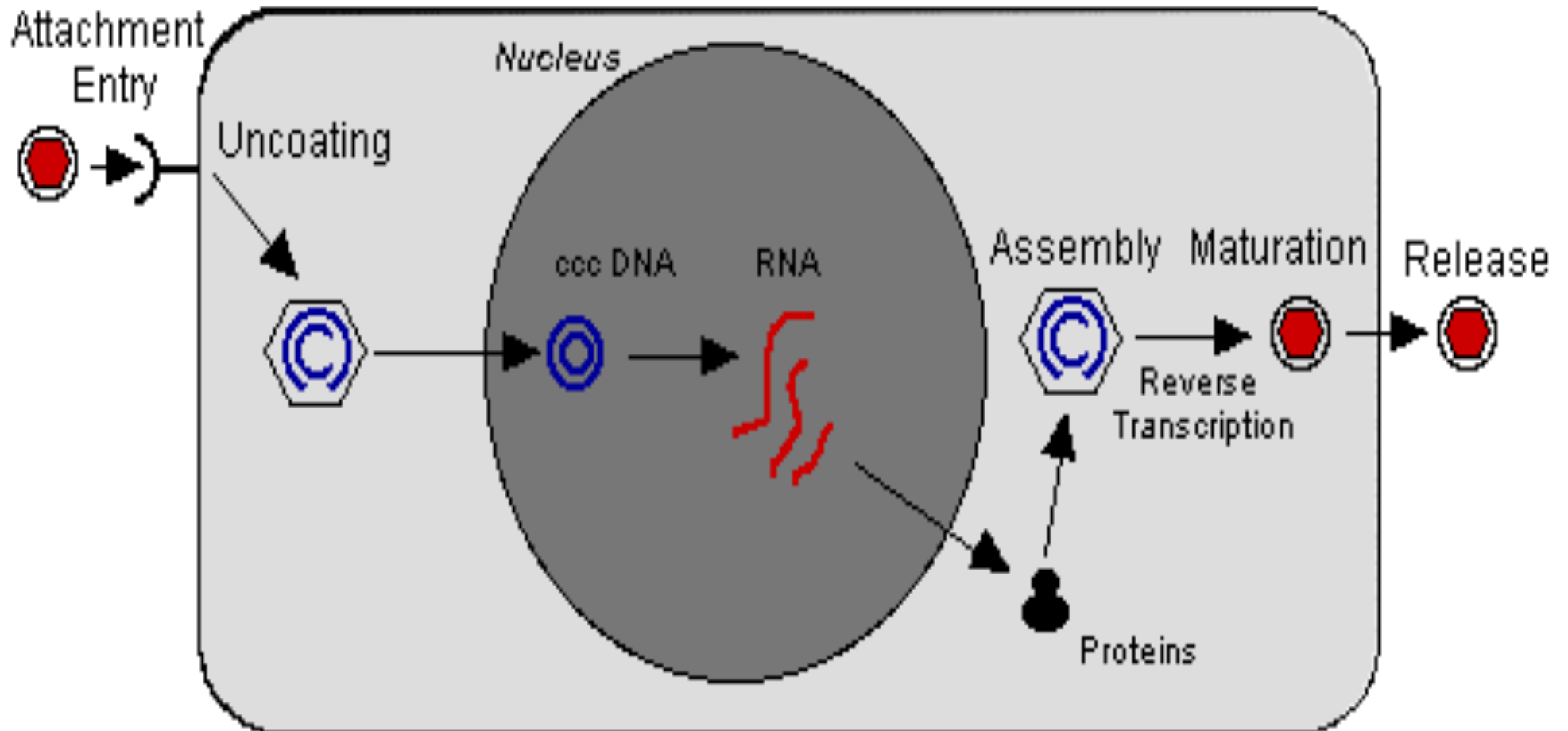
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Hepatitis B, 2007



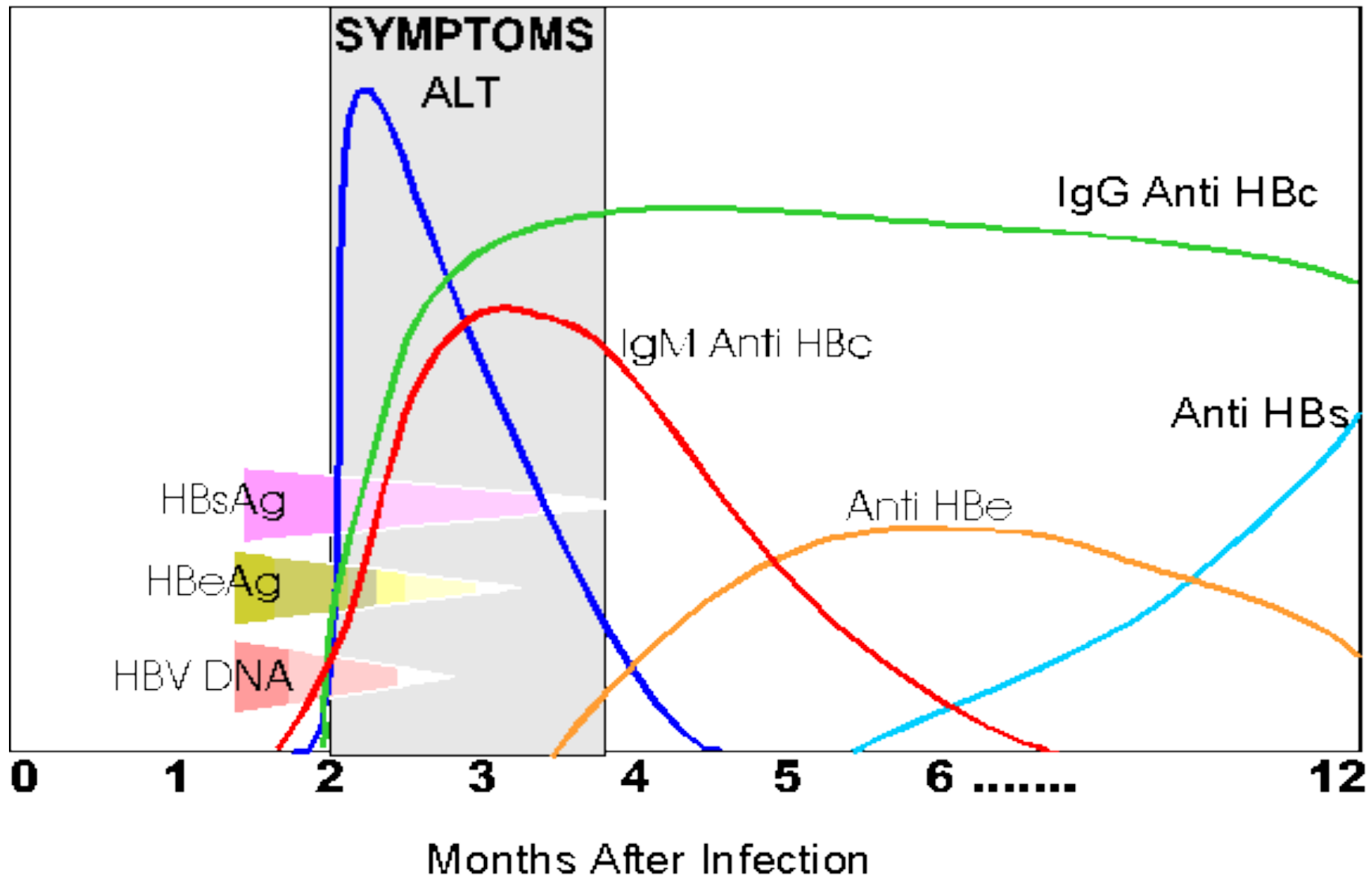


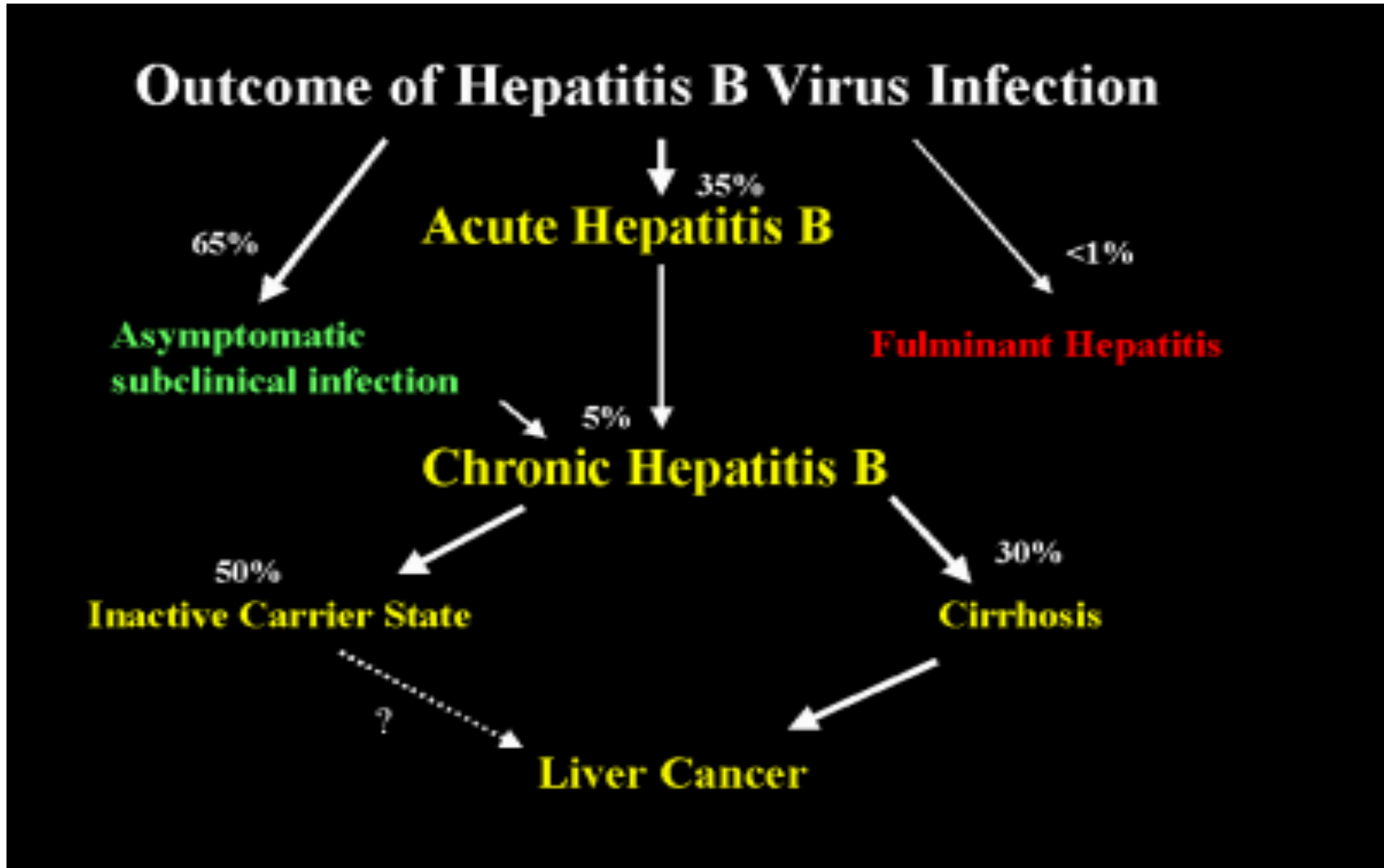
How hepatitis B disseminates





Hepatitis B Typical serological course







Drug therapy for Chronic Hepatitis B

Aims

- Suppression of viral replication
- Reduction in liver injury and progression to cirrhosis/HCC
- Treatment successful in 10-40% of HIV negative patients. Lower in HIV positive patients
- Most patients require long-term therapy
- **Treatments**
- Interferon, Tenofovir, Adefovir



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Side-effects of α -IFN

- Influenza-like symptoms (in 80% patients)
- Mood change, depression, suicidal ideation
- Auto-immune disease (e.g. thyroiditis)
- Myelosuppression (e.g. neutropaenia, thrombocytopaenia)
- Skin disorders (e.g. psoriasis)
- Retinopathy
- Cardiomyopathy, arrhythmias
- Hepatic decompensation



Efficacy of α -Interferon

	Clearance of HBeAg	Clearance of HBsAg
α IFN	33%	8%
Controls	12%	2%



Tenofovir and Adefovir

- Both drugs are reverse transcriptase drug inhibitors with potent antiviral activity against HBV
- Rapidly suppresses HBV replication through inhibition of HBV DNA synthesis.
- Can cause renal problems leading to discontinuation of treatment



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Suggestions for practice

- All HIV positive people to be screened for hepatitis A, B and C
- All people positive for HIV and/or HCV, but non-immune to HAV or HBV should consider vaccination
- People who tested anti-HCV negative, but who have abnormal liver enzymes without a known cause should have a PCR screen
- All HIV + patients must have HBV and HCV status checked before commencing HAART
- Discuss the need for avoiding alcohol
- Discuss how to avoid risks of sexual transmission



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