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"Pathology that **Adds Value**"

Hepatitis B virus: primary care essentials

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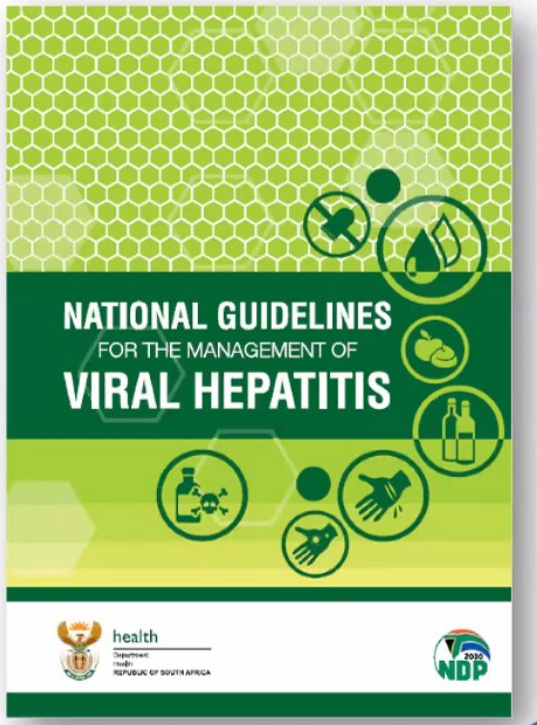
Recording

Welcome!

Outline

1. Setting the scene
2. (A little) virology and epidemiology
3. Clinical presentation
4. Acute vs. chronic disease
5. Diagnosis
6. Management
   - Approach
   - Available therapeutic agents



What this presentation does not aim to do:

- Provide a comprehensive overview of all disease presentations
- Discuss each management option in detail
- Discuss special populations in detail

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Setting the scene

Hepatitis viruses:

- H**A**V
- H**B**V
- H**C**V
- H**D**V
- H**E**V

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Setting the scene

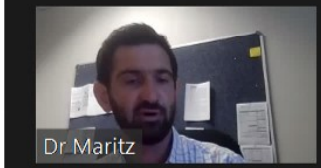
Hepatitis viruses:

- H**A**V
- H**E**V

Faeco-oral viruses
Extremely rarely cause chronic infections

- H**B**V
- H**C**V
- H**D**V

Blood/bodily fluid transmission
Many additional extrahepatic complications
Often cause chronic infections, leading to fibrosis and HCC



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HBV overview

- ~270 million people with chronic HBV
- HBV accounts for >1 million deaths annually from cirrhosis, hepatocellular carcinoma (HCC)
- Incubation period: 6-24 weeks (12-14 average)
- Carriers may be asymptomatic for many years – public health risk, “silent” epidemic
- 100x more infective than HIV!
- Genotypes: 10 known, predominantly **A**, D and E in South Africa
- Vaccines available since 1980’s
  - Introduced into the SA EPI in 1995

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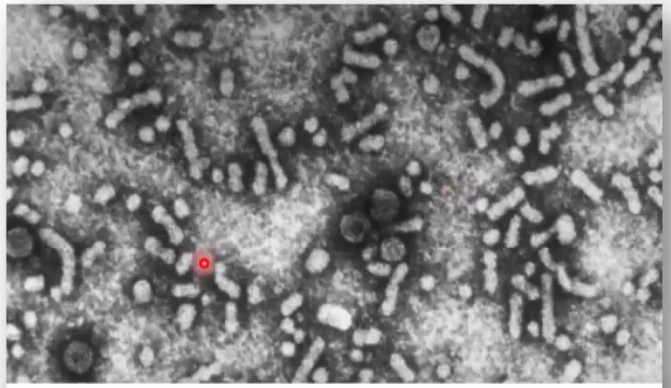
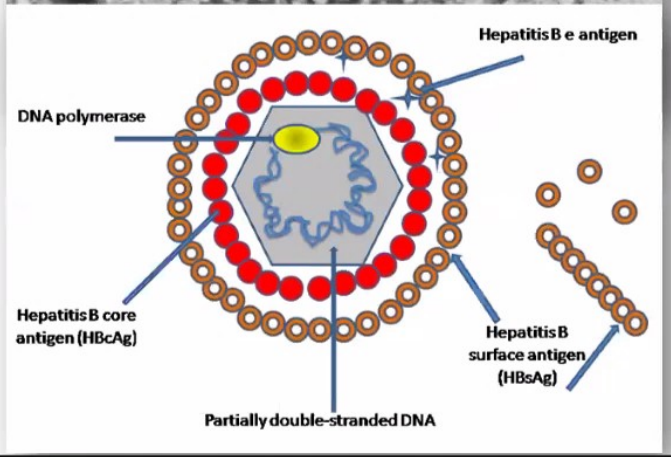
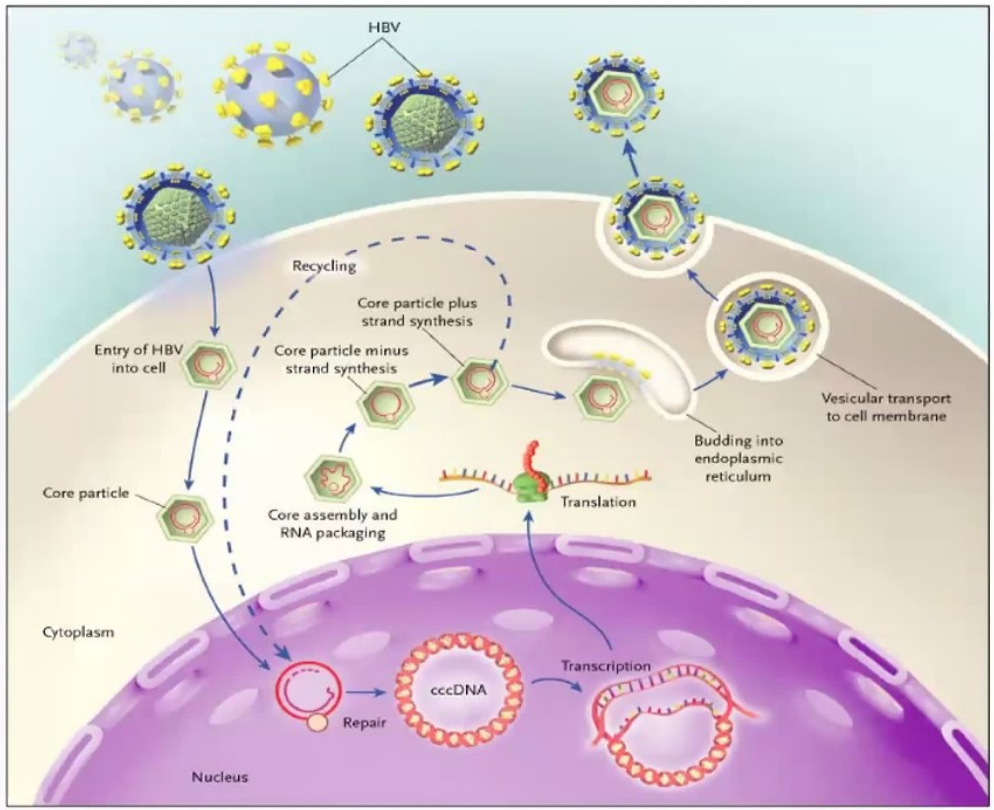
HBV – virion and replication cycle







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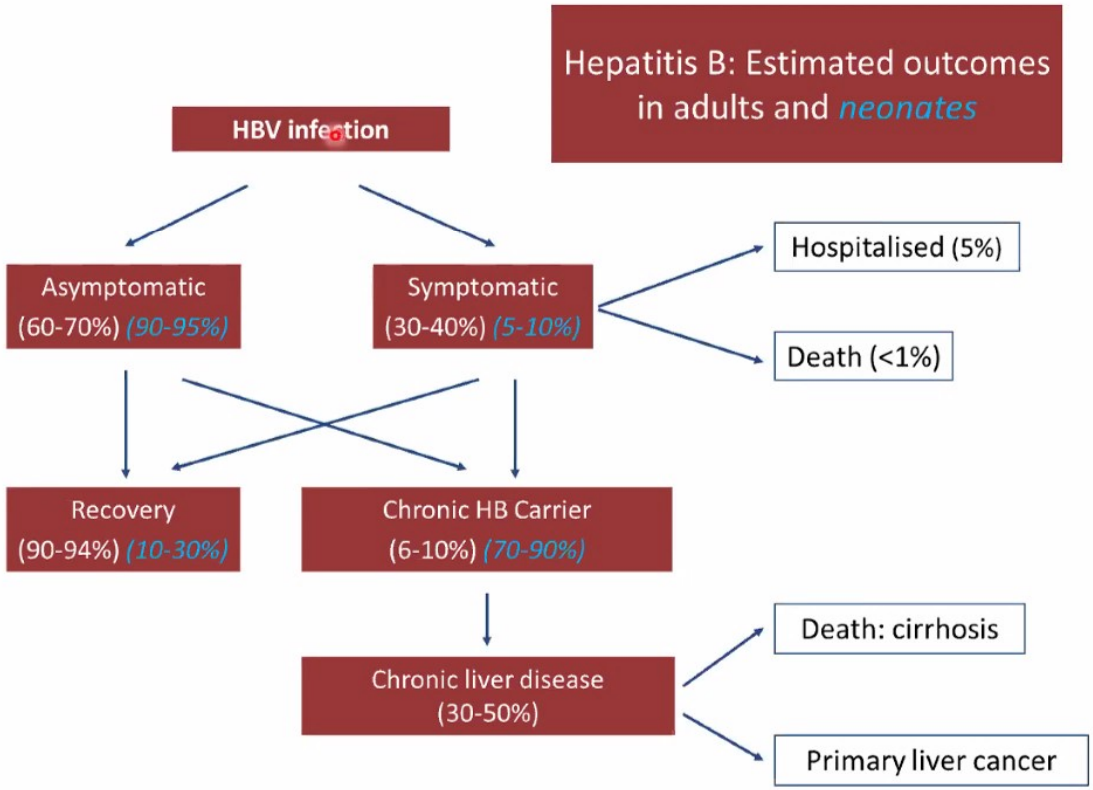
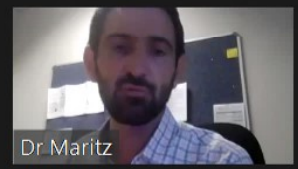
HBV – epidemiology





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Clinical presentation

Acute HBV infection			
Early prodromal phase	**Preicteric phase**	**Icteric phase**	**Convalescent phase**
In symptomatic cases: The illness may be heralded by a serum sickness-like syndrome which precedes jaundice by 14 to 21 days and disappears with the onset of jaundice: • fever • urticaria • arthralgia and arthritis	An abrupt or insidious onset of non-specific constitutional symptoms or an influenza-like illness may occur: • malaise and fatigue • myalgia • anorexia, nausea, vomiting • epigastric or right upper quadrant discomfort Physical examination: • may be unremarkable or may reveal a tender hepatomegaly and splenomegaly • hepatosplenomegaly is usually mild (liver palpable two to three centimetres below the costal margin and spleen tipped)	• With the onset of jaundice approximately a week after the preicteric phase; fever and constitutional symptoms subside. • Anorexia, nausea and vomiting may transiently worsen. • The presence of dark urine and pale stools often raises the clinical concern of obstructive jaundice. • Pruritic scratch marks may be present, if jaundice is severe or prolonged • Weight loss is common.	• Jaundice tends to wane rapidly over days in young individuals, but tends to persist longer (six weeks or more) in adults. • The preicteric phase symptoms disappear, pruritis abates and the hepatosplenomegaly gradually resolves.

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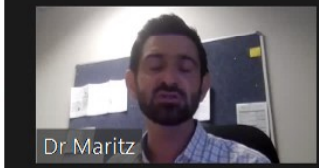

Clinical presentation

Fulminant HBV		
Syndrome is haracterised by: • jaundice • hepatic encephalopathy • Coagulopathy (INR is more than1.5) Occurring within eight weeks of the onset of the acute illness	Complications of acute liver failure include: • development of acute portal hypertension • hepatorenal syndrome • cardiorespiratory dysfunction • metabolic disturbances, including hypoglycaemia • raised intracranial pressure • life-threatening cerebral oedema • susceptibility to bacterial and fungal infections	• Survival rates: 12 to 36 per cent • Liver transplantation: Excellent outcomes if HBV DNA is undetectable and appropriate antiviral prophylaxis given

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Clinical presentation

Chronic HBV		
Persistence of HBsAg-positivity for six or more months: • frequently a clinically silent disease • often identified incidentally during blood donation screening or during routine health/insurance examinations Physical examination • may reveal no or few signs • peripheral stigmata of chronic liver disease: spider naevi and palmar erythema may be present • signs of portal hypertension: Distended abdominal veins, caput medusa, ascites and splenomegaly may be present depending on the phase of chronic infection • concern for HCC: Weight loss, jaundice and rapidly enlarging, tender, hard nodular liver together with a systolic bruit	Natural history:[33,34,39,40] • there are five different phases of chronic infection **(Figure 1)** o HBeAg-positive chronic HBV infection (immune tolerant) o HBeAg-positive chronic HBV (immune clearance) o HBeAg-negative chronic HBV infection (immune control) o HBeAg-negative chronic HBV (immune escape) o Occult HBV • natural history of HBV is dynamic and complex, and may progress non-linearly through the five different phases o not every person with chronic HBV will evolve through all the phases o some persons will be in the "gray zone" where their ALT and HBV DNA levels fall into different phases[34] o longitudinal follow up of ALT and HBV DNA levels is necessary to establish the phase of chronic infection[34] • HBV DNA levels, ALT levels and HBeAg status are important determinants of the risk of cirrhosis and need for treatment[35, 36]	Outcomes of untreated chronic HBV: • HBsAg clearance (whether spontaneous or after antiviral therapy) reduces the risk of hepatic decompensation and improves survival • approximately 0.5 per cent of persons with HBeAg-negative infection (immune control phase) will spontaneously clear HBsAg annually and develop anti-HBs • cumulative five-year incidence of cirrhosis: eight to 20 per cent • amongst those with cirrhosis: o five-year cumulative risk of hepatic decompensation: 20 per cent o risk of HCC is two to five per cent1,40,41 • HBV DNA more than 2 000 IU/ml, HBeAg status and cirrhosis are key predictors of HCC risk[35-38]. • cumulative five-year survival for compensated cirrhosis is 85 per cent, and for decompensated cirrhosis is 14 to 35 per cent[42]

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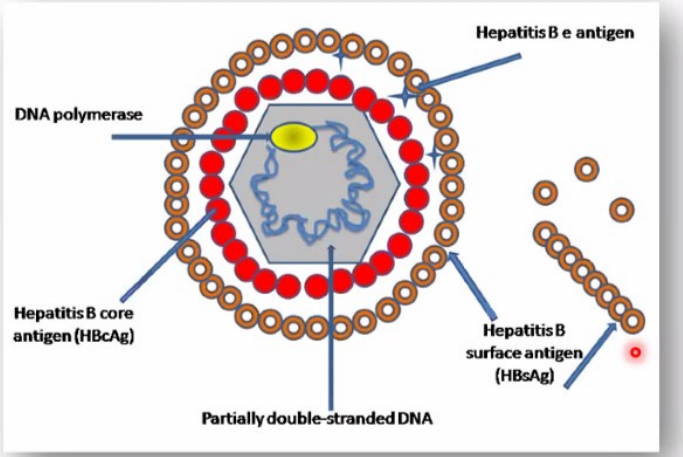
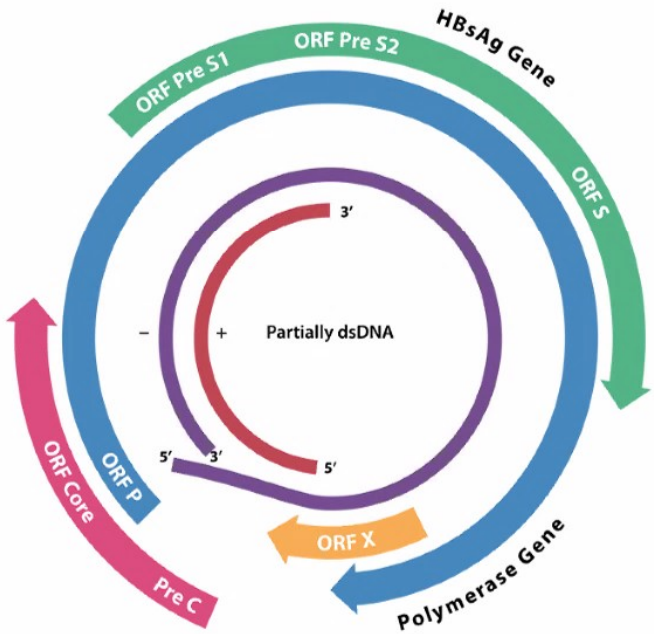
HBV diagnosis

	Direct marker	Indirect marker
Serology	**HBsAg** (HBeAg)	**HBcAb** incl. IgM (HBeAb) **HBsAb**





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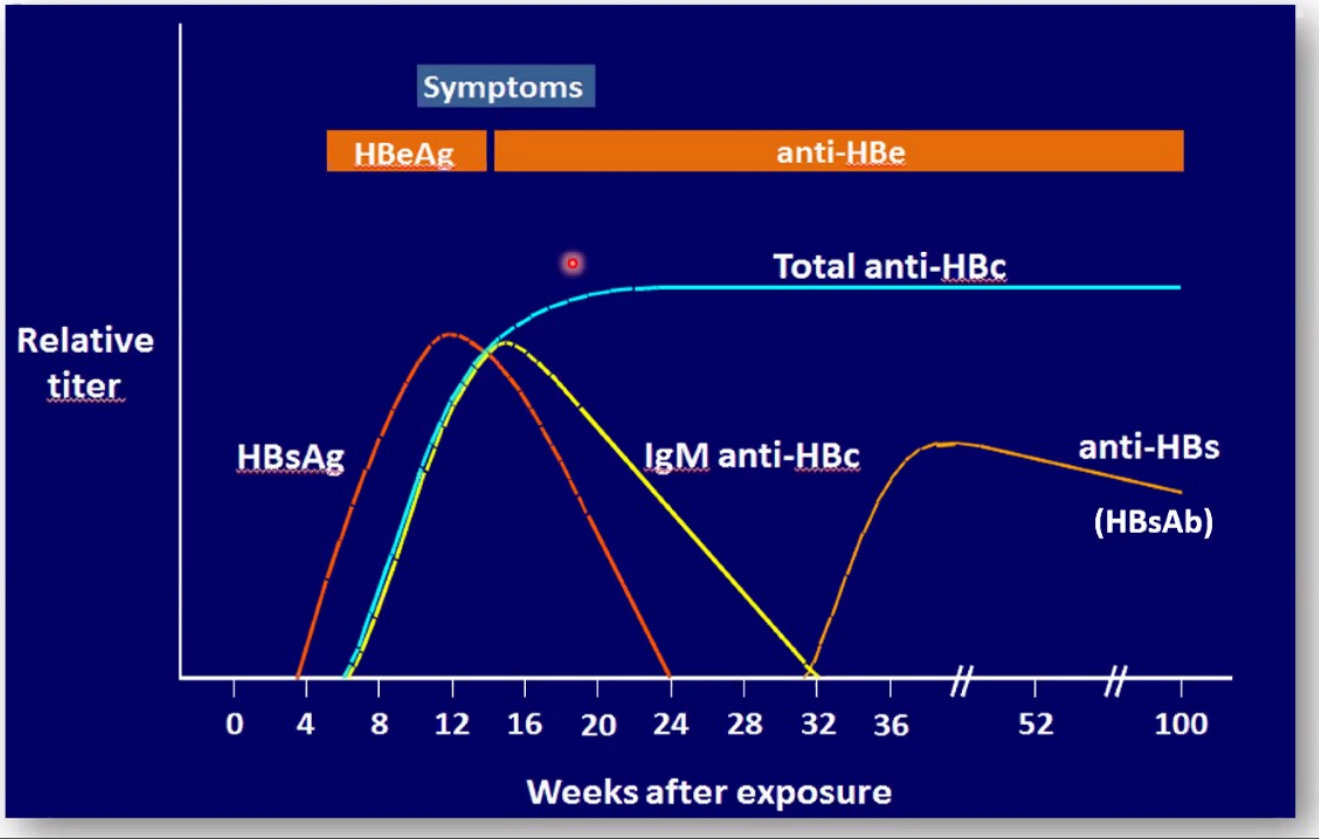
HBV serology – infection which resolves



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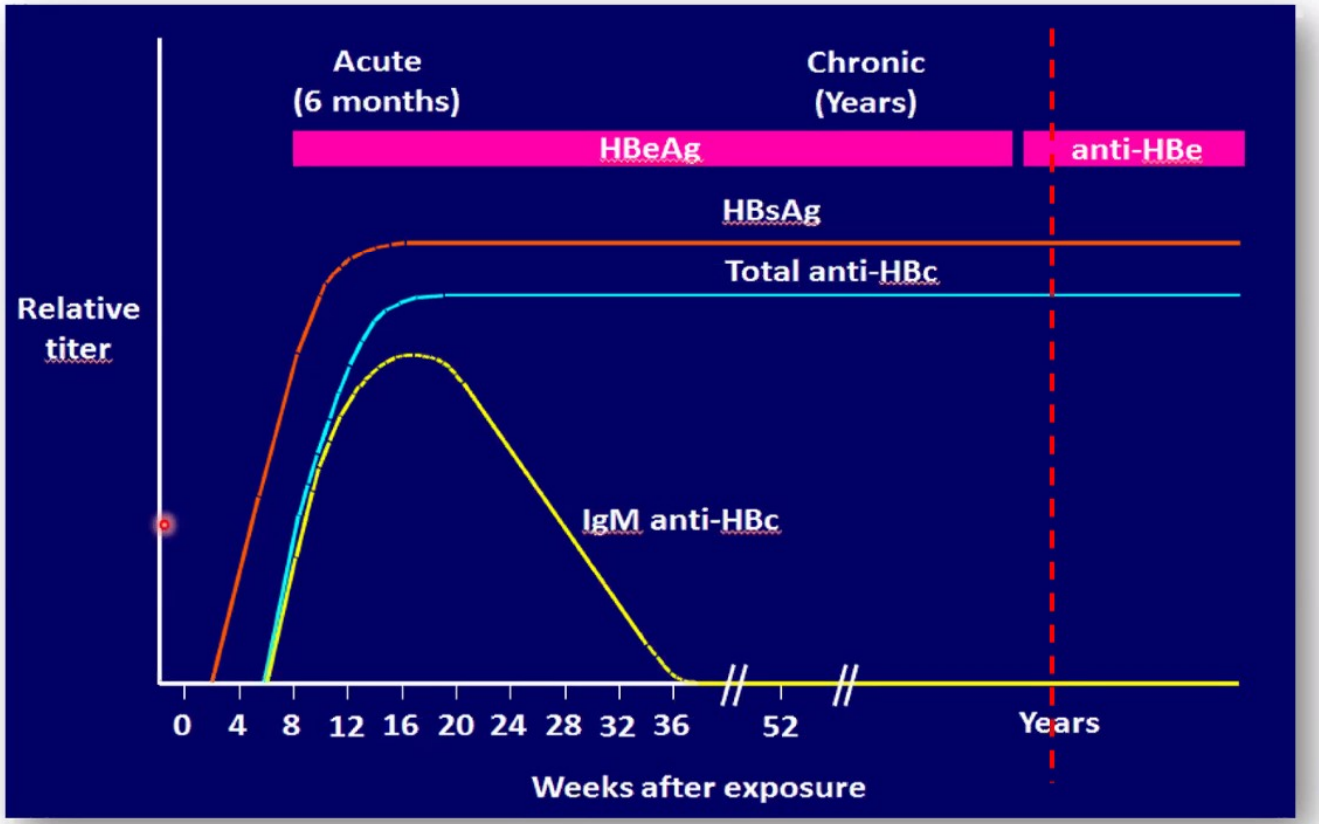
HBV serology – infection which becomes chronic



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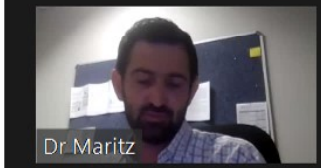
Phases of a chronic infection

- The **immune tolerant** phase
  (HBeAg+, high DNA, normal ALT/AST)
- The **immune clearance** phase
  (HBeAg+, lower DNA, ALT/AST up)
- The inactive HBV carrier or latency state (**immune control** phase)
  (HBeAb+, low to no DNA, normal ALT/AST)
- HBeAg-negative chronic hepatitis B (**immune escape**)
  (HBeAb+, fluctuating ALT/AST, fluctuating DNA, ++inflammation)

❖ **Occult HBV infection**
(HBsAb+, HBcAb+, very low DNA)



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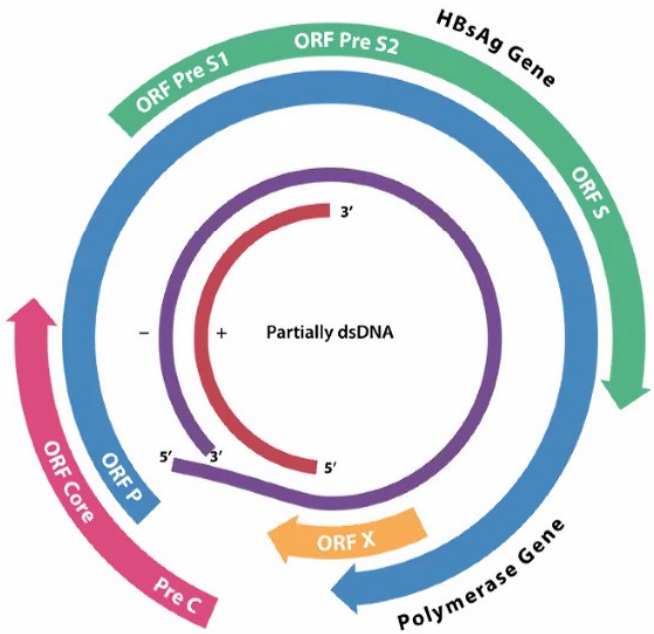
Spearman et al. S Afr Med J 2013;103(5):335-349

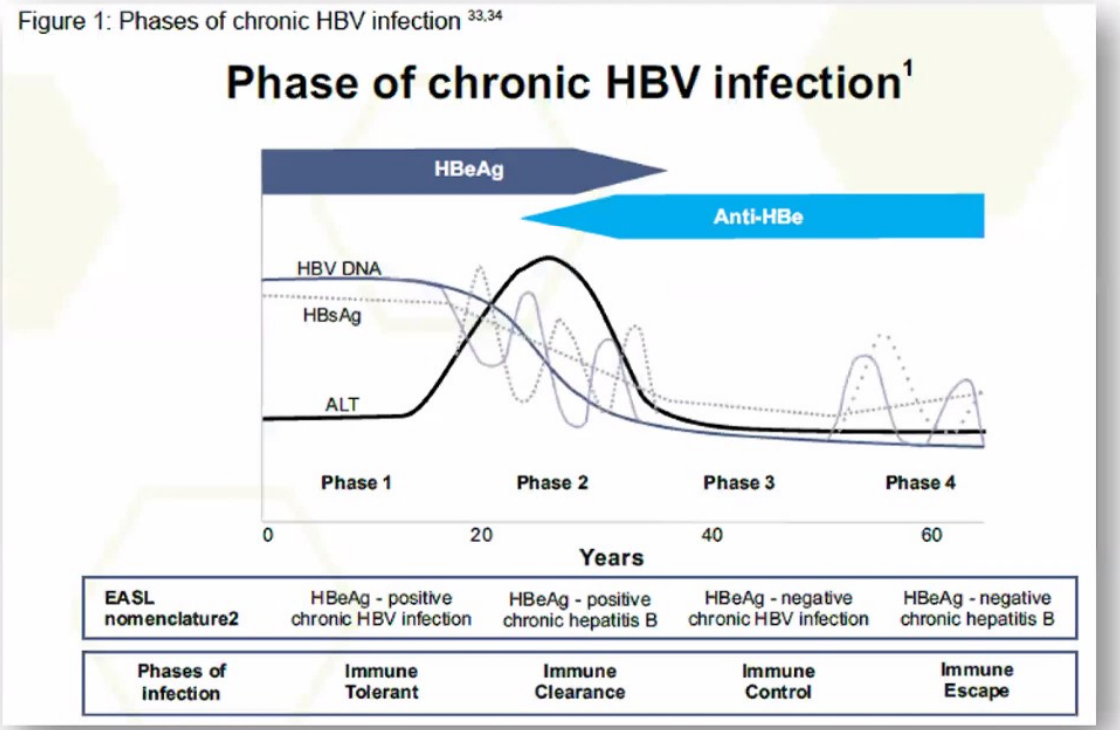
HBV diagnosis

	Direct marker	Indirect marker
Serology	**HBsAg** (HBeAg)	**HBcAb** incl IgM (HBeAb) **HBsAb**
Molecular (PCR)	**HBV DNA**	



Phases of a chronic infection

Figure 1: Phases of chronic HBV infection [33,34]



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Role of DNA testing?

- Can differentiate chronic HBeAg-negative disease (immune escape) from the inactive latency state (e.g. phases of chronic infection)
- Differentiates between occult hepatitis B and resolved infection
- Changes in HBV DNA levels used to monitor response to therapy
- In patients adherent to therapy, increasing HBV DNA levels indicate the emergence of resistant variants

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Spearman et al. S Afr Med J 2013;103(5):335-349

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HBV management - overview

1. Don’t forget a good history
2. Look for associated diseases
3. Assess the stage (acute/chronic) of hepatitis B infection
4. Assess the severity of liver disease prior to therapy, from clinical examination to liver biopsy and imaging
5. Pharmacotherapy

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Table 7: Assessment of liver disease prior to therapy [33,34,48,49,51-64]

Assessment of liver disease prior to therapy [33,34,48,49,51-64]	
Detailed clinical history and physical examination	• age and disease duration • complications of chronic HBV • assessment of compliance with follow-up visits and medications is important • family history of HBV infection; and complications of cirrhosis and HCC
Assessment of the severity of the liver disease	• full blood count (FBC) and differential count • liver profile: Total bilirubin, conjugated bilirubin, ALT, AST, ALP, GGT - aminotransferase levels (ALT and AST) may fluctuate over time - single ALT and AST measurements do not indicate disease activity - ALT levels usually higher than AST, but with disease progression to cirrhosis, AST/ALT ratio ratio may be reversed, but less than two • serum albumin and INR to assess synthetic function • serum creatinine
Look for other co-factors that accelerate fibrosis	• viral co-infection: HCV, HDV, HIV • non-alcoholic fatty liver disease and alcohol-related liver disease • iron overload and drug/toxin-induced liver injury
Serological assessment	• HBsAg, HBeAg and anti-HBe ± IgM anti-HBc (low positive with a flare) • IgG anti-HBc (if assessing for occult HBV or previous cleared infection) • Anti-HAV IgG to assess need for HAV immunisation • HIV status
Virological assessment	• serum HBV DNA quantification • HBV genotype is useful when deciding on potential efficacy of Interferon Rx • precore and basal core promoter mutations help to predict risk of HCC • previous exposure to Lamivudine and concerns re resistance: YMDD mutations can be measured
Alpha fetoprotein	• Alpha fetoprotein in the setting of HBV-associated multifocal HCC with a rapid doubling time, remains an important screening and diagnostic tool for HCC in South Africa • may be elevated in a hepatitis flare
Ultrasound of the liver and dopplers	• assessment of liver size, contour, echogenicity and presence of focal lesions • assessment of bilary system • assessment of portal vein flow, thrombosis, splenomegaly and splenic varices
Non-invasive tests (NITs) to assess stage of liver disease [54,55] NIT results may be impacted by intercurrent diseases that may falsely increase or decrease the scores:[54,55]	• blood and serum markers for fibrosis (APRI and FIB4) can be measured, or transient elastography (Fibroscan) can be performed to rule out advanced fibrosis and cirrhosis • NITs are validated in adults with chronic hepatitis B (CHB), but not validated to assess all stages of fibrosis/cirrhosis

Assessment of liver disease prior to therapy [33,34,48,49,51-64]	
• heavy alcohol intake (AST elevation from alcoholic hepatitis) • use of drugs and traditional herbal medicines may increase ALT and AST • malaria or HIV (may decrease platelet count) • hepatitis flares or acute hepatitis, congestive heart failure or a recent meal may increase liver stiffness (fibroscan) • NITs have good diagnostic accuracy for excluding advanced fibrosis and cirrhosis Use alongside clinical criteria and other laboratory criteria (abnormal ALT and ongoing HBV replication to identify those in need of treatment. • APRI is WHO preferred NIT to assess fibrosis[54] Online calculator for APRI: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri Online calculator for FIB4: https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4	**a) blood/serum-based tests** APRI =(AST/ULN) x 100) / platelet count (109/L) • validated for the diagnosis of both significant fibrosis ≥F2 and cirrhosis (F4) • Single high cut-off >2 for identifying adults with cirrhosis (F4) and in need of antiviral therapy • adults with an APRI score of >2 o detects only one third of persons with cirrhosis **b) transient elastography measures liver stiffness[65]** • Fibroscan (range is between 0 and 75 kPa) • Single cut-off value: Significant fibrosis (≥ F2) >7- 8.5 kPa and Cirrhosis (F4) >11-14 kPa • Mean cut-off of 12.5 kPa to diagnose cirrhosis Sensitivity is improved when combined with non-invasive biomarker scores
Liver biopsy	• a liver biopsy is only required if considering Pegylated Interferon therapy or if assessing the role of other co-factors e.g. non-alcoholic fatty liver disease, alcohol, drugs/toxins and iron overload. These patients should be referred to tertiary level care
Endoscopy	• to assess for varices in cirrhotic individuals

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HBV management - overview

- **Goals of therapy:**
  - Sustained HBsAg loss and DNA suppression
  - Prevent long-term complications (ALT suppression, low DNA and HBeAg loss)
  - Prevent decompensation or reactivation

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Pharmacotherapy options

PEG-IFN:

Usually a 48 week course with stringent monitoring

Factors favouring PEG-IFN as initial therapy:

- Young, high ALT, active necrosis, genotype A

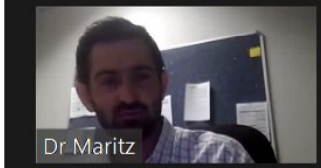
Contraindications:

- Decompensated cirrhosis or fulminant HBV
- Pregnancy
- Significant cardiopulmonary disease
- Uncontrolled seizures, psychiatric disease
- Active autoimmune disease
- Chemotherapy

Spearman et al. S Afr Med J 2013;103(5):335-349

Table 7. Key points in monitoring interferon-based therapy

Time point	Key points
During treatment	
Every 4 weeks	• FBC, differential, INR • Liver profile
Every 12 weeks	• TSH • HBV DNA levels
Every 24 weeks	• HBeAg/anti-HBe (if initially HBeAg positive)
Post-treatment	
Every 12 weeks during the first 24 weeks, then 6 - 12-monthly	• FBC, Differential • Liver profile • TSH • HBV DNA levels • HBeAg/anti-HBe (if initially HBeAg positive) • HBsAg 6-monthly after HBe seroconversion, if HBV DNA undetectable



Pharmacotherapy options

NUC therapy:

Often lifelong, occasionally finite

Options include 3TC, TDF, TAF, Entecavir

Factors favouring NUC as initial therapy:

- Patient demographics: older patients
- Ability to commit to potentially lifelong therapy
- HIV co-infection
- Contraindications to interferon-based therapy
- HBV genotype does not influence response to NUCs

Table 8. Key points in monitoring NUC therapy

Time point	Key points
Weeks 1 and 4	• Liver profile, serum creatinine and amylase • FBC, differential, INR
Every 12 weeks	• Liver profile • Serum creatinine (if receiving tenofovir or entecavir)
Every 12 - 24 weeks	• HBV DNA levels
Every 24 weeks	• HBeAg/anti-HBe (if initially HBeAg positive)
Every 6 - 12 months	• HBsAg in HBeAg-positive patients after anti-HBe seroconversion • HBsAg in HBeAg-negative patients with persistently undetectable HBV DNA

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Spearman et al. S Afr Med J 2013;103(5):335-349

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HBV management – acute HBV

1. Treatment is largely supportive
   - ~95% will resolve spontaneously
   - IPC is important
2. NUC therapy is not routinely indicated
   - But used in cases of very severe disease/liver failure, the elderly, co-infected and immunosuppressed individuals
3. Duration:
   - 3 – 6 months after seroconversion to HBsAb
   - 12 months after HBeAb seroconversion without HBsAg loss
   - Indefinitely if the patient undergoes liver transplantation

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HBV management – chronic HBV

Who should definitely be treated?

- Acute liver failure
- Compensated or decompensated cirrhosis
- Patients on immunosuppressive therapy
- Patients in the immune clearance phase or immune escape phase
- Potentially: HBeAg-positive chronic infection with significant fibrosis and where DNA > log 6 IU/ml

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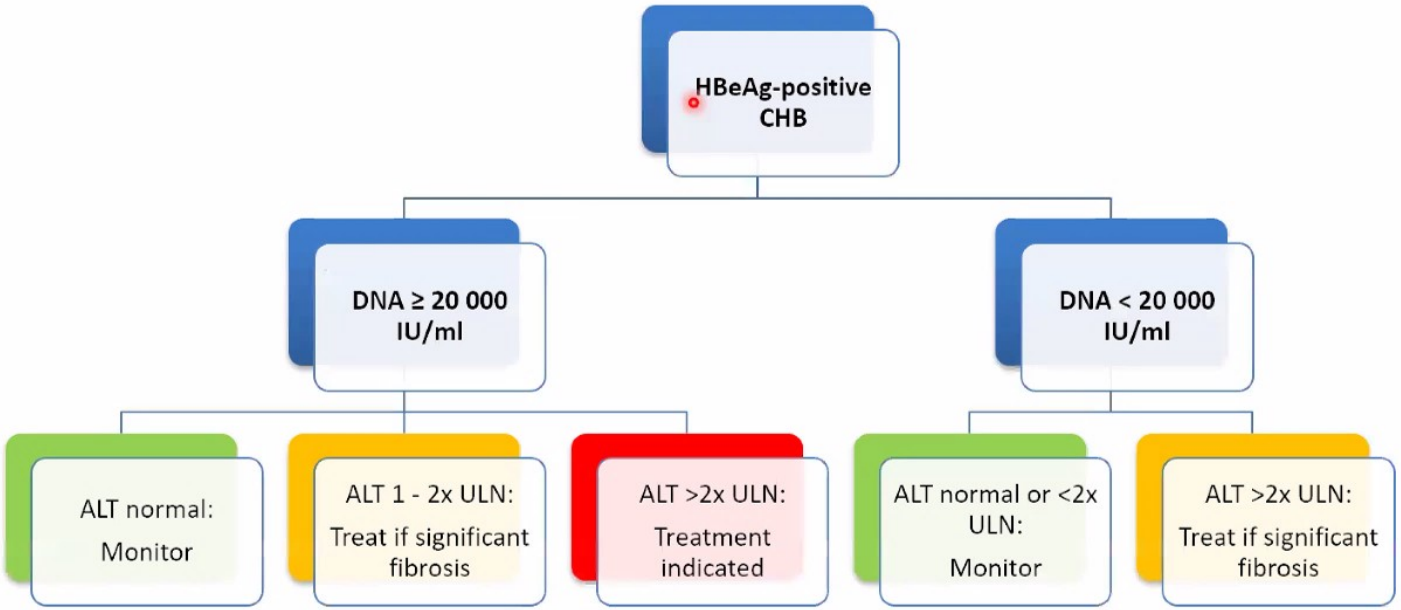
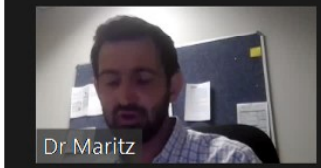
HBV management – chronic HBV





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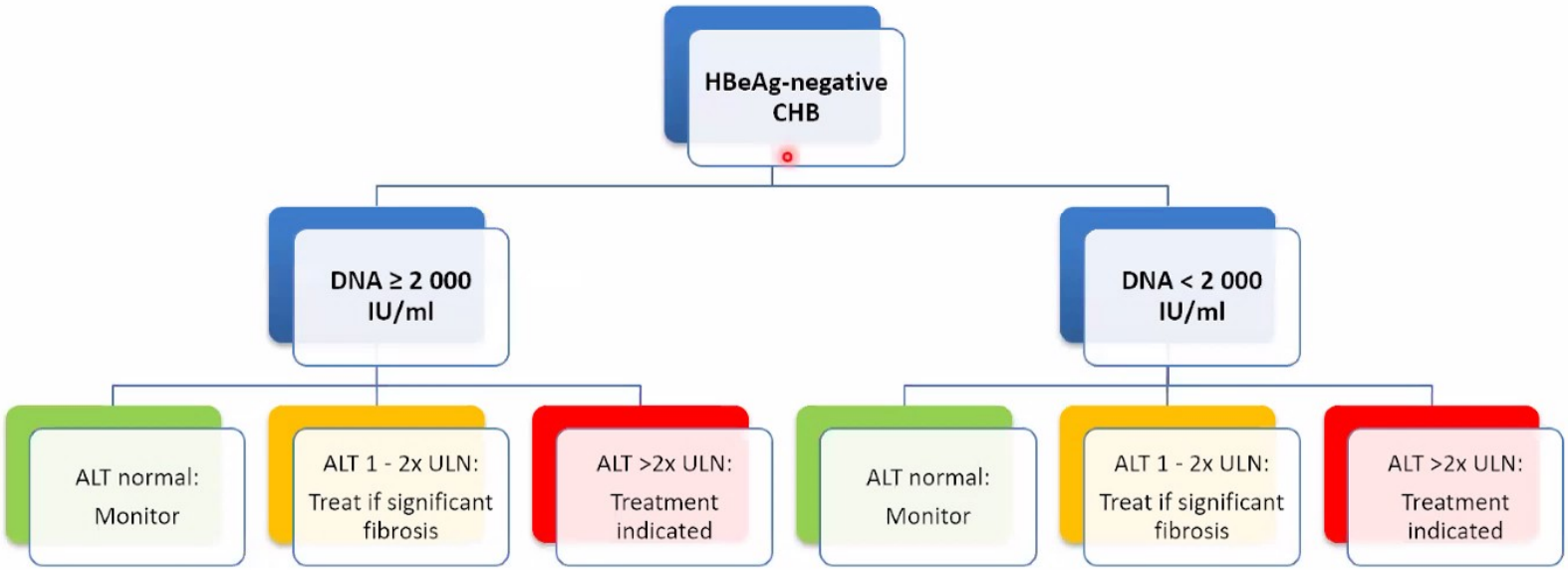
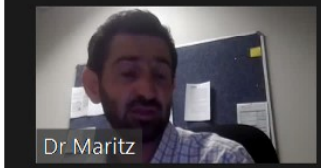
HBV management – chronic HBV





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HBV pharmacotherapy

Special considerations:

1. Indications for therapy differ with immunesuppressive therapies, as do duration of therapy
2. Combination NUC therapy can be considered in special scenarios
3. Monitoring schedules and intervals are not fixed – individualise to the patient's response
4. Special populations with different protocols include:
   - HCWs
   - Pregnancy
   - Dialysis/renal transplant patients
   - Children
   - Co-infections
   - Extrahepatic disease
   - Liver transplant patients

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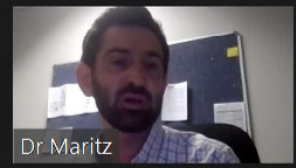
Take home messages

1. South Africa has a "**silent" HBV epidemic** - consider HBV when patients present with extrahepatic complications, and also screen proactively
2. **Serology** is the starting point for diagnosis
3. Treatment decisions can become complex – **refer** when appropriate
4. If you do decide to manage patients with chronic viral hepatitis, **stringent monitoring** per protocol is key
5. Do not forget about screening for or **vaccinating** against other hepatotropic viruses to prevent further liver damage



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