CLINTON HEALTH ACCESS INITIATIVE

HIV/HBV Co-Infection

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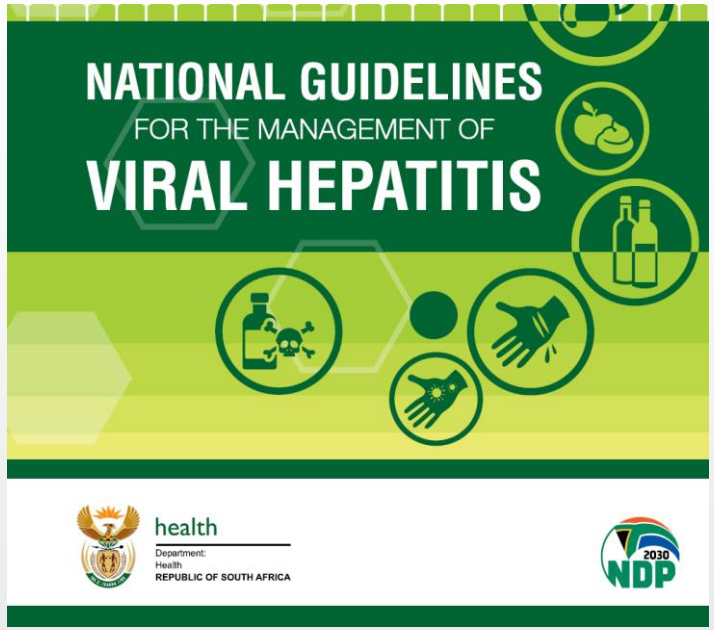
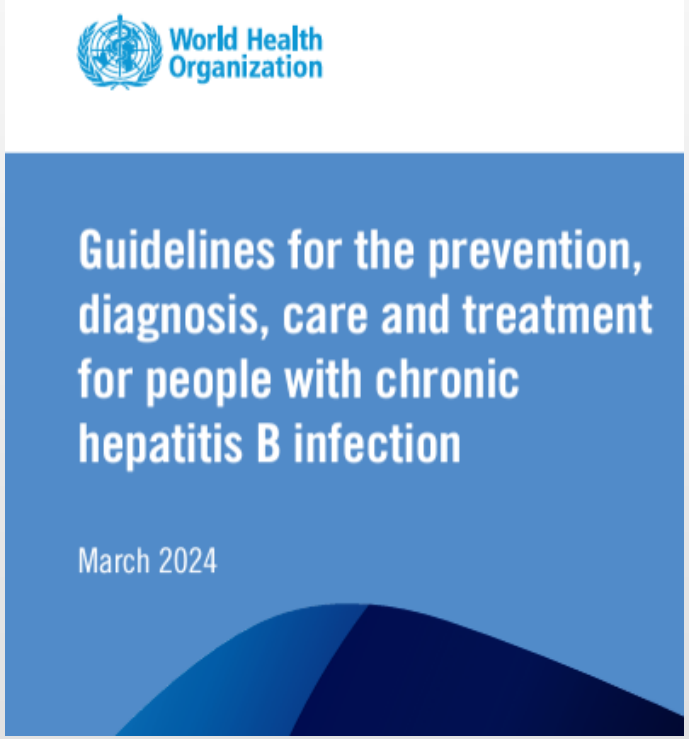
09th May 2024

Please note

This talk is based on

- RSA Hepatitis guidelines,
- RSA NDoH information
- 2024 WHO Hep B guidelines, and
- Published literature.





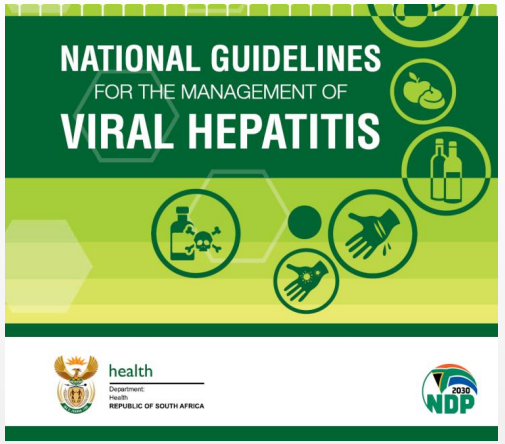
The talk mainly focuses on:

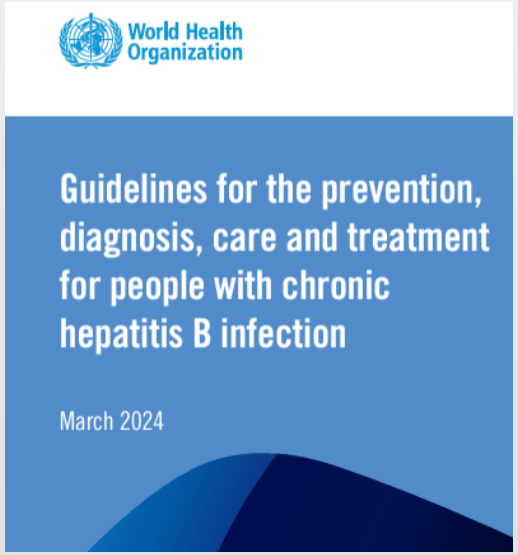
- Laboratory diagnosis of HBV (virology)
- Antiviral management.

Poll 1

Scary stuff in numbers

- Globally, ~2 billion people have been infected with HBV at some point in their lives.
- ~ 300 million people have chronic HBV.
- ~ 1.2 million new infections each year.
- ~ 1 million people die of HBV-related complications annually.
- Only 13% of the infected people are aware of their infection
- **Only 3% of people with chronic HBV infection receive treatment**
- HBV is 100x more infectious than HIV





SA NDoH. National Guidelines for the Management of Viral Hepatitis. 2019
WHO. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. 2024

Why HIV/HBV co-infection

HIV co-infection promotes:

- Increased HBV replication
- Higher rates of HBV reactivation
- Acute liver failure
- Increased rates of occult HBV
- Higher rates of chronicity
- Accelerated progression to fibrosis and cirrhosis
- HCC occurs at a younger age and is more aggressive
- Increased risk of ART hepatotoxicity
- ART- related immune reconstitution hepatitis
- Higher liver-related mortality
- Reduced treatment response compared with people without HIV coinfection

Previous challenges included:

- Cross-resistance between HIV and HBV drugs
- Increased liver injury due to direct hepatoxicity

However,

- improved access to ART that are active against HBV has considerably improved the outcome in recent years.

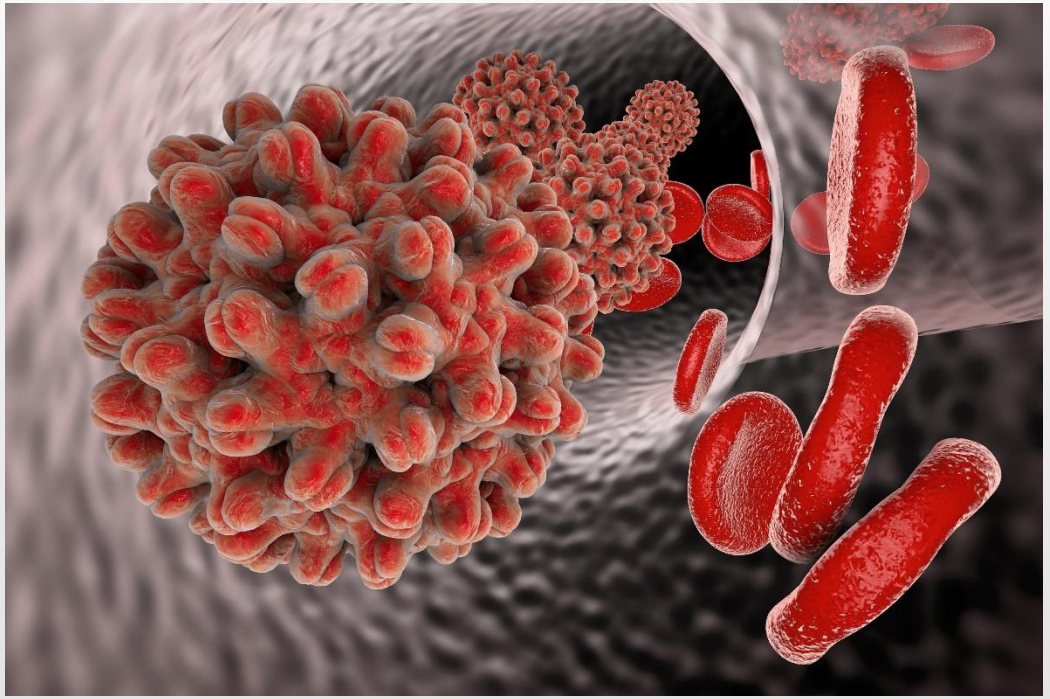
Hence,

- We need to diagnose and treat HIV/HBV co-infection early, and optimally.

Why HIV/HBV co-infection

Both:

- Are endemic in South Africa
- Are transmitted via bodily fluid
- Integrate into host DNA
- Cannot be eradicated… at this stage
- Replicate through reverse transcription
- Are treated with ART



Back to basics - HBV

- Hepadnaviridae
- Partially dsDNA virus
- 10 genotypes (A-J)
  - Genotype A predominates in RSA
  - Sub-genotype A1 makes 97% of infections.
  - Predisposes to chronicity and risk of HCC
- Highly infectious
- Infects hepatocytes
- Reverse transcription replication step
- cccDNA permanently remains in the host nucleus.

Routes of transmission:

- Horizontal
  - Sharing of personal items
    - Toothbrush/ hair clippers/ etc
  - Traditional carification
  - Female genital mutilation
- Perinatal
- Sexual
- Percutaneous
  - Needle stick injury
  - Injectable drug use

Clinical manifestation

Acute HBV

Presentation depends on age of acquisition

- Asymptomatic in 70% if infected at birth or early childhood
- Varying symptoms in 30%
- < 1% may progress to fulminant hepatitis

- Acute HBV infection in adolescents and adults is usually symptomatic, has various phases and is usually associated with full clinical recovery.

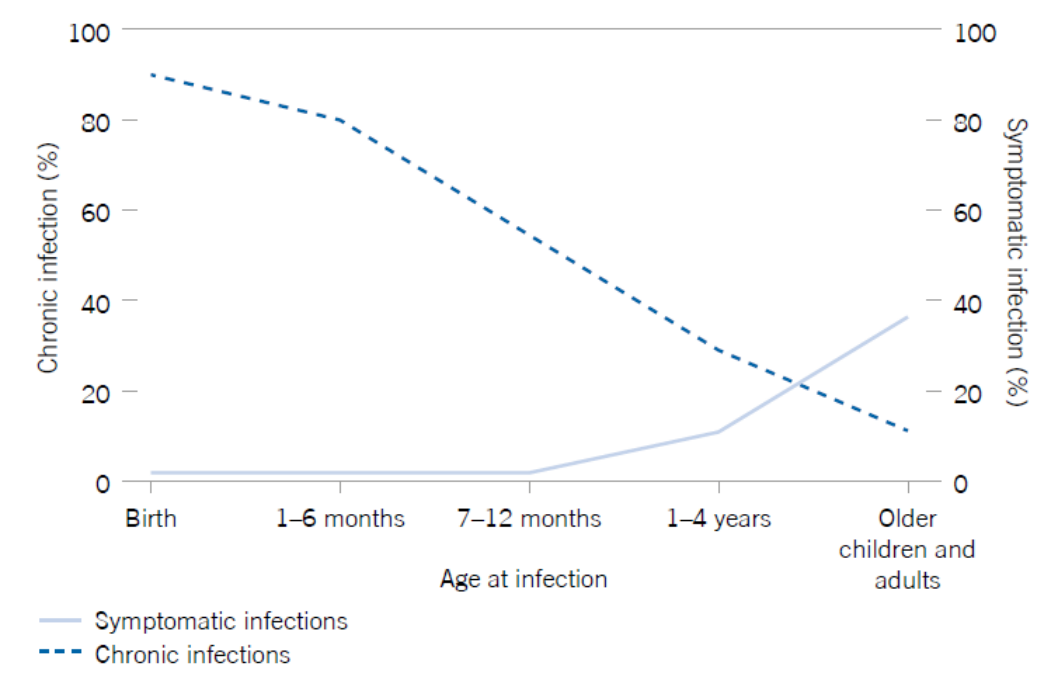
Acute HBV infection			
Early prodromal phase	**Preicteric phase**	**Icteric phase**	**Convalescent phase**
In symptomatic cases: The illness may be heralded by a serum sickness-like syndrome which precedes jaundice by 14 to 21 days and disappears with the onset of jaundice: • fever • urticaria • arthralgia 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.

Chronicity

Chronic HBV infection is defined as persistence of HBsAg positivity for 6 or more months.

The risk of chronicity is dependent on age of acute infection:

- 70 – 95% of infants exposed perinatally
- 25 - 50% of children aged between 1 and 5 years
- 6 - 10% for 5 to 20 years
- 1 - 3 % for adults older than 20 years



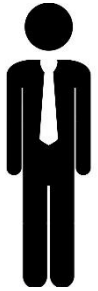
Complications:

Fibrosis/ cirrhosis/ hepatocellular carcinoma.

Extra-hepatic complications:

Vasculitis, polyarteritis nodosa, glomerulonephritis, purpura, arthralgias and peripheral neuropathy

Case



44-yr old male

HIV-positive on ART (TDF/FTC/EFV)

for two years

VL <50 copies/mL

CD4+ count 350 cells/µL

With the following HBV serological markers:

- HBsAg positive
- HBsAb negative
- HBcAb positive

How do you interpret the HBV serology?

- individually, and
- In combination

Poll 2-4

HBV serological markers

HBsAg	• screening marker of infection • first serological marker to appear • may be absent during the window phase of acute infection and in fulminant hepatitis • surrogate marker for transcriptionally active cccDNA • infection is considered chronic if HBsAg persists for more than six months
HBeAg	• indicates active replication of virus • absent or low in pre-core or basal core promoter mutations
anti-HBc total (HBcAb total)	• includes both IgG and IgM HB core antibody
IgM anti-HBc	• marker of acute infection or reactivation • strongly positive in acute infection and possible low positivity in HBV reactivation or flare [50]
anti-HBs (HBsAb)	• recovery and/or immunity to HBV • detectable after immunity is conferred by HBV immunisation
anti-HBe (HBeAb)	• HBeAg to anti-HBe seroconversion and usually indicates that the virus is no longer replicating • also present in HBeAg-negative chronic HBV with active replication due to precore or basal core promotor mutants

HBV serological markers

HBsAg	HBsAb	HBcAb	HBeAg	HBeAb	HBcIgM	Comment
-	-	-	-	-	-	
-	+	-	-	-	-	
-	+	+	-	-	-	
+	-	+	-	+	+/-	
+	-	+	+	-	+/-	
-	-	+	-	-	-	

HBV serological markers

HBsAg	HBsAb	HBcAb	HBeAg	HBeAb	HBcIgM	Comment
-	-	-	-	-	-	Susceptible
-	+	-	-	-	-	
-	+	+	-	-	-	
+	-	+	-	+	+/-	
+	-	+	+	-	+/-	
-	-	+	-	-	-	

HBV serological markers

HBsAg	HBsAb	HBcAb	HBeAg	HBeAb	HBcIgM	Comment
-	-	-	-	-	-	Susceptible
-	+	-	-	-	-	Immunized
-	+	+	-	-	-	
+	-	+	-	+	+/-	
+	-	+	+	-	+/-	
-	-	+	-	-	-	

HBV serological markers

HBsAg	HBsAb	HBcAb	HBeAg	HBeAb	HBcIgM	Comment
-	-	-	-	-	-	Susceptible
-	+	-	-	-	-	Immunized
-	+	+	-	-	-	Clearance following HBV exposure
+	-	+	-	+	+/-	
+	-	+	+	-	+/-	
-	-	+	-	-	-	

HBV serological markers

HBsAg	HBsAb	HBcAb	HBeAg	HBeAb	HBcIgM	Comment
-	-	-	-	-	-	Susceptible
-	+	-	-	-	-	Immunized
-	+	+	-	-	-	Clearance following HBV exposure
+	-	+	-	+	+/-	Current infection – less infectious
+	-	+	+	-	+/-	
-	-	+	-	-	-	

HBV serological markers

HBsAg	HBsAb	HBcAb	HBeAg	HBeAb	HBcIgM	Comment
-	-	-	-	-	-	Susceptible
-	+	-	-	-	-	Immunized
-	+	+	-	-	-	Clearance following HBV exposure
+	-	+	-	+	+/-	Current infection – less infectious
+	-	+	+	-	+/-	Actively replicating and highly infectious
-	-	+	-	-	-	

HBV serological markers

HBsAg	HBsAb	HBcAb	HBeAg	HBeAb	HBcIgM	Comment
-	-	-	-	-	-	Susceptible
-	+	-	-	-	-	Immunized
-	+	+	-	-	-	Clearance following HBV exposure
+	-	+	-	+	+/-	Current infection – less infectious
+	-	+	+	-	+/-	Actively replicating and highly infectious
-	-	+	-	-	-	**Few possibilities:** - Occult HBV infection - Very old HBV infection - Very recent HBV infection - False positive

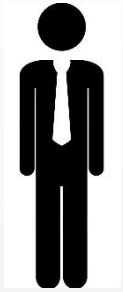
Role of HBV viral load testing

- Diagnosis of occult HBV infection
  - HBsAg negative
  - HBsAb negative
  - HBcAb positive
  - HBV VL <200
- HBV VL levels often correlate with disease progression
- Used to monitor response to therapy
  - If VL increases, and the patient is:
    - On TAF or TDF = consider non-adherence
    - Not on TAF or TDF, and adherent = emergence of resistance

- There are different phases of chronic HBV
  - HBV VL test can differentiate between some phases.
  - Not for this webinar.
- HBV VL tests should be done at:
  - Baseline
  - Week 12, and then
  - Every six to 12 months

Poll 5

Back to our case



44-yr old HIV positive male

on TDF/FTC/EFV

for two years

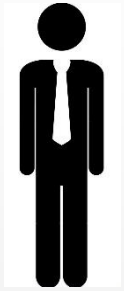
VL <50 copies/mL

CD4+ count 350 cells/µL

HBsAg+

Would you change his treatment?

Back to our case



44-yr old male

HIV-positive on TDF/FTC/EFV

for two years

VL <50 copies/mL

CD4+ count 350 cells/µL

HBsAg+

Would you change his treatment?

Yes.

The 2023 ART Guidelines require patients to be switched to an Optimized ART Regimen… DTG-based regimen.

TLD1 would be the right regimen in this case.

…provided there is no renal impairment.

Therapies with anti-HBV activities

- Tenofovir Disoproxil Fumarate
  - Nucleotide analogue
- Tenofovir Alafenamide
  - Nucleotide analogue
- Lamivudine
  - Nucleoside analogue
- Emtricitabine
  - Nucleoside analogue
- Entecavir
  - Nucleoside analogue
- Adefovir
  - Nucleotide analogue
- Telbivudine
  - Nucleoside analogue
- Peg-INF – **X**

2023 ART Guidelines

- **If a patient is still on TDF/FTC/EFV…**
- **They need to switch to a DTG-containing regimen**

Review the most recent routine VL done in the last 12 months:

If the VL is < 50 c/mL

↓

Switch to TLD 1 same day

If the VL is **> 50 c/mL**

↓

Also switch to TLD 2 same day

↓

ABCDE assessment
Intervene (root cause)
Repeat VL in 3 months

Either way, the patient should be on TLD

Managing HBV in HIV co-infection - TLD

Always include two HBV-active drugs in ART regimen for HIV/HBV co-infection

- There is a risk of HBV drug resistance developing if 3TC or FTC are used without TDF
  - risk of resistance is low with TDF alone without 3TC or FTC.

- There are clinical consequences to the development of HBV drug resistance
  - Hepatitis flare, which may lead to progression of disease.

- Entecavir has weak activity against HIV
  - If used for HBV treatment without ART in patients with co-infection, may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC.

Poll 6

Goal of HBV therapy

Note:

- HBV infection **cannot** be eradicated completely with current available therapies because of the persistence of cccDNA in the hepatocyte nucleus.
- A virological cure, defined as “viral eradication with elimination of cccDNA” is not yet possible.

- At present, the ideal endpoint of treatment is a functional immunological cure with sustained HBV DNA suppression and sustained HBsAg loss, with/without seroconversion to HBsAb.
- To prevent long term complications
  - Cirrhosis/ liver failure/ HCC
- To prevent HBV reactivation
- Dual viral suppression in HIV/HBV co-infection

HBsAg	Negative
HBsAb	Positive
HBcAb	Positive
HBV VL	LDL

Acute HBV

- Management is largely supportive.
- > 95% of immunocompetent adolescents and adults will spontaneously recover, clear HBV and seroconvert to HBsAb.
- The use of nucleoside/tide analogues are not routinely advised.
- Rapid suppression of HBV DNA replication
- impairs the individual's cellular immune cytotoxic response directed against the infected hepatocytes and promotes chronic infection.
- **NB:** For HIV/HBV co-infection, ART initiation is recommended

NUC therapy currently ONLY recommended in acute infection if:	
• Severe disease (rising INR more than two and associated encephalopathy). • Acute liver failure: - patients can stabilise and NUCs prevent re-infection of the liver graft • The elderly and immunosuppressed individuals. • HAV, HCV or HDV co-infection.	• Lamivudine should be used in unstable patients at risk of renal impairment: - rapidly suppresses HBV viral load - viral resistance does not develop with short term LAM use and dosage can easily be adjusted according to renal function

Chronic HBV infection

- Nucleos(t)ide analogues
  - TDF/ TAF/3TC/ FTC/ Entecavir
  - Require dose adjustment in renal impairment
    - While Abacavir is recommended in renal impairment, it does not have anti-HBV activities.

  - Long-term, potentially indefinite treatment.
  - Aim for on-treatment viral suppression
  - Maintained through continuous antiviral therapy.
  - Suppression of replication to undetectable levels to avoid resistance.

Treatment with Nucleos(t)ide analogues has been shown to:

- delay the progression of cirrhosis
- reduce the incidence of HCC, and
- improve long-term survival.

Treatment challenges:

- Daily dose for life
- Non-adherence
- Renal toxicity
- Drug resistance (although rare)

What about those with renal impairment?

- While Abacavir is recommended in renal impairment, it does not have anti-HBV activities.
- TDF dose adjustments are required in those with significant CKD
- Monitor creatinine clearance to adjust TDF dose

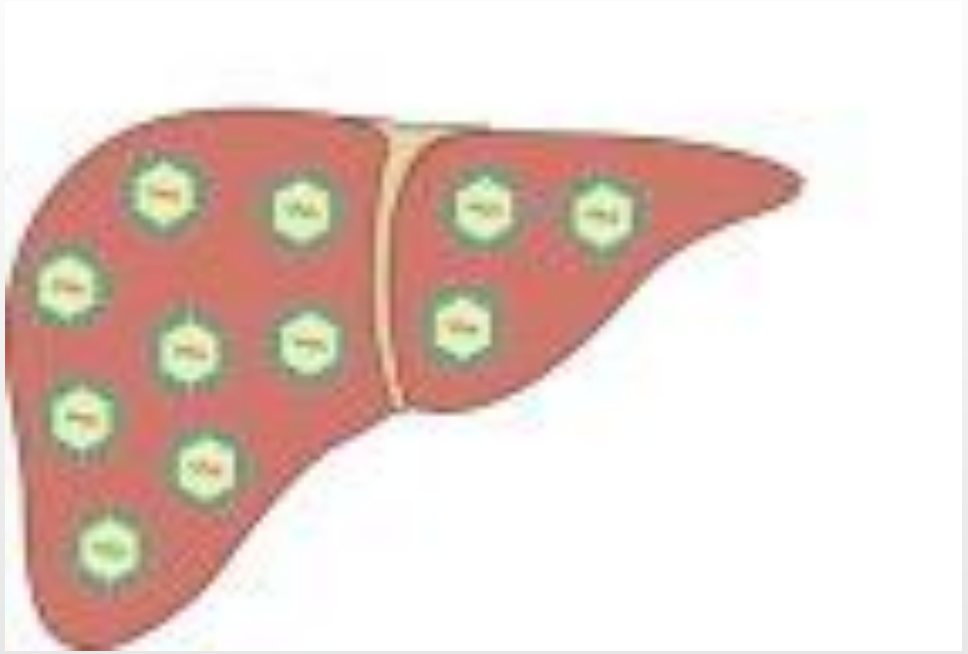
CrCl	TDF dosing frequency
>50	Every 24 hrs
30-49	Every 48 hrs
10-29	Every 72-96 hrs (twice weekly)
<10	Not recommended
Hemodialysis	Every 7 days following completion of hemodialysis session

Mazzaro C, Adinolfi LE, Pozzato G, et al. Extrahepatic Manifestations of Chronic HBV Infection and the Role of Antiviral Therapy. *J Clin Med*. 202

Monitoring of HBV VL

- HBV VL tests done at:
  - Baseline
  - Week 12, and then
  - Every six to 12 months

- If VL increases, and the patient is:
  - On TAF or TDF = consider non-adherence
  - Not on TAF or TDF, and adherent = ??emergence of resistance
    - Consider resistance testing
    - Discuss with a friend.



Poll 7

HBV prevention

- HBV is an entirely vaccine-preventable disease.
- Hep B vaccine is a recombinant vaccine
- Contains purified HBsAg
- RSA EPI (2024)
  - 4x HBV vaccine doses at 6W, 10W, 14W & 18M
  - Birth dose for neonates whose mothers test HBsAg+ during pregnancy (or HBeAg+).
  - WHO recommends birth dose for all newborns
  - All healthcare staff are eligible – including support staff.
- ??Hep B immunoglobulins (??availability)

- Screen all pregnant women for HBsAg
- Avoidance of contact with infected blood and blood products
- Rational use of safe medical injections
- Consistent condom and lubricant use
- Avoid sharing needles, toothbrushes, razors or nail scissors
- Sterile injecting equipment

Knowledge Hub Webinar. Hepatitis B Vaccine - targeted birth dose. 31st October 2023. https://knowledgehub.health.gov.za/system/files/2023-11/KH%20webinar%20Session%202%20Hep%20B%20vaccine%20-%20final.pdf. Accessed 08 May 2024

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What the future holds

Novel therapeutic agents

The most advanced investigational treatments include:

- **Entry inhibitors**
  - Bulevirtide is currently in phase III clinical trials.
  - It inhibits HBV infection by competing with HBV particles for the binding site.
- **Capsid assembly modulators**
  - Inhibit HBV replication by targeting pol-pgRNA encapsidation and blocking early viral life cycle stages, including cccDNA formation.
  - Currently undergoing phase II clinical trial.
- **Immunomodulators:**
  - These include TLR agonists, monoclonal antibodies, checkpoint inhibitors, and therapeutic vaccines.
  - Can enhance the HBV-specific immune response.
- **HBsAg assembly agents**
- **Gene therapy**
  - This is the delivery of functional nucleic acids to specific genetic sites
  - It stalls HBV gene expression through HBV mRNA destabilization/inhibition
- **RNA interference**
  - small interfering RNA (siRNA)
  - used to suppress the post-transcriptional functions of HBV RNA transcripts.
  - Bepirovirsen currently in phase III clinical trials
- **Long-Acting injectables (LAI)**
  - Have potential to simplify regimens and treatment outcomes
  - Preclinical research has been conducted on LAI formulations of emtricitabine, lamivudine, tenofovir, and entecavir

Ogunnaike M, Das S, Raut SS, et al. Chronic Hepatitis B Infection: New Approaches towards Cure. Biomolecules. 2023;13(8):1208. Published 2023 Aug 1. doi:10.3390/biom13081208

Issued: 12 February 2024, London UK

GSK receives US FDA Fast Track designation for bepirovirsen in chronic hepatitis B

- Designation underscores the unmet need for medicines that can achieve functional cure in patients with chronic hepatitis B (CHB)

- Bepirovirsen is a triple action investigational antisense oligonucleotide (ASO), currently being evaluated in phase III clinical trial.
- It is designed to recognise and destroy HBV RNA that can lead to chronic disease, potentially allowing a person's immune system to regain control.
- It inhibits the replication of viral DNA and suppresses the level of HBsAg in the blood.

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Review

https://doi.org/10.3350/cmh.2021.0093
Clinical and Molecular Hepatology 2022;28:17-30

Toward a complete cure for chronic hepatitis B: Novel therapeutic targets for hepatitis B virus

Sun Woong Kim[1,*], Jun Sik Yoon[2,*], Minjong Lee[3], and Yuri Cho[4]

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Thank you!

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