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REVIEW

Demystifying the management of Hepatitis B – the WHO 2024 Guidelines on the management of Hepatitis B

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Globally, an estimated 254 million people are living with Hepatitis B (PLWHB), with the World Health Organization (WHO)Africa region accounting for 63% of new hepatitis B infections (HBV) and where only 18% of newborn children have received the Hepatitis B birth-dose vaccination.[1] In 2022, there were 771 000 new HBV infections and 272 000 deaths in the WHO Africa region due to an entirely preventable and treatable infection. Of the 64.7 million PLWHB in the WHO Africa Region, only 4.2% (2.7 million) had been diagnosed, and 0.2% (150 000) had received treatment.[1]

In South Africa, despite our access to appropriate diagnostics, preventative Hepatitis B vaccines and the full range of effective nucleos(t)ide analogues, we had a 5% HBsAg prevalence with an estimated 2 741 289 chronic HBV infections, 13 339 new infections and 25 564 deaths in 2022. Only 23.1% had been diagnosed, and 0.1% had been treated.[1]

Treatment of Hepatitis B according to International Society Hepatitis B Guidelines has been dependent on understanding the five different phases of the natural history of chronic hepatitis B and assessing three criteria: the degree of necroinflammation (alanine aminotransferase [ALT] levels), HBV replication (HBV DNA concentration), and the stage of the liver disease.[2-4] The decision to initiate therapy based on HBV DNA quantification has been a significant barrier to accessing therapy.

In order to reach the WHO 2030 Viral hepatitis elimination goals of 90% reduction in incidence and 65% reduction in mortality, there needs to be decentralisation and integration of the management of PLWHB at primary care and community level.[5] This will require increased diagnosis and linkage to care, but importantly identifying HBsAg positive pregnant women and preventing mother-to-child transmission of HBV.

The WHO 2024 Guidance on the Management of Hepatitis B aims to simplify the treatment criteria and increase the number of PLWHB who are eligible to access treatment and care.[6]

The updated WHO 2024 HBV Guidelines recommend:

- Four options for meeting treatment eligibility that will capture a much higher proportion (at least 50%) of all HBsAg-positive people versus the previous 8–15% of PLWHB
- New APRI (AST to Platelet Ratio Index) criteria for staging liver disease
- Alternative antiviral regimens for treatment of Hepatitis B
- Expanded access to antiviral prophylaxis for HBsAg positive pregnant women
- The use of point-of-care HBV DNA assays at primary care level
- Reflex Hepatitis D co-infection testing if HBsAg positive

Critical to the decision to initiate antiviral therapy is the importance of assessing the degree of fibrosis. Liver biopsy is no longer needed to assess the need for therapy and is reserved for clinical scenarios where cofactors such as alcohol, drug or toxin-induced liver injury may be contributing to liver injury. Non-invasive tests such as the APRI score (APRI score calculator available on-line) and transient elastography are now recommended to assess for advanced fibrosis and cirrhosis.

The WHO 2015 Hepatitis B Management Guidelines recommended an APRI score of > 2 to diagnose cirrhosis (sensitivity of 35% and specificity of 89%).[7] These criteria detected less than half of those in need of therapy in a large Ethiopian cohort of 1 190 patients with chronic hepatitis B. Of concern, 51.6% of patients who fulfilled the WHO criteria had decompensated cirrhosis.[8] Furthermore, a data meta-analysis by the HEPSANET group of 3 548 chronic hepatitis B patients living in 8 sub-Saharan African countries revealed that the WHO recommended APRI score for cirrhosis had a sensitivity of only 16.5% (95% credible interval 12.5–20.5). The HEPSANET study identified an optimised APRI rule-in threshold for cirrhosis of > 0.65 for a liver stiffness measurement > 12.2 kPa with sensitivity and specificity of 56.2% (50.5–62.2) and 90.0% (89.0–91.0) respectively; and an optimised rule-out threshold of < 0.36 with sensitivity and specificity of 80.6% (76.1–85.1) and 64.3% (62.8–65.8), respectively.(9) These studies emphasised the need for guidance on treatment initiation criteria to be validated in different regions, and this has been acknowledged in the recent WHO 2024 Guidance on the Management of chronic Hepatitis B.

WHO 2024 Guidelines: four Options for initiating therapy for chronic hepatitis B

These recommendations apply to adults, adolescents (≥ 12 years) and pregnant women.[6]

1. Treat all with significant fibrosis (previously only cirrhosis) based on the revised thresholds of non-invasive tests for staging of liver disease (APRI score > 0.5 or transient

elastography (if available) > 7 KPa), regardless of HBV DNA or ALT levels. This recommendation will capture an estimated 20–25% of all HBsAg-positive people.

2. Treat all with HBV DNA > 2 000 IU/mL (previously > 20 000 IU/mL) and ALT above the upper limit of normal (ULN). This recommendation will capture an estimated 20-35% of all HBsAg-positive people. The ULN for ALT has been defined as < 30 U/L for men and boys and < 19 U/L for women and girls.
3. Treat all with co-infections (HIV, hepatitis D or hepatitis C); family history of liver cancer or cirrhosis; immune suppression (such as long-term steroid use, solid organ or stem cell transplants); comorbidities (such as diabetes or metabolic dysfunction–associated steatotic liver disease); or extrahepatic manifestations (such as glomerulonephritis or vasculitis), regardless of HBV DNA or ALT levels. This recommendation will capture an estimated 5–8% of HBsAg-positive people.
4. If there is no access to HBV DNA quantification, one can treat those with chronic hepatitis B based on persistently abnormal ALT levels alone which is defined as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period. ALT levels fluctuate with chronic hepatitis B and require longitudinal monitoring to determine the trend. This recommendation will capture an estimated 20% of all HBsAg positive people.

Prevention of HBV mother-to-child transmission

Prevention of HBV mother-to-child transmission is essential to break cycles of infection and prevent the long-term complications of cirrhosis and hepatocellular carcinoma, which increase with early childhood acquisition of HBV.[10] All pregnant women should be tested for HIV, syphilis and HBsAg at least once and as early as possible during their pregnancy and should be assessed first for eligibility for long-term HBV treatment for their own health.[11]

Timely administration of Hepatitis B birth dose vaccination within 24 hours of delivery is 90–95% effective in preventing HBV infection and in reducing new infections among children. This risk is further reduced by the addition of Tenofovir prophylaxis in pregnant women with HBV DNA levels > 200 000 IU/ml.[12]

The updated WHO guidelines recommend the introduction of tenofovir prophylaxis from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series (2 or 3 vaccinations according to Expanded Programme of Immunisation schedule). In settings where neither HBV DNA nor HBeAg testing is available, Tenofovir disoproxil fumarate (TDF) prophylaxis is recommended for all HBsAg-positive pregnant women. For women and adolescent girls of childbearing age who are planning additional pregnancies, TDF prophylaxis can also be maintained after delivery and during subsequent pregnancies, according to women's choice.[6]

In South Africa, with the introduction of universal Hepatitis B vaccination in April 1995, the HBsAg prevalence has decreased from 9% to 5%, but further reduction requires implementation of the Hepatitis B birth dose vaccination. In 2022, it was estimated that there were 76 000 HBV-infected children under the age of 5 years with a prevalence of 1.1%.[13] Since 2023, South Africa has recommended screening of pregnant women for HBsAg and has initiated targeted Hepatitis B birth dose vaccination of neonates born to HBsAg positive pregnant women.

In order to break cycles of infection, it is important to screen sexual partners, siblings and other children; and vaccinate unexposed individuals and link to care those who are HBsAg positive.

Recommended treatment for Hepatitis B

TDF or entecavir remain the preferred first-line treatment regimens, but access to Tenofovir monotherapy is often difficult for HBV monoinfected individuals. Combination therapy such as TDF + lamivudine (3TC) or TDF + emtricitabine (FTC) are often more easily accessible through existing antiretroviral drug procurement processes and HIV clinics where these combination therapies are recommended for PrEP.

The updated guidelines now recommend that combination therapy can be used if TDF monotherapy is not available. Tenofovir alafenamide (TAF) is recommended for people with established osteoporosis and/or impaired kidney function.

HBV point-of-care diagnostics

Molecular diagnostics (HBV DNA quantification) are often more expensive than the costs of 1 year of TDF therapy. The success of decentralisation and task-shifting of management of chronic hepatitis B to primary and community level care will depend on the access to affordable and reliable point-of-care diagnostics. WHO prequalified HBsAg point-of-care tests must be available at primary care level to identify and link PLWHB to care.[14] The use of point-of-care HBV DNA nucleic acid testing assays is now recommended as an alternative approach to laboratory-based HBV DNA testing to assess treatment eligibility and to monitor treatment response. Reflex HBV DNA testing in those with a positive HBsAg test result is recommended as an additional strategy to promote linkage to care and treatment and for monitoring of treatment response.[6]

Anti-HDV antibody testing

There are an estimated 1.6 million [95% CI 1.1–2.5] living with hepatitis D-HBV co-infections in the WHO Africa region and these co-infections accelerate the risk of HBV-related cirrhosis and hepatocellular carcinoma.[15-17]

In view of the aggressive natural history of hepatitis D-HBV co-infection, the WHO 2024 HBV Guidelines recommends serological testing for anti-HDV antibodies followed by a confirmatory nucleic acid test (NAT) to detect HDV RNA and active viraemia for all individuals who are HBsAg positive. Reflex testing for anti-HDV antibody following a positive HBsAg test result and also for HDV RNA testing (where available) following a positive anti-HDV antibody test result, may be used as an additional strategy to promote diagnosis and linkage to appropriate care.[6]

The challenge in Africa is access to and the cost of Bulevirtide, the recommended treatment for Hepatitis D; and the molecular HDV RNA tests lack sensitivity for the HDV genotypes 5-8 seen in Africa.[15,18]

In South Africa, the prevalence of hepatitis D-HBV co-infections is <1%, so anti-HDV screening can be reserved for people born in HDV-endemic countries, regions and areas; and people receiving HBV treatment with features suggesting HDV infection (such as low HBV DNA with high ALT levels).

Conclusion

The 2024 WHO HBV guidelines demystify the management of chronic hepatitis B and enable decentralisation and task-sharing at a primary and community care level. We have the tools to diagnose, treat and prevent chronic hepatitis B – there is no longer any justifiable reason to delay active implementation of these guidelines and reduce the burden of disease in Africa.

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