Treatment of chronic hepatitis B infection in Nigeria: The need for a paradigm shift

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Abstract

Viral hèpatitis is inflammation of the livèr which is causèd by hepatotropic virusès that primarily infèct the livèr, mainly viral hepatitis A to E. Out of thèse virusès, both the hepatitis B virus (HBV) and hepatitis C virus (HCV) have the tendency to cause chronic infection with the resultant complications which are mainly cirrhosis and cancer of the liver. The current prevalence of HBV infection in Nigeria is 8.1% making Nigeria highly endemic for HBV and among the countries with the greatest burden of the infection globally.

One of the factors driving the increase in HBV prevalence and its related complications in Nigeria is the criteria for commencement of antiviral for HBV infection according to the current guideline for the management of chronic hepatitis B and C by the Society for Gastroenterology and Hepatology in Nigeria (SOGHIN) which only few infected individuals fulfil. This is especially true in places where liver biopsy services or fibroscan are not available to ascertain necroinflammation and/or fibrosis in the liver.

It is obvious that the current guideline for thè management of chronic HBV infèction in Nigeria by SOGHIN is deficient and may not help the country to put an end to hepatitis B infection including its related complications anytime soon. Therefore, this article tries to propose a better alternative guideline of the ***"test and treat"*** strategy for HBV infection in the country.

Traitement de l'infection chronique par l'hépatite B au Nigéria: nécessité d'un changement de paradigme

Resume

L'hépatite virale est une inflammation du foie causée par des virus hépatotropes qui infectent principalement le foie, principalement les hépatites virales A à E. Parmi ces virus, le virus de l'hépatite B (VHB) et le virus de l'hépatite C (VHC) ont tendance à provoquer une infection chronique avec les complications qui en résultent qui sont principalement la cirrhose et le cancer du foie. La prévalence actuelle de l'infection par le VHB au Nigéria est de 8,1 %, ce qui fait du Nigéria un pays hautement endémique du VHB et l'un des pays où le fardeau de l'infection est le plus lourd au monde.

L'un des facteurs à l'origine de l'augmentation de la prévalence du VHB et de ses complications associées au Nigéria est le critère de début du traitement antiviral contre l'infection par le VHB, conformément aux lignes directrices actuelles pour la prise en charge des hépatites chroniques B et C de la Société de gastroentérologie et d'hépatologie du Nigéria (SOGHIN) que seuls quelques individus infectés remplissent. Cela est particulièrement vrai dans les endroits où les services de biopsie hépatique ou de fibroscan ne sont pas disponibles pour vérifier la nécroinflammation et/ou la fibrose du foie.

Il est évident que les lignes directrices actuelles pour la prise en charge de l'infection chronique par le VHB au Nigeria par la SOGHIN sont déficientes et pourraient ne pas aider le pays à mettre fin à l'infection par l'hépatite B, y compris ses complications associées, dans un avenir proche. Par conséquent, cet article tente de proposer une meilleure ligne directrice alternative à la stratégie « tester et traiter » pour l'infection par le VHB dans le pays.

INTRODUCTION

Viral hèpatitis is caused by hepatotropic viruses that primarily infect the liver and are mainly hepatitis A to E viruses. Even though these viruses manifest similarly, their mode of transmission, prevention and treatment differ remarkably (1). Only the hèpatitis B virus (HBV) and hèpatitis C virus (HCV) have the tendency to causè chronic infection with the resultant complications which are mainly cirrhosis and cancer of the liver (2).

Globally, an estimated 240 million peoplè arè carriers of chronic hepatitis B surfacè antigèn (HBsAg), with a wide regional variation between high and low endemicity levels which are >8% and <2% of the population respectively (3). Globally, an estimated 1.4 million dèaths, 7% of hepatocellular carcinoma (HCC) and 54% of liver cirrhosis, are attributed to viral hepatitis annually (1). In Africa, failure to prevent, diagnose and more importantly to treat HBV infection is the major factor driving the rise in cirrhosis and HCC burden (4). The current prevalence of HBV infection in Nigeria is 8.1% making Nigeria highly endemic for HBV and among the countries with the greatest burden of the infection globally (5).

In spite of being among the top infectious cause of mortality annually (6), the knowledge and awareness of viral hepatitis is reportedly low in Nigeria (7). Consequently, majority of thè estimatèd 20 million Nigèrians living with HBV and HCV arè not diagnosed, therefore their chances of transmission to others unknowingly is higher also increasing their risk of developing severe chronic complications (1).

Another factor driving the increase in HBV prevalence and its related complications globally is the criteria for commencement of antiviral treatment. It was estimated in 2021 that, of the 82 million people living with HBV (PLWHB) in Africa, only 19% meet the WHO 2015 treatment criteria, and only 0.1% of all PLWHB are on treatment (8). In Nigeria, some infected individuals are also unable to meet the treatment criteria according to the current guideline for the management of chronic hepatitis B and C by the Society for Gastroenterology and Hepatology in Nigeria (SOGHIN) (the guideline currently-in-use by gastroenterologist in the country for the management of HBV and HCV infection) (9). According to the guideline, liver biopsy or fibroscan is required to ascertain presence of moderate or severe necroinflammation and/or significant fibrosis in the liver (which is also another criteria for commencement of antiviral treatment in chronic hepatitis B (CHB) infection) whenever there is a discordance between alanine aminotransferase (ALT) and HBV DNA levels. However, liver biopsy services are not widely available even among gastroenterologists in the country and fibroscans are also not widely available or affordable. Therefore, most infected individuals may not be on treatment with attendant complications developing.

This article tries to propose a better alternative guideline for the management of CHB in Nigeria in other to reduce the burden of the disease in the country.

PATHOGENESIS OF HBV INFECTION

Hepatitis B virus is an enveloped, hepatotropic DNA virus belonging to the family of hepadnaviridae. The viral genome is a small (3.2 kb), partially double-stranded, relaxed circular (rc) DNA that encodes for 4 genes which are S, C, X and the P gene (10). After HBV entry into hepatocytes, the viral nucleocapsid gets integrated into the nucleus of the hepatocyte where the viral rcDNA is transformed into a covalently closed circular DNA (cccDNA), which is enveloped by both histone and non-histone proteins to form cellular chromatin (2). This becomes a template for subsequent transcription for viral RNAs which are translated into various viral proteins. The viral proteins are assembled entirely within the hepatocytes, and the resultant progeny virions are secreted into the bloodstream non-cytopathically (11).

Thè clinical manifestation of HBV infection usually arises as a result of thè intèrplay between the host immunè system ánd thè virus, this immune response that is capable of eradicating the virus also in the process causes liver injury. Impaired immune response to HBV which is characterized by immune tolerance or exhaustion of the immune cells resulting in their inability to attack and eradicate the HBV infected hepatocyte including the cccDNA within the nucleus is thè hallmárk of chronic HBV infection (12).

TREATMENT OF CHRONIC HEPATITIS B INFECTION

Thè available treatmènt options currently for CHB infection are nucleos(t)idè analoguès (NA) and pegylatèd intèrferon alpha-2A (PegIFN α-2A) (2).

Nucleoside Analoguès

NAs that arè approvèd in the united states for the treatment of CHB infection are entecavir (ETV), lamivudine (LAM), adefovir dipivoxil

(ADV), telbivudine (TBV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), however, the recommended ones are those with a high barrier against HBV resistance which are ETV, TDF and TAF while others have been shown to have a low barrier against HBV resistance (13,14).

Although treatments with NAs block the production of new virions by suppressing HBV DNA replication below detectable levels via inhibition of DNA synthesis, they however, hardly result in HBsAg loss and are also unable to eliminate the cccDNA within the nucleus of infected hepatocytes. Therefore, treatment with NAs are considered lifelong with the potential risk of long-term toxicity and viral rebound following treatment cessation (15).

NAs with a high barrièr to resistancè have been recommended as the first linè treatment for CHB due to their high long-term antiviral efficacy and safety profiles. These drugs are safe for the management of anyone with hepatitis B infection, more so, are the only recommended therapy to some categories of patients like those with acute fulminant hepatitis B, extra-hepatic manifestations, severe CHB exacerbation, decompensated chronic liver disease and post-liver transplants (2).

Pegylated interferon Alpha-2A (PegIFN α-2A)

Its antiviral effect is brought about via induction of the natural innate antiviral response of the body by binding to and activation the human type 1 interferon receptors, and thus they are referred to as immunomodulators (16).

Thè main advantagè of trèatment with PegIFN α-2A is its long tèrm immunological control with finitè treatment duration. It ensures sustained virological response in responders and can achieve sustained off-treatment control. Although viral rebound after an initial undetectable level of HBV DNA is quite common following treatment suspension with NAs, however, response to PegIFN α-2A is more durable as loss of Hepatitis B envelope antigen (HBeAg) and HBsAg is possible even after treatment withdrawal. The main disadvantages of treatment with PegIFN α-2A are that it requires parenteral administration, high response variability, its several adverse effects, and its contraindication in patients with decompensated liver cirrhosis, fulminant hepatitis and those with psychiatric and autoimmune illnesses (17).

Logically, the combination of PegIFN α-2A and NA may suggest a better therapeutic option through the combined action of an effective immune modulator and an antiviral respectively. However, the supremacy of this combinèd strategy over individual therapies has never been proven scientifically, and may therefore not recommended as at now (18).

LIMITATION OF CURRENT THERAPIES FOR HBV

The currently available treatment may in some cases results in a functional cure, a clinical state defined by undetectable levels of HBsAg and HBV DNA in the serum, normal levels of ALT with or without hepatitis B surface antibody (anti-HBs) seroconversion. However, a true or complete sterilizing cure for CHB defined by complete viral eradication from the host including the intrahepatic cccDNA is currently not feasible due to the inability of these antiviral agents to eradicate the intrahepatic cccDNA which serves as a reservoir for future HBV reactivation whenever the immune system is suppressed (15,17).

Therefore, a true cure will only be possible via immunotherapeutic strategies that aim to reinforce the immune systems to eradicate HBV infected hepatocytes including the intrahepatic cccDNA (15). These strategies target various components of the immune system and are all currently at different experimental phases of clinical trials. These strategies include:

1. Therapeutic strategies targeting the innate immune system which are designed to trigger activation of innate cytokines. Examples of these in clinical trials are toll-likè recèptor (TLR) ágonists è.g. TLR-7 (GS-9620), ánd TLR-8 agonists (19).
2. Therapeutic strategies targeting adaptive immunity designèd to enhancè HBV-spècific cytotoxic T cèll responsès in chronic HBV pátients. Two stratègies cán bè contemplated:

A. Boosting thè defèctive HBV-spècific cytotoxic T-cèlls prèsent in some chronic HBV patiènts through thè usè of chèckpoint inhibitors [anti-programmèd cèll deáth-1 (PD-1) ánd ánti-cytotoxic T-lymphocytè antigen 4 (CTLA-4), etc.] or therapèutic vaccinès (20, 21).

B. To engineèr nèw HBV-specific cytotoxic T-cells thát cán bè adoptivèly transfèrred into patiènts. This strategy is known as adoptive cellular immunotherapy for CHB (22).

Other promising drugs under trial which are not immunotherapeutic agents are;

1. REP 2139 and REP 2165: These are nucleic acid polymers that block assembly of subviral particles in hepatocytes. This eventually blocks the release of HBsAg with rapid clearance of both serum and intracellular HBsAg but delayed clearance of serum HBV DNA (23).
2. ccc_R08: This is a non-cytotoxic and orally active cccDNA inhibitor and destabilizer. This molecule directly act on the cccDNA resulting in reduced cccDNA, HBV DNA and HBsAg levels in the infected hepatocyte of experimental mice (24).

WHO TO TREAT

According to the recommendation from the current guideline for the management of chronic hepatitis B and C by SOGHIN second edition published in 2021 (9).

1. Treatment is recommended for any individual with CHB at the immune reactive phase who are HBeAg positive, HBV DNA >20 000 IU/mL, elevated/flunctuating ALT levels with or without at least moderate necroinflammation and/or significant fibrosis on liver histology or fibroscan
2. Treatment is recommended for any individual with CHB at the reactivation phase who are HBeAg negative, HBV DNA ≥ 2,000 IU/ml, elevated/flunctuating ALT with or without at least moderate necroinflammation and/or significant fibrosis on liver histology or fibroscan
3. Treatment should be considered for any individual with CHB who are HBeAg negative, having HBV DNA/ALT discordance (normal ALT, HBV DNA >2000 IU/ml or vice-versa) but with at least moderate necroinflammation and/or significant fibrosis on liver histology or fibroscan.
4. Treatment may also be considered in certain individuals who do not meet above criteria like those with family history of HCC, healthworkers in direct contact with HBV patients and Nigerians aged >30years.

According to the guideline, elevated ALT is termed ALT >2/3 upper limit of normal (ULN) in males and >1/2 ULN in females.

WHO NOT TO TREAT BUT CONTINUE TO MONITOR

1. Treatment is not recommended and can be deferred in persons with CHB at the immune tolerance phase who are HBeAg positive, normal ALT, HBV DNA >20,000 IU/ml with mild necroinflammation and/or mild fibrosis on liver histology or fibroscan.
2. Treatment can be deferred in any individual with CHB at the immune control or inactive carrier state who are HBeAg negative, persistently normal ALT, HBV DNA <2000 IU/ml with mild necroinflammation and/or mild fibrosis on liver histology or fibroscan
3. Treatment can also be deferred in any individual with CHB who are HBeAg negative with HBV/ALT discordance (normal ALT, HBV DNA >2000 IU/ml or vice-versa) but with mild necroinflammation and/or mild fibrosis on liver histology or fibroscan (9).

PROBLEMS ASSOCIATED WITH THE CURRENT SOGHIN GUIDELINE ON WHO TO TREAT

1. For any patient with CHB to meet the criteria of who to treat, the individual must have done at least HBsAg screening, Hepatitis B serology panel, HBV DNA load, Abdominal ultrasound scan, liver function tests (LFTs), alpha feto protein (AFP) with or without percutaneous liver biopsy during the initial assessment. Therefore, the implication of this is that any patient who cannot afford these gamuts of investigations will not have the opportunity of being started on treatment even if they will eventually be indicated for treatment. Moreso, with the socioeconomic status of Nigeria where 40% of people in the country live below the poverty line according to the national bureau of statistics (25), many patients with CHB who are indicated for treatment would have been denied due to their inability to do these investigations. Therefore, they will eventually be lost to follow up just to present later with complications with also possibility of spreading the virus unknowingly in the community to susceptible individuals.

Alali AA et al in a recent cross-sectional survey estimated the total cost of managing CHB patient per year as ₦564,959 ($1,487) in Nigeria. A figure which is more than the average minimum wage for an average Nigerian in a year. This

amount include cost of investigations, drugs, transportation to health facility and consultation fee at every clinic visits (26). This posed a lot of financial burden on the patient due to out-of-pocket healthcare financing among majority of Nigerians, and those who cannot afford this huge amount either stay at home or seek for a cheaper alternative care including herbal medications with consequent risk of developing HBV-related complications.

2. For any patient with CHB who will eventually fall among the categories of those with HBV DNA/ALT discordance, the decision to treat these set of individuals only lies with presence of at least moderate necroinflammation and/or significant fibrosis on liver histology or fibroscan. Therefore if the expertise for liver biopsy is not available and fibroscan which is very expensive in some part of the country is not affordable, the patient will also not be placed on treatment.
3. The current guideline also places the management of CHB in the hands of specialist gastroenterology and hepatologists alone whom may not be available in rural communities. There is a need for the decentralization of this management to other non-specialist general practitioners as it is done for HIV/AIDS through simplifying treatment and management protocols so that anyone can access care wherever they are be it in rural or urban communities if we really want to eradicate hepatitis B infection in Nigeria.

PROBLEMS ASSOCIATED WITH THE CURRENT SOGHIN GUIDELINE ON WHO NOT TO TREAT BUT TO CONTINUE MONITORING

The CHB patients that fall into the categories of 'who not to treat but continue to monitor' above especially those in the inactive carrier state form a significant portion of CHB patients globally, they have a very low risk of disease progression, however, they still stand the risk of spontaneous reactivation or non-spontaneous following immunosuppressive therapy as well as HCC due to the oncogenic potential of HBV (27). The risk of loss to follow up is greatly increased in this category of patients, as they mostly won't be able to maintain the 6monthly monitoring as recommended. Therefore most of them won't be aware when the disease has progressed to a stage when treatment is now indicated, only for them to present later with complications.

The above claim has been corroborated by a study from Sierra Leone where Nyama et al reported that less than one third of those with CHB who were ineligible for treatment during their initial assessment maintained follow up after 1 year (28). A similar report from Nigeria by Jemilohun et al found a high clinic attendance default of 61.8% among a cohort of CHB patients after their first clinic visit. The reasons for the default given by the patients among others include inability to do requested investigations while some gave reason of being apparently well (29).

Therefore, if we must end Hepatitis B in Nigeria including reducing the incidence of CHB related complications, the following way forward is proposed by this article:

WAY FORWARD TO ENDING HEPATITIS B IN NIGERIA

From the foregoing, it is obvious that the current treatment guideline for chronic hepatitis B in Nigeria maybe deficient and may not help the country to end hepatitis B infection including its related complications in years to come. Therefore, this opinion report tries to propose the following new treatment strategy for chronic hepatitis B infection in Nigeria.

Nigeria should adopt the **"test and treat"** strategy for hepatitis B infection as it was adopted for HIV/AIDS (regárdless of WHO stagè or CD4+ cell count at diagnosis) in 2016 (30). Studies have shown that the advantages of this new strategy for HIV/AIDS over the previous strategies which use CD4+ cell count threshold in HIV infected individuals for ART initiation, include patient retention and thus reduction of loss to follow up, increase viral suppression, reduced risk of transmission of the virus to other individuals and therefore help in epidemic control. This has greatly helped in reducing the prevalence of HIV/AIDS in Nigeria in recent years. These benefits of the **'test and treat'** strategy can also be replicated for hepatitis B infection.

Treating all patients with CHB has recently being proposed by some authors, (a strategy termed treat-all strategy) (31,32). Moreso, in another recent study by Devin Razavi-Shearer et al, in the United State of America (USA), the authors have also proposed a similar treat-all strategy for patients with HBV infection. Their study demonstrated both health and

economic benefits of treating all Hepatitis B positive individuals in the USA. (33). The economic benefit of the treat all strategy using the direct cost, disability-adjusted life years (DALY) as well as cost-effective analysis was found superior to the current treatment guideline by the American Association for the study of Liver disease (AASLD) which makes treatment of HBV too complicated for the average general practitioner in USA and also limits treatment to only CHB patients with liver cirrhosis, those with elevated ALT ($\geq$ 2 x ULN) or significant necroinflammation and/or fibrosis and those with high viral load (34).

The proposed revised treatment guideline based on the test and treat strategy is as follows:

1. All newly diagnosed patients with confirmed CHB as evidenced by positive anti-Hepatitis B core IgG or negative anti-Hepatitis B core IgM but positive total anti-Hepatitis B core, who also has a normal liver on abdominal ultrasound scan, should be allowed to commence treatment immediately without any delay regardless of their age, viral load, HBeAg status, ALT level, or stage of liver fibrosis after proper counselling on the need for treatment adherence.
2. All CHB patients whose renal status are not known or those with known renal impairment should commence treatment with tenofovir alafenamide (TAF) 25mg daily while treatment with tenofovir disoproxil fumarate (TDF) 300mg daily should be reserved for those with known good renal status.
3. Treatment is not indicated in patient with acute viral hepatitis as evidenced by positive anti-Hepatitis B core IgM. However, treatment should be commenced for them if their HBsAg is still positive after 6months.
4. Treatment for CHB with the oral antiviral above should be indefinite. However, treatment should only be suspended whenever patient achieve loss of the HBsAg.
5. All newly diagnosed patient with CHB with an abnormal liver on abdominal ultrasound scan should be refered to a specialist gastroenterologist for proper evaluation before commencement of treatment.
6. CHB patients on treatment should be adviced on yearly HBV DNA, LFTs, AFP and abdominal ultrasound scan to monitor their treatment, for complication surveillance and to ensure drug resistance has not set in. Yearly HBsAg screening should be added to the above investigations after the patient has achieved undetectable HBV DNA level for two consecutive years in other to be sure when patient will lose the surface antigen. Those that develop complication or drug resistance while on treatment should be referred to specialist gastroenterologist for proper evaluation.
7. All pregnant women who are newly diagnosed with HBV infection should be allowed to commence TDF, only in their third trimester (after 28weeks of gestation) and continue after delivery indefinitely like other non-pregnant individual as stated above regardless of their age, viral load, HBeAg status or ALT level in other to rèduce thè risk of mothèr to child tránsmission and also to reduce risk of diseáse progrèssion in the mother.
8. Babies born to mothers with positive HBsAg should have Hepatitis B immunoglobulin (HBIG) within 12hours of birth, plus birth-dose hèpatitis B vaccine within 24hours of birth at different sites regardless of whether the mother is on antiviral treatment or not.
9. Women with CHB who become pregnant while on treatment with TDF should be allowed to continue treatment, while those on TAF who become pregnant should be adviced to change their TAF to TDF. However, the TDF may be changed back to TAF after their delivery.

BENEFITS OF THE PROPOSED GUIDELINE

1. This proposed guideline will allow everyone who have CHB to commence treatment immediately without any delay regardless of their age, HBV DNA load, HBeAg status, ALT level or stage of liver fibrosis.
2. This guideline will eventually reduce the rate of both vèrtical ánd horizontál tránsmission of hepatitis B in the community, thereby enhancing epidemic control of the infection with a consequent drastic decrease in its incidence and prevalence in Nigeria.
3. Early commencement of antiviral therapy in HBV infection has been confirmed by different studies to significantly reduce viral load, reduce markers of liver inflammation and long term therapy can result into regression of

liver fibrosis and cirrhosis (2, 35). This will undoubtedly prevent disease progression and forestall HBV related complications and consequently reduce the prevalence and incidence of these complications in Nigeria.

4. Management of HBV infection will be decentralized to the primary healthcare levels as well as rural communities that has no specialist gastroenterologist. Only cases with complication or those with initial abnormal liver on ultrasound scan will be referred to the specialist gastroenterologist.
5. Hopefully, it will help the country to achieve the WHO target for viral hepatitis elimination by 2030.

CONCLUSION

This guideline is proposed for the stakeholders in the fight against viral hepatitis in Nigeria to critically review it and possibly subject it to a clinical trial so that it can be backed up with scientifically proven evidence for subsequent adoption by thè Fèderal Ministry of Hèalth of Nigèria, the WHO and therefore the world at large.

It is high time the Federal Ministry of Health mandate the National Health Insurance Scheme to incorporate the evaluation of CHB including the HBV DNA and the treatment into the coverage of the scheme. This will lessen the financial burden of these investigations and the long term treatment of CHB on Nigerians and therefore will improve treatment adherence.

Nigeria being among the worst-hit countries with Hepatitis B infection in the world, therefore, it is very paramount for the country to develop strategies and policies with a strong political will to tackle this **'hard to treat'** infection to save the citizens and not to always wait for strategies developed by countries with a lower burden of the infection.

Finally, while we await the various immunotherapeutic strategies or other newer drugs currently in various stages of clinical trials geared towards achieving a true cure for CHB infection, there is a need for us to maximize the benefits of therapies that are currently available to get the best out of them by not preventing any infected person from getting treatment.

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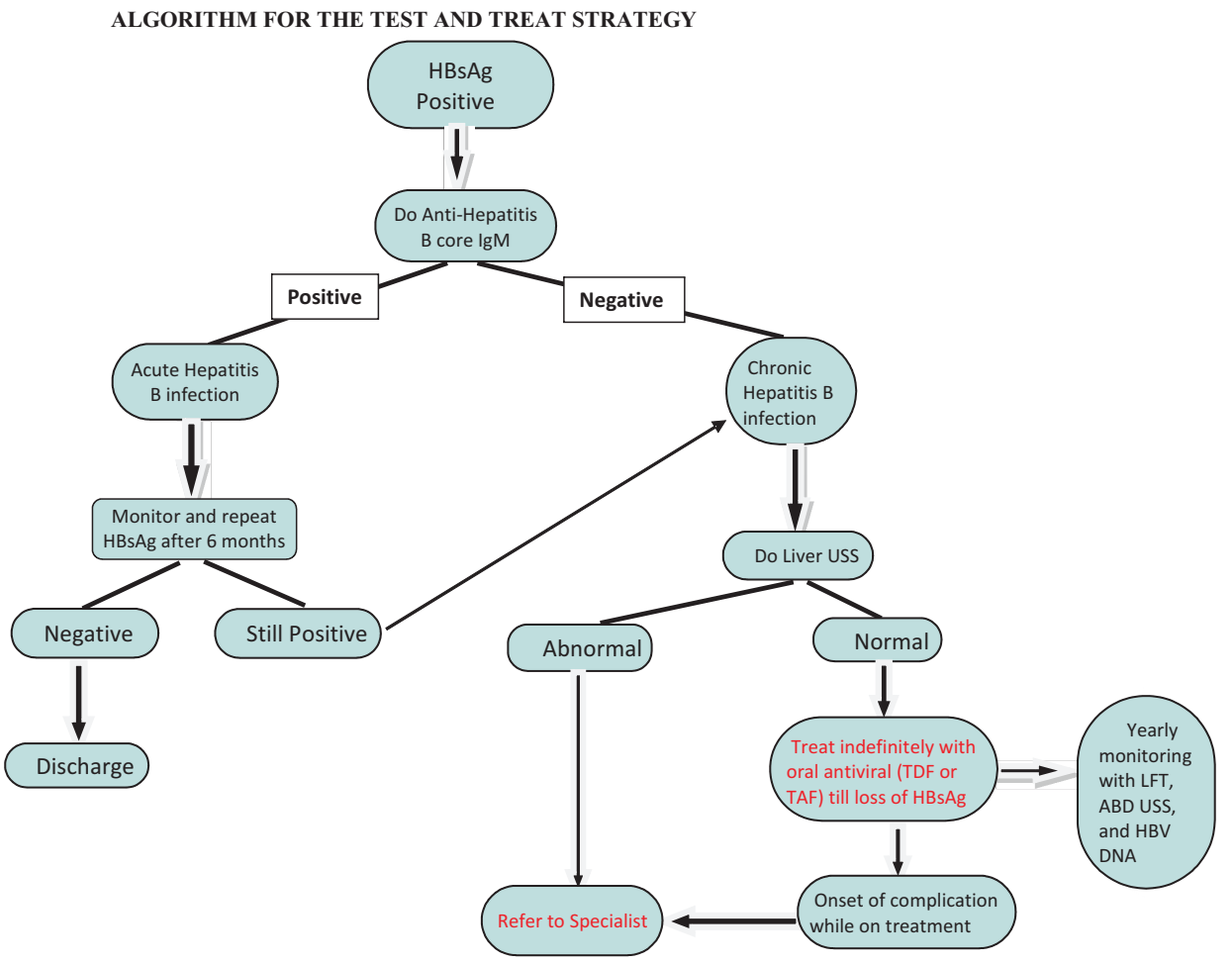

Figure 1: Showing the algorithm of the test and treat strategy

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