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Review Article

HBeAg-negative Patients with Chronic Hepatitis B Virus Infection and Normal Alanine Aminotransferase: Wait or Treat?

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Abstract

Alanine aminotransferase (ALT) is a common clinical indicator of liver inflammation. The current Chinese guidelines for the management of chronic hepatitis B (CHB) recommend antiviral treatment for patients with detectable hepatitis B virus (HBV) DNA and persistent ALT levels (ALTs) exceeding the upper limit of normal. However, it has been recently reported that patients with chronic HBV infection, especially HBeAg-negative patients with persistently normal ALTs, may have liver biopsy findings of significant inflammation and fibrosis. For HBeAg-negative patients with chronic HBV infection and normal ALTs, many controversial questions have been asked. To treat or not? When to initiate the treatment? Which drug is appropriate? In this review, we summarize the available data on the management of HBeAg-negative patients with chronic HBV infection and normal ALTs with the aim of improving the current clinical management.

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Introduction

For patients with chronic hepatitis B virus (HBV) infection, the currently used antiviral drugs do not eradicate covalently closed circular DNA (cccDNA) of HBV, and their efficacy is closely related to the degree of liver inflammation and fibrosis. Therefore, the current guidelines recommend starting antiviral treatment only in patients with chronic HBV infection and signs of continued necroinflammation in the liver. Although liver biopsy is regarded as the gold-standard technique for evaluating liver inflammation and fibrosis, it has not been widely used in clinical practice because of its limitations, such as its invasiveness and the possibility of sampling error. Alanine aminotransferase (ALT) provides a sensitive and accurate index of liver tissue inflammation that is conveniently and repeatably accessible and widely used to determine when to initiate antiviral therapy.

The Chinese guidelines for the management of chronic hepatitis B (CHB; 2019 version, hereinafter referred to as the guidelines) recommend that antiviral treatment should be initiated for patients if HBV DNA is detected and the ALT levels (ALTs) are abnormal (i.e. exceed the upper limit of normal). The guidelines also suggest that some groups of patients with normal ALTs should also be treated, including those with a liver histology grade (G) ≥2 or stage (S) ≥2; patients with a family history of HBV-related liver cirrhosis, or hepatocellular carcinoma (HCC) and over 30 years of age. Treatment is also recommended for patients over 30 years of age with obvious liver inflammation or fibrosis on examination with a noninvasive diagnostic technique or patients with HBV-related extrahepatic complications (e.g., HBV-associated glomerulonephritis vasculitis, polyarteritis nodosa, and others.). Except for the four groups mentioned above, the guidelines emphasize that patients with normal ALTs generally do not require antiviral therapy.[1]

Nonetheless, recent clinical studies have confirmed that in patients with chronic HBV infection and normal ALTs, especially HBeAg-negative patients, liver biopsy has found that more than 50% have significant inflammation or fibrosis of their liver tissues and require prompt antiviral treatment. HBeAg-negative patients are generally older and have a longer disease course than HBeAg-positive patients, who are more likely to progress to fibrosis. Without timely antiviral treatment, the disease can insidiously progress to liver cirrhosis or even HCC. Studies have reported that new-generation oral antiviral drugs like entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) and subcutaneous injection of polyethylene glycol-interferon alfa (PEG-IFN-α) can also be effective in HBeAg-negative patients with normal ALTs. In this review, we summarize

Keywords: Hepatitis B virus; Chronic hepatitis B; Hepatitis e antigen; Alanine aminotransferase; Antiviral therapy.

Abbreviations: ADV, adefovir dipivoxil; ALT, alanine aminotransferase; ALTs, ALT levels; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; ETV, entecavir; G, grade; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; IHCs, inactive hepatitis B surface antigen carriers; IT, immune tolerance; LSM, liver stiffness measurement; NAs, nucleos(t)ide analogues; PEG-IFN-α, polyethylene glycol-interferon alfa; QALYs, quality-adjusted life years; S, stage; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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the known current conclusions with information on controversial issues to improve the clinical standard of treatment.

Need for antiviral therapy for HBeAg-negative patients with chronic HBV infection and normal ALTs

An elevated serum ALT indicates hepatocyte injury and therefore suggests active inflammation and hepatocyte damage caused by an antiviral immune response. However, the degree of hepatic inflammation or fibrosis cannot be predicted from the degree of ALT elevation, and clinically severe histological injury cannot be excluded when the ALTs is normal. An increasing number of studies have confirmed that ALT is not the only key indicator in determining whether to initiate antiviral therapy.

Patients in the gray zone of HBV have hepatic inflammation or fibrosis

The natural course of chronic HBV infection can be divided into four phases based on the virus replication status and immune response state. They are immune tolerance (IT), immune clearance, low or nonreplication, and reactivation phases. The low or nonreplication phase and much of the reactivation phase are HBeAg-negative. Patients in the reactivation phase are characterized by HBeAg negativity, anti-HBe antibody positivity, HBV DNA >2000 IU/mL, persistently or repeatedly abnormal ALTs, and moderate to severe liver tissue inflammation and/or fibrosis. They are clinically diagnosed with HBeAg-negative CHB, and such patients should receive antiviral treatment as soon as possible to limit disease progression. Patients in the low or nonreplication phase are HBeAg-negative, with persistently normal ALTs, HBsAg <1000 IU/mL, HBV DNA <2000 IU/mL, and slight histological liver damage, are clinically referred to as inactive hepatitis B surface antigen carriers (IHCs). Those patients are considered to have a favorable prognosis and antiviral therapy is not recommended.

However, the inactivity does not last forever. Some patients may have persistently normal ALTs and be negative for HBeAg while the virus replicates insidiously and the disease progresses insidiously. Such patients are clinically defined as in the gray zone of the low or nonreplication phase.[2] Yao *et al*.[3] conducted a retrospective study of 4759 untreated HBV-infected patients in China, of whom 21.4% were in the gray zone of the immune control period. Several studies have found that after 4–5 years of follow-up, 37–54.3% of HBeAg-negative patients with chronic HBV infection were still in the gray zone, 43.5–85% of whom transitioned to IHCs, and 2.2–15% of them to HBeAg-negative CHB.[4–7] The results indicated that HBeAg-negative patients with chronic HBV infection and normal ALTs were not a homogeneous population. Some of them were IHCs who can be left temporarily untreated, whereas others may be in a quiescently or mildly active phase of HBeAg-negative chronic HBV infection, which is the gray zone of disease progression.

Multiple studies have demonstrated that HBeAg-negative patients with chronic HBV infection and normal ALTs may have high viral loads or significant liver inflammation or fibrosis. In one of our studies, 258 HBV patients with chronic infection and ALTs <2 times the upper limit of normal were included. Liver biopsy verified that 42.2% of them had liver inflammation (G≥2), 24% had liver fibrosis (S≥2), and 35.2% had necroinflammation (G≥2 and S≥2).[8] A multicenter study was conducted in 253 patients with chronic HBV infection and normal ALTs. The results of liver biopsy showed that 48.9% of HBeAg-positive patients and 51.6% of HBeAg-negative patients had serious pathological changes.[9] In a study by Wu *et al*.,[10] 117 HBeAg-negative patients with chronic HBV infection, normal ALTs and positive HBV DNA were included. The liver biopsy results showed that 57.2% had severe liver disease, which met the indications for antiviral therapy.

Some studies have reported repeated and intermittent small-scale damage of the liver tissue of HBeAg-negative patients with chronic HBV infection and normal ALTs, and the extent of fibrosis surpasses that of inflammation. In a study of 327 HBeAg-negative patients with chronic HBV infection and ALTs of <40 U/L, Zhuang *et al*.[11] found that 59.0% (193/327) were in the gray zone, 32.4% (106/327) had HBV DNA ≥2000 IU/mL, and 37.3% (122/327) had significant liver inflammation. Significant liver fibrosis occurred in 61% (174/327) of the patients.

The above studies found that it was not rare for HBeAg-negative patients with chronic HBV infection and normal ALTs to have significant inflammation or fibrosis. Patients whose infection duration was relatively long experienced HBeAg seroconversion, broken IT, and had significant liver inflammation and/or fibrosis. Although they showed normal serum ALTs, liver tissue changes had occurred, HBV DNA was replicated at a high level, and their disease insidiously progressed.

Disease progression is seen in patients in the gray zone who have not received antiviral therapy

Previous studies have indicated that most HBeAg-negative patients with normal ALTs are in the immune control phase, with a low prevalence of adverse events, and can be monitored and followed up regularly. However, it should not be ignored that some of them are in the gray zone, and there is also hidden disease progression leading to adverse clinical outcomes. In a meta-analysis of 2771 patients with chronic HBV infection and normal ALTs, the incidence of pathologically confirmed intrahepatic inflammation, fibrosis, and cirrhosis was 35% (95% CI: 27–43), 30% (95% CI: 25–36), and 3% (95% CI: 1–5), respectively. Patients over 40 years of age had significant fibrosis (44% vs. 26%, p=0.012), and cirrhosis (4.8% vs. 1.8%, p<0.001) was significantly higher than those under 40 years of age.[12] A Korean study reported that HBeAg-negative CHB patients with HBV DNA ≥2000 IU/mL had an increased risk of clinical events in patients with normal ALT but not treated compared with those with elevated ALT who received treatment.[13] Deng *et al*.[14] conducted a study in untreated HBeAg-negative patients with chronic HBV infection and HBV DNA levels <2000 IU/mL, and found that 96% of them had normal ALTs. A second liver biopsy was performed at an average interval of 4.5 years. Significant liver tissue damage (G≥2 and/or S≥2) increased from 50.0% to 90.0%, cirrhosis increased from 10.0% to 30.0%, and one case of HCC occurred in patients without antiviral treatment.

In a joint study in the USA and Taiwan that included 3366 untreated patients with chronic HBV infection, 1303 (38.7%) with undetermined staging were overwhelmingly ALT-normal and HBeAg-negative. After a mean follow-up of 12.5 years, with half still had uncertain staging and one-fifth transitioned to immunological activity. HBV-infected patients with a persistent uncertain stage had a 14-fold higher risk of HCC than nonactive patients.[15] That reminds us that if patients in the gray zone are not treated for a long time, then some of them may experience disease progression, or HBV reactivation, which will increase the risk of death from liver cirrhosis or HCC.

Timing of antiviral therapy for HBeAg-negative patients with chronic HBV infection and normal ALTs

It is recommended that patients in the low or nonreplication phase be monitored to initiate treatment when they meet

the criteria. The guidelines recommend that such patients undergo liver biopsy. Nevertheless, as an invasive examination, liver biopsy is not currently accepted by the majority of patients. Therefore, clinicians should pay attention to the HBV DNA viral load and the quantitative level of HBsAg, noninvasive liver inflammation, evaluation of fibrosis, liver imaging, and other aspects to monitor disease progression. The emphasis is on accurate judgment of liver inflammation and finding the best time for antiviral treatment.

Precise HBV DNA load provides guidance for antiviral therapy

In recent years, studies have confirmed that some HBeAg-negative patients may not express the e antigen because of pre-C region mutations and other reasons, but their DNA is still duplicated at a high level.[16] The results of a study by Zhuang *et al*.[11] indicated that for HBeAg-negative patients with chronic HBV infection and normal ALTs, the proportion of liver inflammation or fibrosis in those with HBV DNA ≥2000 IU/mL significantly exceeded the proportion of those with HBV DNA <2000 IU/mL (58.5% vs. 27.1% and 67.9% vs. 46.2%, $p<0.01$). The REVEAL study demonstrated that high baseline HBV DNA in CHB patients increased the risk of liver cirrhosis and HCC.[17] A large-sample prospective cohort study by Chen *et al*.[18] that included 3653 HBV-infected patients from 30 to 65 years of age found that the higher the HBV DNA load, the greater the risk of HCC. The association was stronger in noncirrhotic patients with normal ALTs. Therefore, for HBeAg-negative patients with chronic HBV infection, normal ALTs, and high HBV DNA loads, early antiviral treatment is required to reduce the risk of disease progression.

It should be noted that HBeAg-negative patients with chronic HBV infection, normal ALTs, and low HBV DNA loads (<2000 IU/mL) cannot be ignored. A previous study by Deng *et al*.[14] reported disease progression in those with low HBV DNA loads. Yenilmez *et al*.[19] also found that the risk of liver fibrosis cannot be ignored in CHB patients with low viral loads. In brief, the risk of disease progression exists as long as we can detect virus replication with an available assay, which is equivalent to an antiviral therapy indication. With improvements in nucleic acid detection, the sensitivity limit of HBV DNA detection can reach 10 IU/mL. In the future, we will implement more accurate quantitative detection technology of HBV DNA to assist in determining the timing of antiviral treatment.

Dynamic detection of quantitative changes in HBsAg levels to guide treatment

HBsAg is transcribed from cccDNA or the integrated viral genome of HBV DNA, which can reflect the quantity of hepatic cccDNA to some extent,[20] thereby evaluating the active degree of HBV DNA replication in the liver. Currently, an HBsAg of <1000 IU/mL is taken as a cutoff value to assist in identifying IHCs with a lower risk of HBV reactivation.[21] Although the cutoff value is still controversial, quantitative combination of HBsAg with HBV DNA load and ALTs can help to distinguish active and inactive stages. IHCs with normal ALTs, HBV DNA ≤2000 IU/mL and HBsAg <1000 IU/mL were reported to have an annual hepatitis recurrence rate of 1.1%. Meanwhile, the risk of hepatitis recurrence in patients with HBV DNA <2000 IU/mL but HBsAg >1000 IU/mL was 1.5 times that of the former.[6,21,22]

For truly inactive carriers, Liaw recommends that HBsAg levels should be quantitatively tested at least every 2 years. More frequent detection is required if HBsAg levels decline rapidly by more than 0.5 $\log_{10}$IU/mL within 1 year or more than 1 $\log_{10}$IU/mL within 2 years, or if HBsAg decreases to <200 IU/mL.[23] Clinically, IHCs can be further stratified and managed according to the HBsAg level, and a clinical cure can be actively pursued for patients whose HBsAg levels are below a certain critical threshold.[24]

Noninvasive liver assessment to guide treatment

For patients with chronic HBV infection and normal ALTs, many guidelines advocate dynamic follow-up and active liver histological examination. However, as an invasive assessment, many patients resist liver puncture. At present, some noninvasive assessments can also indicate liver pathological changes. A 2018 clinical consensus on transient elastography for the detection of liver fibrosis[25] recommended that CHB patients with normal ALTs and a liver stiffness measurement (LSM) of <6.0 kPa should be followed up regularly. Liver puncture is recommended when the LSM value is between 6.0 and 9.0 kPa. If the LSM value is between 9.0 and 12.0 kPa, progressive fibrosis is considered and antiviral therapy should be initiated. When the LSM value is >12.0 kPa, liver cirrhosis is considered to have occurred.[25] A foreign study in 357 CHB patients reported that transient elastography accurately predicted liver fibrosis and avoided liver tissue puncture in two-thirds of the CHB patients.[26] Others have reported that indicators such as the aspartate aminotransferase to platelet ratio index, fibrosis-4 score, and liver magnetic resonance were helpful in determining the extent of disease progression in the liver.[1] In conclusion, for HBeAg-negative patients with chronic HBV infection and normal ALTs, comprehensive evaluation should be carried out based on laboratory indicators, imaging, age, family history, and other factors to screen out patients with significant intrahepatic lesions in a timely manner to avoid delayed treatment (Fig. 1).

Antiviral therapy strategy and evaluation of effectiveness in HBeAg-negative patients with chronic HBV infection and normal ALTs

More than 20 years of experience in antiviral therapy has proven that the choice of antiviral drugs for CHB is closely related to clinical efficacy. The new generation of oral antiviral drugs (ETV/TDF/TAF) and subcutaneous injection of PEG-IFN-α are both first-line antiviral therapies recommended by current guidelines. They have achieved excellent clinical efficacy in CHB patients with abnormal ALTs, and can achieve nondetectable HBV DNA, reverse liver tissue inflammation and fibrosis, and prevent disease progression. Recent studies have proven that the above drugs are also effective in patients with normal ALTs, especially in those with negative HBeAg.

Antiviral effectiveness in patients with normal ALTs is not inferior to that in patients with elevated ALTs

Previous studies have shown that antiviral drugs are effective in patients with active liver inflammation. However, a normal ALT level does not mean absence of active inflammation or fibrosis, and that good effectiveness can be achieved. In a multicenter study, 57 patients with persistently normal ALTs and pathological indications of antiviral therapy were treated with ETV and followed up for 78 weeks with a second liver biopsy. Following treatment, HBV DNA was undetectable in 38 cases (66.7%), and 25 (43.9%) had histological improvement. The ratio of HBV DNA <20 IU/mL, HBeAg clearance or seroconversion, fibrosis improvement or stabilization, and

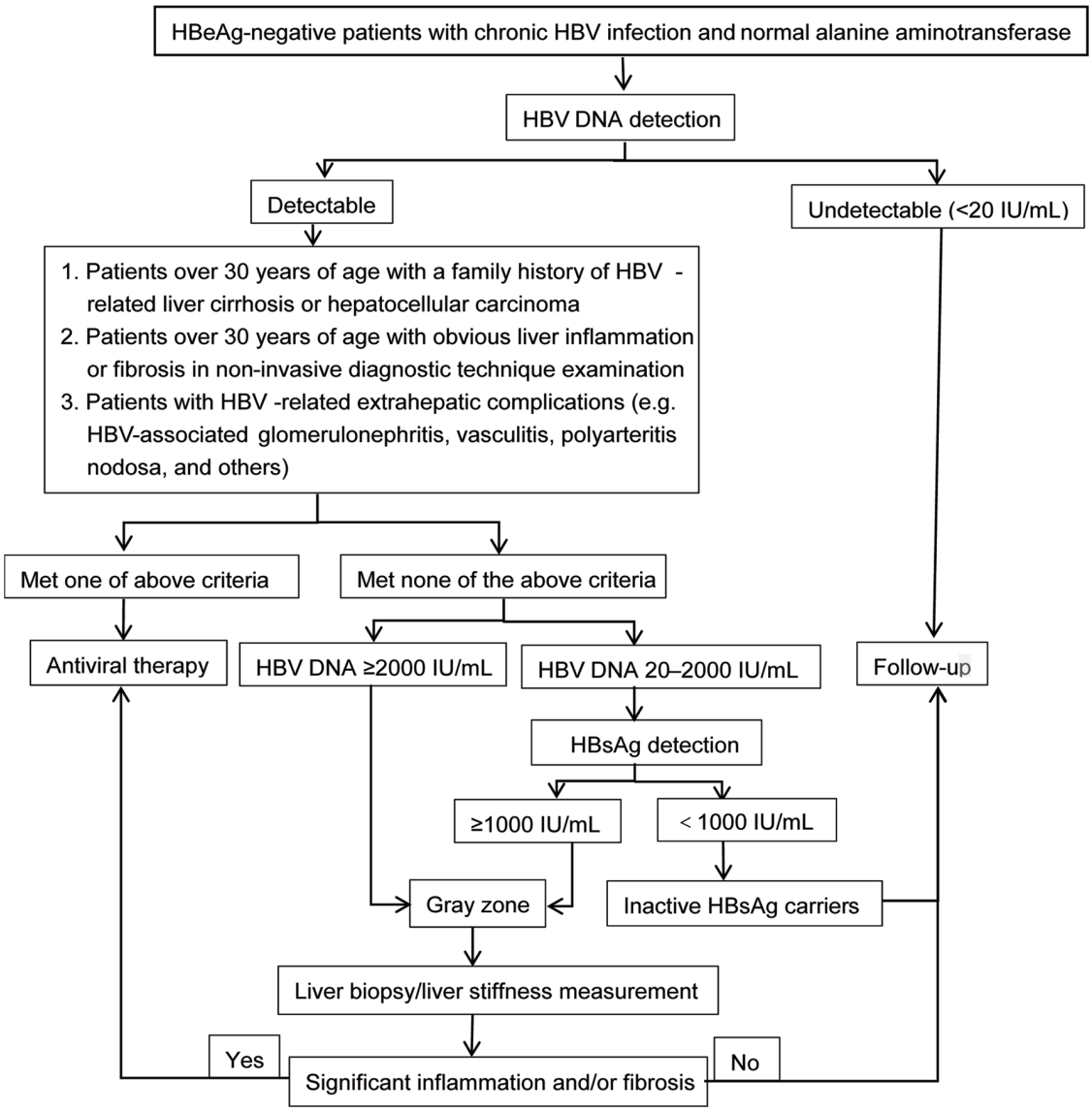

Fig. 1. Algorithm for the management of HBeAg-negative patients with chronic HBV infection and normal alanine aminotransferase. HBV, hepatitis B virus.

fibrosis progression at 78 weeks in patients with normal ALTs was comparable to that of a control group with elevated ALTs ($p>0.1$).[9] A randomized double-blind study by Tseng *et al*. enrolled 42 CHB patients with persistent normal ALTs but liver histological changes, including 26 HBeAg-negative cases (60.4%). Twenty-two patients were randomly assigned to ETV treatment, and 20 to the same dose of placebo. After 52 weeks, the virological response (i.e. undetectable HBV DNA) rate in the ETV group was 76.2%, and no one in the placebo group achieved a virological response.[27] The above studies indicate that antiviral treatment for patients with chronic HBV infection and normal ALTs can achieve good results that were not inferior to those in patients with elevated ALTs.

Drug choice and efficacy evaluation of antiviral therapy

Nucleos(t)ide analogues (NAs) and interferon are currently first-line antiviral therapeutic agents. Yan *et al*. performed liver biopsies in 123 HBeAg-negative patients with chronic HBV infection and normal or mildly elevated ALTs. The results showed that 69.96% (86) of patients met the treatment criteria. After 72 weeks of antiviral treatment with ETV or adefovir dipivoxil (ADV), 90.70% of patients had undetectable HBV DNA loads. However, the HBsAg clearance rate with NA treatment is extremely low. Studies have shown that HBeAg-negative subjects treated with NAs are more likely to obtain a reduction in HBsAg after switching to interferon.[28] A prospective cohort study by Chen *et al*.[29] included 144 HBeAg-negative patients with chronic HBV infection including a treatment group of 102 cases and a control group of 42 cases. Treatment was with PEG-IFN-α alone or in combination with ADV, depending on the HBV DNA load. The HBsAg clearance rate was 29.8% and the seroconversion rate was 20.2% at week 48, and increased to 44.7% and 38.3%, respectively, at week 96. The HBsAg clearance rate in the untreated control group was 2.4% at both 48 and 96 weeks, and no patients achieved HBsAg seroconversion.

A study by Xie *et al*.[30] treated 101 HBeAg-negative patients who had normal or mildly elevated ALTs with NAs or PEG-IFN-α with pathology evaluations that met the treatment criteria. The virological response rate of the NAs group was 95.51% (85/89) and that of the PEG-IFN-α group was 100% (12/12) after 48 weeks of treatment. The between-group differences were not significant. The average HBsAg values decreased by 0.176 $\log_{10}$IU/mL and 0.816 $\log_{10}$IU/mL in the two groups (p<0.001). The decrease in the rate of HBsAg positivity in the interferon group was better than that in the NAs group. Particularly noteworthy is that there are some disadvantages of interferon, including strict application conditions, adverse reactions, and a high price. Therefore, for HBeAg-negative patients with normal ALTs, the best treatment plans should take age, HBV DNA, and HBsAg level into account.

Antiviral therapy can achieve long-term benefits

For patients with chronic HBV infections and normal ALTs, the fundamental goal of antiviral treatment is to avoid adverse events, including hepatic fibrosis, cirrhosis, or even HCC, caused by latent disease progression. Yan *et al*. reported that a second biopsy after NA treatment of HBeAg-negative patients with chronic HBV infection and normal or mildly elevated ALTs for 72 weeks showed that antiviral therapy effectively improved liver histology.[28] A study by Xie *et al*.[30] reported that liver stiffness indexes measured by the FibroScan test were distinctly improved by 48 weeks of antiviral treatment in 136 HBeAg-negative patients with chronic HBV infection and normal ALTs. A study conducted by Deng *et al*.[14] included 23 HBeAg-negative patients with chronic HBV infection and obvious inflammation and/or fibrosis in first-stage liver pathology who received a second liver biopsy at an interval of 4.5 years. Thirteen had improved liver histology after antiviral treatment with NAs. The percentage of patients with obvious liver inflammation and/or fibrosis (G≥2 and/or S≥2) dropped from 61.5% to 46.2%, and the percentage with cirrhosis dropped from 23.1% to 0%. In contrast, liver pathology deteriorated in patients without antiviral therapy, and some of them developed liver cirrhosis or HCC. A historical cohort study in South Korea showed that for HBeAg-negative patients with chronic HBV infection and a normal or mildly elevated ALTs and high viral load, the risk of developing HCC was significantly reduced by antiviral therapy.[31] The above studies confirm that liver histology can be improved significantly and that the incidence of adverse events can be significantly reduced by antiviral therapy. With the gradual improvement of the accessibility and affordability of current antiviral drugs, antiviral treatment for patients with normal ALTs should be actively carried out to avoid missing the best treatment time.

Financial cost-benefit of antiviral therapy

For patients with chronic HBV infections, normal ALTs, and low levels of viral replication, it was previously considered that they did not require treatment because disease progression was slow, antiviral drugs would add additional economic burden, and the benefits did not justify the expenses. Therefore, we must re-evaluate the costs and benefits of expanding treatment coverage.

Firstly, some studies have analyzed the cost-effectiveness of antiviral therapy for CHB patients. A study from South Australia found that maximizing the treatment (TDF therapy) uptake in the existing HBV population from 2.9% to 15% was cost-effective for periods of 2 years or more.[32] A Study in Spain by Oyagüez *et al*.[33] analyzed the cost-effectiveness of antiviral strategies in both HBeAg-positive and -negative CHB patients. Patients initially were treated with PEG-IFN-α for 48 weeks. After that, patients who did not achieve immune control were retreated with oral antivirals (50% ETV and 50% TDF). Full treatment increased survival by up to 2.13 life years and 3.05 quality-adjusted life years (QALYs) gained in HBeAg-negative populations. The total was €93,754 for 100% of treatment coverage. The incremental cost-effectiveness ratio (ICER) resulted €8,942 per QALY compared with the natural history. Compared with no treatment, it was considered a cost-effective alternative.

Untreated minimally active CHB patients with normal ALTs do not meet the reimbursement criteria for NAs therapy (ETV or TDF) of the national health insurance service of some countries. A 2021 study in Korea used a Markov cost-effectiveness model to compare the cost-effectiveness of receiving and not receiving NAs therapy for 10,000 50-year-old patients with low-activity HBV infection. It showed that 720 HCC cases and 465 CHB-related deaths could be avoided if 10,000 patients received antiviral therapy rather than remaining untreated for 10 years. Compared with no treatment, the simulation of NAs treatment predicted USA$2,201 incremental costs and 0.175 incremental QALYs per patient for 10 years, with an ICER of $12,607/QALY, suggesting cost-effectiveness of NAs treatment. When the duration was extended to 20 years, NAs treatment was also highly cost-effective with an ICER of USA$2,036/QALY. This means that antiviral treatment for patients with a long-term low viral load is a cost-effective option that benefits both individual interests and national healthcare budgets.[34] Another recent study from South Korea focused on the IT phase CHB patients in a Markov model that compared expected costs and QALYs in two groups over a 20-year horizon. One group started antiviral treatment (ETV or TDF) at the IT phase, the "treat-IT" group. The other started treatment until the active hepatitis phase, the "untreat-IT" group. The treat-IT strategy was preferred to the untreat-IT strategy when the annual HCC incidence was higher than 0.54% based in a cost-effectiveness threshold of USA$20,000/QALY from a healthcare system perspective.[35] In a Chinese population, Chen *et al*.[36] reported that combination therapy with NAs and PEG-IFN-α for HBeAg-negative patients with HBsAg ≤1,000 IU/mL not only increased the QALYs, but also reduced medical costs and was more cost-effective than NAs monotherapy.

An interesting recent study by Mehlika analyzed the economic impact of a potential cure for CHB in the USA, China, and Australia, to estimate the threshold drug prices below which a CHB cure would be cost-saving and/or highly cost-effective. They found that compared with long-term antiviral therapy (ETV and TDF), a 30% effective functional cure among patients with cirrhosis would yield 17.50 QALYs/patient in the USA, 17.32 in China, and 20.42 in Australia and 20.61, 20.42, and 20.62 QALYs per patient, respectively, in those without cirrhosis. If the treatment that achieves a functional cure is 30% effective, the price tag for the new drug needs to be no more than USA$11,944 and USA$6,694 in the USA, USA$1,744 and USA$1,001 in China, and USA$12 063 and USA$10,983 in Australia, for it to be cost-saving compared with current antiviral therapy in patients with and without cirrhosis, respectively.[37] We look forward to the early launch of new drugs with an ideal price.

In addition, because chronic HBV infections is a contagious disease, patients generally have a serious psychological burden that may result in problems involving work or marriage. Therefore, for patients with the potential of achieving HBsAg clearance, antiviral treatment administered as soon as possible is beneficial for disease control, reducing subsequent costs, and also comprehensively improves the quality of life in patients with CHB, with intangible social benefits.

Limitations

This review has some limitations. Most of the case reports and analyses we discussed set the normal upper limit of ALT as 40 U/L, but some studies recommend that the normal ALT value be lower, so the definition of normal ALT may need to be further studied.

Expectations for the future

Of the patients with chronic HBV infection in China, 62.4% (53.69 million) have normal ALTs, including both HBeAg-positive and -negative patients. The majority (66.3%, 35.6 million) are HBeAg-negative and have normal ALTs.[38] In the face of such a large population of HBeAg-negative patients with chronic HBV infection and normal ALTs, more clinical attention must be paid to disease assessment and treatment timing. The definition of the gray zone of the immune control phase and the indications for antiviral treatment must be updated in the clinical guidelines. With the existing test methods, it is still impossible to accurately and noninvasively distinguish patients who are really in the immune control stage and those in the gray zone. We require more accurate noninvasive indicators that can evaluate liver inflammation and fibrosis to guide clinical treatment. Drug studies with large patient cohorts and long-term clinical follow-up are required to confirm the clinical benefits of antiviral therapy for patients with normal ALTs. We look forward to finding more efficient and safe antiviral drugs to help HBeAg-negative patients with chronic HBV infection and normal ALTs achieve HBsAg clearance, and a clinical cure, and to minimize the morbidity of the complications associated with liver disease.

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Conflict of interest

XD has been an associate editor of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

Study design (XD, YD), acquisition, analysis, and interpretation of data (QS, NW, YL, CH, ZW, SW), drafting of the manuscript (QS, NW), critical revision of the manuscript for important intellectual content (CZ, YF, YD), obtained funding (QS, YD, YL), and study supervision (XD, YD). All authors have made a significant contribution to this work and have approved the final manuscript.

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