CHB in immunocompromised patients and Real world study for long term outcome of antiviral treatment in chronic hepatitis B patients

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Approximately 240 million people, or about 6% of the world’s population, are chronically infected with HBV.

China accounts for nearly one-third of all chronic HBV infection globally.
All patients with HBV and HIV coinfection should initiate ARVT, regardless of CD4 count. The ARVT regimen should include 2 drugs with activity against HBV. The backbone of the ARVT regimen should be TDF or TAF plus LAM or emtricitabine.

Patients who are already receiving effective ARVT that does not include a drug with antiviral activity against HBV should have treatment changed to include TDF or TAF with emtricitabine or LAM. ETV is reasonable if patients are receiving a fully suppressive ARVT.

When ARVT regimens are altered, drugs that are effective against HBV should not be discontinued without substituting another drug that has activity against HBV.
Asian-Pacific (2015)

HIV/HBV Co-infection

Consider early dual anti-HIV and anti-HBV therapy, irrespective of immunological, virological or histological considerations

- Lamivudine naive
  - HAART including Tenofovir plus Lamivudine or Emtricitabine

- Lamivudine experienced
  - Add or Substitute one NRTI with Tenofovir as part of HAART

Among patients with CD4 count >500/ml unwilling to start HAART, HBV can be treated before the institution of anti-HIV therapy; PEGIFN,* Adefovir# and Telbivudine#, which are not proven to be active against HIV, should be used.

* Peg-IFN may be used if genotype A, low HBV-DNA and high ALT
# However, if Adefovir or Telbivudine use does not lead to the goal of undetectable HBV DNA after 12 months of therapy, treatment of HIV infection should be considered.

对于近期不需要进行ART治疗（CD4+T 淋巴细胞 > 500/μL），如符合CHB 抗病毒治疗标准的患者，建议使用PegIFN-α或ADV 抗HBV 治疗（C1）。

CD4+T 淋巴细胞 ≤ 500/μL 时，无论CHB 处于何种阶段，均应开始ART，优先选用TDF加拉米夫定，或TDF 加恩曲他滨（A1）。

对于正在接受ART 且治疗有效的患者，若ART 方案中无抗HBV 药物，则可加用NAs 或PegIFN-α治疗（C2）。

对一过性或轻微ALT 升高（1 ~ 2 倍ULN）的患者，建议肝组织活检或无创肝纤维化评估（B2）。

当需要改变ART 方案时，除非患者已经获得HBeAg 血清学转换、并完成了足够的巩固治疗时间，不应当在无有效药物替代前中断抗HBV 的有效药物（B1）。

中华医学会肝病学分会（2015）
Management of patients who receive immunosuppressive or cytotoxic therapy

**Risk groups**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>HBV risk estimates (HBsAg positive or anti-HBc positive)</th>
<th>Potential disorders for treatment</th>
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<tbody>
<tr>
<td>High-risk group (&gt;10%)</td>
<td>B cell–depleting agents such as rituximab and ofatumumab</td>
<td>Lymphoma/leukemia, rheumatoid arthritis, idiopathic thrombocytopenic purpura, cryoglobulinemia</td>
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<td></td>
<td>- HBsAg positive/anti-HBc positive: 30%–60% (A)</td>
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<td>- HBsAg negative/anti-HBc positive: &gt;10% (A)</td>
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<td>Anthracycline derivatives such as doxorubicin and epirubicin</td>
<td>Breast, ovarian, uterine, and lung cancers; lymphoma and leukemias; transarterial chemoembolization</td>
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<td>- HBsAg positive/anti-HBc positive: 15%–30% (A)</td>
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<td><strong>Corticosteroid therapy for ≥4 wk</strong></td>
<td>Inflammatory bowel disease, vasculitis, sarcoidosis, autoimmune disorders</td>
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<td></td>
<td>- HBsAg positive/anti-HBc positive: &gt;10% (B) (moderate/high dose)</td>
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Definition of HBV reactivation

A sudden increase in serum HBV DNA level that is most often associated with a hepatitis flare several weeks later, as defined by an increasing ALT level.

Meta analysis: Antivirals vs. Placebo

HBsAg and anti-HBc testing should be performed in all persons before initiation of any immunosuppressive, cytotoxic, or immunomodulatory therapy.

HBsAg +, anti-HBc + patients should initiate anti-HBV prophylaxis before immunosuppressive or cytotoxic therapy.

HBsAg -, anti-HBc + patients could be carefully monitored with ALT, HBV DNA, and HBsAg with the intent for on-demand therapy, except for patients receiving anti-CD20 antibody therapy or undergoing stem cell transplantation, for whom anti-HBV prophylaxis is recommended.

When indicated, anti-HBV prophylaxis should be initiated as soon as possible before or with the onset of immunosuppressive therapy.

Anti-HBV drugs with a high resistance barrier (ETV, TDF, or TAF) should be preferred over low-barrier agents.
All candidates for chemotherapy and immunosuppressive therapy should be tested for HBV markers prior to immunosuppression.

All HBsAg-positive patients should receive ETV or TDF or TAF as treatment or prophylaxis.

HBsAg-negative, anti-HBc positive subjects should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation.

All candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg and anti-HBc prior to initiation of treatment.

Prophylactic anti-viral therapy should be given to HBsAg (+) patients who receive cytotoxic or immunosuppressive therapy.

Physicians should be aware of the risk of HBV reactivation in lymphoma patients with resolved HBV infection who receive rituximab-containing chemotherapy.

HBsAg-negative patients with positive antiHBc antibodies should be tested for HBV DNA.

HBsAg-negative, anti-HBc positive patients who receive chemotherapy and/or immunosuppression regardless of anti-HBs status should be followed, and be treated with NA therapy upon confirmation of HBV reactivation before ALT elevation.
HBsAg、抗HBc和HBV DNA，并评估接受免疫抑制剂的风险程度。在开始免疫抑制剂及化疗药物前一周开始应用抗病毒治疗。对HBsAg阴性、抗HBc阳性者，若使用B细胞单克隆抗体等，可以考虑预防使用抗病毒药物。（A1）。

在化疗和免疫抑制剂治疗停止后，应当继续NAs治疗至少6个月；若应用B细胞单克隆抗体者，停止化疗后继续NAs治疗至少12个月。NAs停用后可出现复发，甚至病情恶化，应注意随访和监测（A1）。
HBV is the predominant cause of HCC in China

What we have known

➢ NAs delay clinical progression in patients with CHB by significantly reducing the incidence of hepatocellular carcinoma.
➢ Patients with sustained virological response had lower risk of HCC.

What we do not know

➢ What’s the difference among variant anti-viral therapies
➢ What’s the best strategic for preventing HCC by antiviral treatent?
Milestone study: NAs reduce the incidence of hepatocellular carcinoma

- A multicenter, centrally randomized, double-blind, placebo-controlled, parallel group study for five years or less. Patients were randomly assigned in a 2:1 ratio to receive LAM or placebo.
- The primary end point was time to disease progression.

Disease progression was defined as: decompensated cirrhosis, hepatocellular carcinoma, SBP, bleeding gastric or esophageal varices, death related to liver disease

C-TEAM study
ETV therapy is associated with HCC risk reduction in CHB-related cirrhosis patients

- A nationwide, multicenter, retrospective and prospective study. 1315 patients were enrolled in the entecavir cohort. 503 patients were enrolled in the untreated cohort.
- HCC was significantly greater in the untreated cohort compared with the entecavir cohort.

China real world study (080 study)
Patients with sustained virological response had lower risk of HCC

➢ A prospective, observational and open-label study conducted in China.
➢ A total of 5305 patients from 50 centers were enrolled.
NAs reduce the incidence of hepatocellular carcinoma

Studies published in English up to July 2014 studies that assessed outcomes of HCC in patients treated with the ETV and TDF.

24 studies were finally included.

In CHB patients treated with the first-line antivirals ETV or TDF, the observed HCC risk was low <5%.
NAs reduce the incidence of hepatocellular carcinoma

Current clinical evidence for nucleos(t)ide analogues in patients with HBV-related hepatocellular carcinoma

Yiqi Yu, Jingwen Ai & Wenhong Zhang

Key issues

- A high prevalence of HBV infection is associated with an increased incidence of HCC
- Antiviral Nucleos(t)ide analogues (NA) treatment improves HBV-related HCC prognosis
NAs reduce the recurrence rate and increase in patients with HBV-related hepatocellular carcinoma

In patients with HBV-related HCC, after surgical resection or local ablation therapy:

- Lower HCC recurrence (33.3 vs. 52.9%, \( P = 0.07 \)) (45.6% vs. 54.6%, \( P < 0.001 \))
Comparison between different NAs: Data from Japan

Patients treated with first-line NAs had lower risk of HCC

➢ A retrospective cohort study.
➢ HCC suppression effect greater in ETV-treated (P < 0.001) than non-rescued LAM-treated (P=0.019) cirrhosis patients when they were compared with the control group.

HCC incidence in patients with cirrhosis

ETV vs. control: p<0.001
LAM vs. control: p=0.019
ETV vs. LAM: p=0.043

HCC incidence in patients without cirrhosis

ETV vs. control: p=0.440
LAM vs. control: p=0.879
ETV vs. LAM: p=0.126

TDF vs. ETV: Real world results from Korea

- A nationwide, population-level, historical cohort study
- **Statistical analysis**: Propensity score-matching analysis, Competing risk analysis, Univariate and multivariable Cox proportional hazards models

Tenofovir treatment was associated with a significantly lower risk of HCC.
A multi-center study of entecavir vs. tenofovir on prognosis of treatment-naive chronic hepatitis B in the Republic of Korea

Seung Up Kim, Yeon Seok Seo, Han Ah Lee, Mi Na Kim, Yu Rim Lee, Hye Won Lee, Jun Yong Park, Do Young Kim, Sang Hoon Ahn, Kwang-Hyub Han, Seong Gyu Hwang, Kyu Sung Rim, Soon Ho Um, Won Young Tak, Young Oh Kweon, Beom Kyung Kim, Soo Young Park

➢ A large-scale, retrospective cohort study
➢ **Statistical analysis:** Propensity score-matching analysis, Univariate and multivariable Cox proportional hazards models

The overall prognosis in terms of HCC and death or OLT were statistically not different between the ETV and TDF groups.

PEG better! NAs vs. PegIFN: data from Taiwan

- A retrospective cohort study
- 330 patients were enrolled

Peginterferon treatment was associated with a reduced incidence of HCC compared with nucleos(t)ide analogs therapy.
Suppression of HBV replication and Immune control of HBV: not the same?

Figure 1  Greater incidence of hepatocellular carcinoma (HCC) in the nucleos(t)ide analogue complete responder (NUC CR) group is shown compared with inactive chronic hepatitis B (CHB) group, regardless of the presence of baseline liver cirrhosis. (A) Cumulative incidence of HCC in the NUC CR group was significantly higher compared with the inactive CHB group. Cumulative incidence of HCC in patients without liver cirrhosis (B) and with liver cirrhosis at baseline (C) showed greater incidence of HCC in the NUC CR group.
Summary

1. NUC do reduce the incidence of HCC but not comparably to that of inactive carrier.
Real world study for IFN add-on therapy

**Sequential Combination Therapy** with Pegylated Interferon Leads to Loss of Hepatitis B Surface Antigen and Hepatitis B e Antigen (HBeAg) Seroconversion in HBeAg-Positive Chronic Hepatitis B Patients Receiving Long-Term Entecavir Treatment

Guo-Jun Li, Yi-Qi Yu, Shao-Long Chen, Ping Fan, Ling-Yun Shao, Jia-Zhen Chen, Chang-Shui Li, Bin Yi, Wei-Cun Chen, Shu-Yuan Xie, Xiao-Na Mao, He-Hui Zou, Wen-Hong Zhang*

Department of Hepatology, the Second Hospital of Yinchuan of Ningxia, Ningxia, China; Department of Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, China; Department of Hepatology, PLA Hospital, Ningbo, China; Institute of Biomedical Sciences, Fudan University, Shanghai, China; MOH and MOE Key Laboratory of Medical Molecular Virology, Shanghai Medical College, Fudan University, Shanghai, China

Antimicrob Agents Chemother. 2015 Jul;59(7):4121-8

![Graph showing HBeAg seroconversion and HBsAg disappearance](image-url)
NAs - PEG IFNα sequential combination therapy increase HBsAg clearance

2017年AASLD

Han MF, et al. AASLD 2017; Abstract 29.
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<th>Study</th>
<th>Study design</th>
<th>Prior NA</th>
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<th>Intervention*</th>
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<td>RCT, multicentre</td>
<td>ETV treated</td>
<td>94</td>
<td>PegIFN α-2a; 48 weeks</td>
<td>1 year</td>
<td>ETV; 19.9 months</td>
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<td>PegIFN α-2a; 48 weeks</td>
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<td>ETV, ADV or LAM; 1–3 years</td>
<td>28.2 PE IU/mL</td>
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<td>Chen X, 2013 (25) China</td>
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<td>ETV treated, with VR</td>
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<td>96 weeks</td>
<td>ETV; 296 weeks</td>
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<td><strong>Add-on combination strategy</strong></td>
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<td>Brouwer WP, 2015 (30) (ARES) Asia, Europe</td>
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<td>ETV pretreated</td>
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<td>Add-on PegIFN α-2a; 48 weeks</td>
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<td>1.1 log_{10} PE IU/mL</td>
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<td>Li GI, 2015 (28)</td>
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<td>Chi H, 2015 (31) (PEGON study) China, Europe</td>
<td>Randomised, multicentre</td>
<td>ETV or TDF treated</td>
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<td>Add-on PegIFN α-2b for 48 weeks</td>
<td>48 weeks</td>
<td>ETV or TDF; 2.4 years</td>
<td>21.0</td>
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^a Short-term treatment with PegIFN or PegIFN plus TDF.

^b Higher virological suppression rates in the PegIFN plus TDF group.

^c Higher rates of virological suppression with PegIFN plus TDF compared to PegIFN alone.

^d Different study populations with varying baseline characteristics.

^e Higher rates of virological suppression with PegIFN plus TDF versus PegIFN alone in Asian populations.
The ultimate goal of clinical cure

Clinical cure after "Sandwich" therapy

Antiviral therapy to inhibit viral replication and decrease serum viral load

Neutralizing monoclonal anti-HBs antibodies therapy to decrease serum HBsAg levels

Specific immune therapy to induce effective host immune responses

Fig. 1 Diagram of expected therapeutic efficacy under proposed "sandwich" strategy

Emerg Microbes Infect. 2018 17;7(1):91
Clinical cure therapy after suppression of HBV DNA

Relationship between serum HBV-RNA levels and intrahepatic viral as well as histologic activity markers in entecavir-treated patients

Graphical abstract

Highlights

- Detectable HBV-RNA in serum of NUC successfully treated patients.
- Serum HBV-RNA is indicative of the transcriptional activity of cccDNA.
- Quasispecies of serum HBV-RNA and intrahepatic HBV-RNA are similar.
- Levels of HBV-RNA correlate with histopathological scores.

Authors

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Lay summary

Serum HBV-RNA levels are indicative of the intrahepatic transcriptional activity of covalently closed circular DNA and are associated with liver histological changes in patients with chronic B hepatitis who are receiving nucleos(t)ide analogue therapy.

The study sheds light on the nature of HBV-RNA in the pathogenesis of chronic HBV infection and has implications for the management of chronic hepatitis B during NUC therapy.

HBV-RNA distribution is highly relevant to METAVIR Score

Benefit beyond ALT normalization

More data from China real world study

- Pyramid (2015)
- Anchor (2014)
- ICURE (2013)
- S-C研究 (2015)
- NEW SWITCH (2011)
- OSST (2009)
- 珠峰工程 (2018)
Will Clinical Cure affect the ultimate outcome of CHB?

<table>
<thead>
<tr>
<th>类别/药物名称</th>
<th>作用机制</th>
<th>生产企业</th>
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<td>临床上已批准的药物</td>
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<td>与病毒mRNA结合以阻止病毒蛋白生成</td>
<td>Ionis Pharma, USA with GSK</td>
<td>未列出</td>
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<td>IO68-HBV-RNA (GSK3389040)</td>
<td>反义RNA</td>
<td>Ionis Pharma, USA with GSK</td>
<td>未列出</td>
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<td>IO68-HBV-RNA</td>
<td>反义RNA</td>
<td>Ionis Pharma, USA with GSK</td>
<td>未列出</td>
</tr>
<tr>
<td>核糖核酸</td>
<td>抑制病毒RNA的合成</td>
<td>Arbutus Biopharma, USA</td>
<td>临床前</td>
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<tr>
<td>ARB-452</td>
<td>核糖核酸</td>
<td>Arbutus Biopharma, USA</td>
<td>临床前</td>
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HEPATITIS B FOUNDATION
http://www.hepb.org/treatment-and-management/drug-watch/
Thank you!
谢谢！