ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2024 July 14; 30(26): 3185-3263

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 30 Number 26 July 14, 2024

EDITORIAL

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

Basic Study

CASE REPORT

LETTER TO THE EDITOR

Contents

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF
Xian-Jun Yu (Pancreatic Oncology), Jian-Gao Fan (Chronic Liver Disease), Hou-Bao Liu

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
July 14, 2024

COPYRIGHT
© 2024 Baishideng Publishing Group Inc

PUBLISHING PARTNER
Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

POLICY OF CO-AUTHORS
https://www.wjgnet.com/bpg/GerInfo/310

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
https://www.shca.org.cn
https://www.zs-hospital.sh.cn

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2024 July 14; 30(26): 3193-3197

DOI: 10.3748/wjg.v30.i26.3193

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Reactivation of hepatitis B virus infection – an important aspect of multifaceted problem

Sergey Morozov, Sergey Batskikh

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade A
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Wang Z

Received: March 14, 2024
Revised: May 28, 2024
Accepted: June 19, 2024
Published online: July 14, 2024
Processing time: 117 Days and 2.9 Hours

Sergey Morozov, Department of Gastroenterology, Hepatology and Nutrition, Federal Research Center of Nutrition, Biotechnology and Food Safety, Moscow 115446, Russia

Sergey Batskikh, Department of Hepatology, Moscow Clinical Scientific Center N.A. A.S. Loginov, Moscow 111123, Russia

Corresponding author: Sergey Morozov, DSc, MD, PhD, Doctor, Senior Researcher, Department of Gastroenterology, Hepatology and Nutrition, Federal Research Center of Nutrition, Biotechnology and Food Safety, Kashirskoye Shosse 21, Moscow 115446, Russia.
morosoffsv@mail.ru

Abstract

In this editorial we comment on the article published in the recent issue of the W*orld Journal of Gastroenterology*. We focus specifically on the problem of occult hepatitis B virus (HBV) infection, that is a result of previous hepatitis B (PHB) and a source for reactivation of HBV. The prevalence of PHB is underestimated due to the lack of population testing programs. However, this condition not only complicate anticancer treatment, but may be responsible for the development of other diseases, like cancer or autoimmune disorders. Here we unveil possible mechanisms responsible for realization of these processes and suggest practical approaches for diagnosis and treatment.

Key Words: Occult hepatitis B virus infection; Hepatitis B virus reactivation; Previous hepatitis B; Cancer; Autoimmune disorders

Core Tip: Occult hepatitis B virus (HBV) infection is a result of previous hepatitis B (PHB) and source for reactivation of HBV. This may be a challenge when anti-cancer treatment is provided. However, PHB is a reason of other disorders, like cancer and autoimmune disorders development. We discuss this multifaceted problem from the viewpoint of pathogenetic mechanisms, and possible practical approaches.

Citation: Morozov S, Batskikh S. Reactivation of hepatitis B virus infection – an important aspect of multifaceted problem. *World J Gastroenterol* 2024; 30(26): 3193-3197
URL: https://www.wjgnet.com/1007-9327/full/v30/i26/3193.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i26.3193

INTRODUCTION

Reactivation of hepatitis B virus (HBV) infection in patients receiving chemotherapy for solid tumors is a known phenomenon that attracts the attention of researchers and healthcare practitioners due to the possible complications, need for the change of the treatment strategy for the main disease, and lack of unified approaches. The continuing interest to the problem may be confirmed by the fact that near 150 papers on this topic was published yearly during 10 recent years. Two of them, including a recent Commentary are available for the readers of *World Journal of Gastroenterology*[1,2].

HBV reactivation may occur decades after hepatitis B is resolved due to impaired or suppressed immune control and persistence of molecular basis for the replication in the form of covalently closed circular DNA (cccDNA). There are three main groups of factors that are associated with higher risks of reactivation: (1) Host factors: male gender, older age, presence of liver cirrhosis and a concurrent disease that requires immune suppression; (2) Viral factors: high baseline viral load, positive hepatitis B e antigen, non-A HBV genotype, coinfection with human immunodeficiency virus (HIV), hepatitis C or D viruses; and (3) Factors of immunosuppression: highest risk is associated with B-cell-depleting agents[3].

A number of drugs that are used for the management of patients with cancer, including tyrosine kinase inhibitors, may also lead to reactivation of resolved HBV infection and this underlines the need for special studies, allowing to identify the risks and provide evidence-based algorithms for the prophylaxis. However, the problem is wider than it looks at first glance.

PREVIOUS HEPATITIS B AND DEVELOPMENT OF OTHER DISEASES

It is well known that HBV has cancerogenic properties. It may lead to hepatocellular carcinoma development, but also is a cause of extrahepatic malignancies[4]. The reported risks vary significantly, and this may be caused by methodological issues. For example, in a number of studies subjects of the main and the control groups were tested only for serum hepatitis B surface antigen (HBsAg), and no analysis for hepatitis B core antibody (anti-HBc) positivity was performed. This could lead to underestimation of risks, because in HBsAg-negative/anti-HBc-positive subjects the odds of cancer development are greater than in those not exposed to HBV[4-8].

According to the current knowledge, natural history of chronic HBV infection is a long-lasting dynamic process that includes V phases[9]. At the final (HBsAg-negative) phase, the commonly used main screening serum marker is cleared out of the blood, and the infection persists either in the form of low-level replication (occult HBV infection), and/or in the form of integrations of viral DNA to the host genome[10].

Duration of exposure to the products of viral gene expression may be crucial for the development of HBV-associated malignancy. It might take several decades from the infection to malignant tumor appearance. Carcinogenic mechanisms of HBV may be realized through direct participation of its X gene and highly conservative HBx protein, which modulates the expression and activity of numerous other genes[11]. Point mutations in the X gene region of HBV and the C-terminal truncation of HBx have been reported responsible for the formation of malignant tumors[12-15]. Due to the fact that in the structure of the HBV genome, the X gene overlaps the C-end of the polymerase gene and the N-end of the core gene, the appearance of mutations and/or deletions in the X gene can disrupt regulation and transcription in both of these genes simultaneously[16,17]. Numerous features confirm participation of HBx in the host immune response, oncogenic signaling pathways, proliferation, apoptosis, inflammation, fibrogenesis and angiogenesis[18].

Integration of HBV DNA and associated production of HBx, leading to genetic instability and insertion mutagenesis [10] may occur not only within the liver, but in other organs[4,19].

Another important issue is the involvement of HBV infection in the pathogenesis of other diseases, including those of an autoimmune nature, with hyperactivation of the immune response after contact with viral antigens[20]. Molecular mimicry, epitope spreading, bystander activation and/or immortalization of infected B cells are possible mechanisms for the development of virus-induced autoimmune reactions in genetically predisposed individuals[21]. It should be born in mind that patients with autoimmune disorders and previous hepatitis B (PHB) are potential candidates for immunosuppressive therapy. This forms a vicious circle, when PHB acts as a trigger or a risk factor for autoimmune disorders or cancer, and at the same time may serve as a source of HBV reactivation when treatment for these diseases is provided (Figure 1)[3].

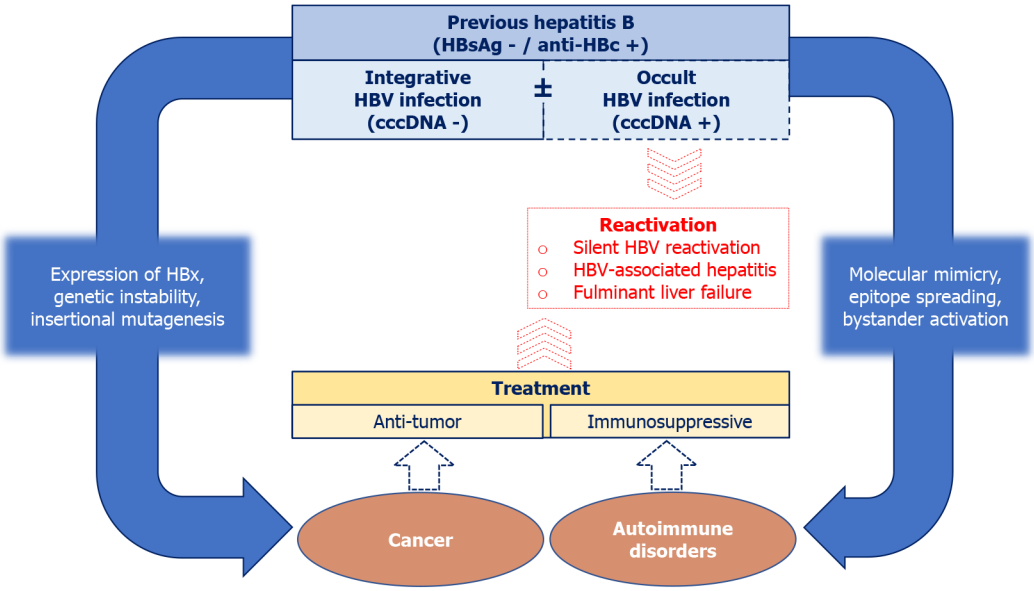

Figure 1 "Vicious circle" of previous hepatitis B. HBV: Hepatitis B virus.

SUGGESTIONS FOR THE COMMON TERMINOLOGY AND REVISION OF OPTIMAL GOALS OF TREATMENT

Current understanding of the mechanisms by which HBV influence host health requires a change of the terminology used. To date, there is no single generally accepted term for a condition that occurs after the resolution of acute or chronic hepatitis B and is characterized by a special set of serological viral markers: negative HBsAg and positive anti-HBc class IgG (in combination with anti-HBs or not). To describe subjects with such a serological profile, when no certain data on the disease history are available, different definitions are used in the literature: "previous HBV infection"[22], "past exposure to hepatitis B"[23], "past HBV infection"[24], "resolved HBV infection"[25], and even "anti-HBc alone"[26]. In case of a sustained HBsAg loss and undetectable level of HBV DNA, combined with the absence of clinical or histological signs of active viral infection in an individual who was previously HBsAg-positive, the term "resolved chronic hepatitis B" is proposed[27].

Keeping in mind that cccDNA (responsible for new virions synthesis) and fragments of the viral DNA integrated into the host genome (some of them can express viral proteins) are usually preserved after HBsAg clearance, it is not correct to talk about the *infection* in the past tense. At the same time, *hepatitis* caused by HBV, which usually implies the presence of inflammatory changes in the liver, has different activity at certain stages of the disease and practically disappears in the final (V) phase (HBsAg-negative). In this regard, the term we propose, "previous hepatitis B" (PHB), which indicates the presence of an integrative infection (with or without occult HBV infection), more accurately reflects the essence of this condition and indicates clinically relevant status in those HBsAg-negative/anti-HBc-positive patients who were not tested for serum HBV DNA, or in whom the result was negative.

It is important that not just current active infection, but previous contact with the virus (PHB) itself may cause damage to liver tissue, development of liver cirrhosis and cancer. Therefore, current approaches for treatment of HBV infection with "functional cure" (defined as sustained HBsAg clearance with or without HBs seroconversion and undetectable HBV DNA in the blood after treatment) as a primary goal seems not to be sufficient. Functional cure may help to reduce the problem of HBV reactivation to some degree, but is not able to stop the expression of oncogenic HBV proteins. Only "sterilizing cure", with complete elimination of viral DNA fragments from the host genome, may solve the problem of reactivation of HBV infection (when different classes of anticancer and immunosuppressive drugs are used) and cancer development.

Although elimination of cccDNA and integrated fragments of the viral genome is not possible using current treatment options, it should be indicated as the ultimate therapeutic target for the future.

PRACTICAL POINTS

There is an obvious need for several practical measures, including: (1) Wider population screening for HBV markers (not only HBsAg, but also, at least, anti-HBc), especially in endemic regions; (2) Stratification of complex risks of HBV reactivation in subjects with PHB receiving anticancer or immunosuppressive medications in consideration of all factors, including those of host, viral and the type of treatment; (3) Development of integrated system (including those based on the artificial intelligence) for the assessment of personalized risks of cancer of different organs in subjects with PHB; and (4) Implementation of advanced algorithms of screening, follow-up and management of comorbid disorders in subjects

with PHB to minimize the risks of HBV reactivation and provide optimal and safe treatment.

CONCLUSION

Previous hepatitis B is a multifaceted problem that includes not only HBV reactivation, but also participation of the virus in pathogenesis of autoimmune disorders and cancer. Subjects with PHB and occult infection may have a potential risk for virus transmission during blood transfusion and transplantation.

FOOTNOTES

Author contributions: Morozov S and Batskikh S contributed to this paper; Morozov S and Batskikh S designed the overall concept and outline of the manuscript. All authors contributed to the discussion and design of the manuscript. All authors contributed to the writing, and editing the manuscript, illustrations, and review of literature.

Supported by Ministry of Science and Higher education of Russia, No. FGMF-2022-0005; and Moscow Healthcare Department, No. 123040700014-4.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country of origin: Russia

ORCID number: Sergey Morozov 0000-0001-6816-3058; Sergey Batskikh 0000-0002-5917-203X.

Corresponding Author's Membership in Professional Societies: International Society for Diseases of the Esophagus, No. 45108704; European Society for Neurogastroenterology and Motility, No. 22458; American Society for Nutrition, No. 87591.

S-Editor: Qu XL
L-Editor: Kerr C
P-Editor: Yuan YY

REFERENCES

1 **Colapietro F**, Pugliese N, Voza A, Aghemo A, De Nicola S. Risk of hepatitis B virus reactivation in oncological patients treated with tyrosine kinase inhibitors: A case report and literature analysis. *World J Gastroenterol* 2024; **30**: 1253-1256 [PMID: 38577192 DOI: 10.3748/wjg.v30.i9.1253]

2 **Mak JWY**, Law AWH, Law KWT, Ho R, Cheung CKM, Law MF. Prevention and management of hepatitis B virus reactivation in patients with hematological malignancies in the targeted therapy era. *World J Gastroenterol* 2023; **29**: 4942-4961 [PMID: 37731995 DOI: 10.3748/wjg.v29.i33.4942]

3 **Loomba R**, Liang TJ. Hepatitis B Reactivation Associated With Immune Suppressive and Biological Modifier Therapies: Current Concepts, Management Strategies, and Future Directions. *Gastroenterology* 2017; **152**: 1297-1309 [PMID: 28219691 DOI: 10.1053/j.gastro.2017.02.009]

4 **Song C**, Lv J, Liu Y, Chen JG, Ge Z, Zhu J, Dai J, Du LB, Yu C, Guo Y, Bian Z, Yang L, Chen Y, Chen Z, Liu J, Jiang J, Zhu L, Zhai X, Jiang Y, Ma H, Jin G, Shen H, Li L, Hu Z; China Kadoorie Biobank Collaborative Group. Associations Between Hepatitis B Virus Infection and Risk of All Cancer Types. *JAMA Netw Open* 2019; **2**: e195718 [PMID: 31199446 DOI: 10.1001/jamanetworkopen.2019.5718]

5 **Coppola N**, Onorato L, Sagnelli C, Sagnelli E, Angelillo IF. Association between anti-HBc positivity and hepatocellular carcinoma in HBsAg-negative subjects with chronic liver disease: A meta-analysis. *Medicine (Baltimore)* 2016; **95**: e4311 [PMID: 27472708 DOI: 10.1097/MD.0000000000004311]

6 **Yip TC**, Chan HL, Wong VW, Tse YK, Lam KL, Wong GL. Impact of age and gender on risk of hepatocellular carcinoma after hepatitis B surface antigen seroclearance. *J Hepatol* 2017; **67**: 902-908 [PMID: 28652084 DOI: 10.1016/j.jhep.2017.06.019]

7 **Luo G**, Hao NB, Hu CJ, Yong X, Lü MH, Cheng BJ, Zhang Y, Yang SM. HBV infection increases the risk of pancreatic cancer: a meta-analysis. *Cancer Causes Control* 2013; **24**: 529-537 [PMID: 23306552 DOI: 10.1007/s10552-012-0144-2]

8 **Wang Y**, Yang S, Song F, Cao S, Yin X, Xie J, Tu X, Xu J, Xu X, Dong X, Lu Z. Hepatitis B virus status and the risk of pancreatic cancer: a meta-analysis. *Eur J Cancer Prev* 2013; **22**: 328-334 [PMID: 23165286 DOI: 10.1097/CEJ.0b013e32835b6a21]

9 **European Association for the Study of the Liver**. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]

10 **Budzinska MA**, Shackel NA, Urban S, Tu T. Cellular Genomic Sites of Hepatitis B Virus DNA Integration. *Genes (Basel)* 2018; **9** [PMID: 30037029 DOI: 10.3390/genes9070365]

11 **Liu S**, Koh SS, Lee CG. Hepatitis B Virus X Protein and Hepatocarcinogenesis. *Int J Mol Sci* 2016; **17** [PMID: 27314335 DOI: 10.3390/ijms17060940]

12 **Ng KY**, Chai S, Tong M, Guan XY, Lin CH, Ching YP, Xie D, Cheng AS, Ma S. C-terminal truncated hepatitis B virus X protein promotes hepatocellular carcinogenesis through induction of cancer and stem cell-like properties. *Oncotarget* 2016; **7**: 24005-24017 [PMID: 27006468 DOI: 10.18632/oncotarget.8209]

13 **Tu H**, Bonura C, Giannini C, Mouly H, Soussan P, Kew M, Paterlini-Bréchot P, Bréchot C, Kremsdorf D. Biological impact of natural COOH-terminal deletions of hepatitis B virus X protein in hepatocellular carcinoma tissues. *Cancer Res* 2001; **61**: 7803-7810 [PMID: 11691796]

14 **Wang D**, Cai H, Yu WB, Yu L. Identification of hepatitis B virus X gene variants between hepatocellular carcinoma tissues and pericarcinoma liver tissues in Eastern China. *Int J Clin Exp Pathol* 2014; **7**: 5988-5996 [PMID: 25337243]

15 **Wang Y**, Zeng LI, Chen W. HBV X gene point mutations are associated with the risk of hepatocellular carcinoma: A systematic review and meta-analysis. *Mol Clin Oncol* 2016; **4**: 1045-1051 [PMID: 27284442 DOI: 10.3892/mco.2016.847]

16 **Pollicino T**, Vegetti A, Saitta C, Ferrara F, Corradini E, Raffa G, Pietrangelo A, Raimondo G. Hepatitis B virus DNA integration in tumour tissue of a non-cirrhotic HFE-haemochromatosis patient with hepatocellular carcinoma. *J Hepatol* 2013; **58**: 190-193 [PMID: 22989571 DOI: 10.1016/j.jhep.2012.09.005]

17 **Levrero M**, Pollicino T, Petersen J, Belloni L, Raimondo G, Dandri M. Control of cccDNA function in hepatitis B virus infection. *J Hepatol* 2009; **51**: 581-592 [PMID: 19616338 DOI: 10.1016/j.jhep.2009.05.022]

18 **Tarocchi M**, Polvani S, Marroncini G, Galli A. Molecular mechanism of hepatitis B virus-induced hepatocarcinogenesis. *World J Gastroenterol* 2014; **20**: 11630-11640 [PMID: 25206269 DOI: 10.3748/wjg.v20.i33.11630]

19 **Batskikh S**, Morozov S, Dorofeev A, Borunova Z, Kostyushev D, Brezgin S, Kostyusheva A, Chulanov V. Previous hepatitis B viral infection-an underestimated cause of pancreatic cancer. *World J Gastroenterol* 2022; **28**: 4812-4822 [PMID: 36156926 DOI: 10.3748/wjg.v28.i33.4812]

20 **Batskikh S**, Morozov S, Vinnitskaya E, Sbikina E, Borunova Z, Dorofeev A, Sandler Y, Saliev K, Kostyushev D, Brezgin S, Kostyusheva A, Chulanov V. May Previous Hepatitis B Virus Infection Be Involved in Etiology and Pathogenesis of Autoimmune Liver Diseases? *Adv Ther* 2022; **39**: 430-440 [PMID: 34762287 DOI: 10.1007/s12325-021-01983-5]

21 **Smatti MK**, Cyprian FS, Nasrallah GK, Al Thani AA, Almishal RO, Yassine HM. Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms. *Viruses* 2019; **11** [PMID: 31430946 DOI: 10.3390/v11080762]

22 **Lok AS**, Everhart JE, Di Bisceglie AM, Kim HY, Hussain M, Morgan TR; HALT-C Trial Group. Occult and previous hepatitis B virus infection are not associated with hepatocellular carcinoma in United States patients with chronic hepatitis C. *Hepatology* 2011; **54**: 434-442 [PMID: 21374690 DOI: 10.1002/hep.24257]

23 **Yeo D**, Hossain I, Lim ST, Farid M, Tao M, Quek R, Tang T, Chan A. Management of hepatitis B reactivation in lymphoma patients on rituximab with past hepatitis B exposure: An observational study. *J Oncol Pharm Pract* 2019; **25**: 1042-1052 [PMID: 29554828 DOI: 10.1177/1078155218763039]

24 **Iossa D**, Vitrone M, Liotti A, Portella G, Durante-Mangoni E, Zampino R. Hepatitis B core-related antigen to detect hepatitis B virus (HBV) reactivation in heart transplant recipients with past HBV infection: A pilot study. *Clin Transplant* 2019; **33**: e13574 [PMID: 31013373 DOI: 10.1111/ctr.13574]

25 **Kotake T**, Satake H, Okita Y, Hatachi Y, Hamada M, Omiya M, Yasui H, Hashida T, Kaihara S, Inokuma T, Tsuji A. Prevalence and risk factors of hepatitis B virus reactivation in patients with solid tumors with resolved HBV infection. *Asia Pac J Clin Oncol* 2019; **15**: 63-68 [PMID: 29984542 DOI: 10.1111/ajco.13050]

26 **Wang Q**, Klenerman P, Semmo N. Significance of anti-HBc alone serological status in clinical practice. *Lancet Gastroenterol Hepatol* 2017; **2**: 123-134 [PMID: 28403982 DOI: 10.1016/S2468-1253(16)30076-0]

27 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com