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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63182

Title: Viral hepatitis update: progress and perspectives

Reviewer's code: 03646555

Position: Peer Reviewer

Academic degree: FRACP, MBBS

Professional title: Attending Doctor, Lecturer, Staff Physician

Reviewer's Country/Territory: Australia

Author's Country/Territory: Argentina

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Reviewer chosen by: Man Liu

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The authors must be commended for a comprehensive review. There are areas to improve: 1) Very minor English language polishing is needed, some sentences have minor grammar errors e.g. page 5 "Despite that HAV was discovered more than 4 decades ago" e.g. page 13 "One of the most appealing strategies implies targeting HBV cccDNA and its transcriptional activity" page 21 "However, it should be bear in mind that besides treatment is expected to eliminate the risk" page 22 "it is expected a risk reduction since the viral clearance lower morbidity and mortality rates" 2) The sections on each type of hepatitis should have subheadings to break them up, for ease of reading (e.g. molecular basis, epidemiology, treatment, vaccination) 3) Given how wide-ranging and discursive this article is, I think an additional table/box would be helpful that concisely summarises the key recent advancements for each hepatitis, the strategies currently under investigations, and the future research needs. 4) In the abstract the sentence "Viral acute hepatitis can be resolved without intervention or it can sometimes turn into a chronic infection" should be clarified that this pertains only to hepatitis B, C, D and E, not hepatitis A. 5) It is stated in the Hepatitis A section discussing circulation patterns "a) in high endemicity areas from low- and middle-income countries, where the incidence varies from low to high, there is a peak age of infection in early childhood, the transmission pattern is person-to-person, and outbreaks are uncommon". This sentence is a bit confusing. What does "where the incidence varies from low to high" mean? Does it mean the incidence varies over time? Or between different regions of the country? Similarly, why would outbreaks be uncommon in a region of high endemicity, and common in regions of low endemicity?

6) It is stated that "Because of HAV pediatric immunization, in addition to the improvement of socio-economic, hygienic and sanitation measures, young adults are now becoming more susceptible to HAV infections, so the prevalence of symptomatic

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cases in this age group has increased." I don't understand the link between the two clauses of this sentence. Why would better immunization and improvement of hygiene lead to young adults becoming more susceptible to infection, not the other way round?

7) The HAVNET should be defined. 8) In the hepatitis B section it is stated "from HBeAg-negative infection (formerly called inactive carrier state) to chronic hepatitis with different degrees of severity". I think this definition of inactive carrier state is inadequate. Not all HbeAg-negative infection is an inactive carrier state, which was defined as (as per Kumar et al, Virol J. 2005; 2: 82) "absence of HBeAg and presence of anti-HBe, undetectable or low levels of HBV DNA in PCR-based assays, repeatedly normal ALT levels, and minimal or no necroinflammation, slight fibrosis, or even normal histology on biopsy". 9) It is stated regarding hepatitis B chronicity that "gender, alcohol intake, obesity, and comorbidities were also reported to play a role"- in what way? Can the effect of these factors be described in more detail? 10) The authors quote a study by Liu et al stating "Nonetheless, qHBsAg has become a useful diagnostic tool to discriminate low replicative chronic HBeAg-negative infections from HBeAg-negative chronic hepatitis" in a paragraph that is discussing the correlation of qHBsAg with cccDNA. However the study by Liu et al does not analyse cccDNA levels at all. Furthermore, its findings were not exactly that once-off qHBsAg measurement helps to "discriminate low replicative chronic HBeAg-negative infections from HBeAg-negative chronic hepatitis". In fact, "The correlation between baseline HBsAg and HBV DNA levels was moderately low, with a correlation coefficient $R = 0.369$ ($P < 0.001$)." Instead, it was useful in predicting an inactive carrier state over an 18 month follow up period, wherein the viral load remained persistently <2000 IU/mL. The practical applicability of qHBsAb measurement was in obviating the need for regular viral load measurements over time.

11) The authors state "NAs rarely achieves functional cure and have high chances of HBV reactivation when therapy is discontinued, implying lifelong therapy". However

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there is an increasing body of literature discussing the prevalence of sAg loss and functional cure with a "therapeutic flare" after NA discontinuation. See Hadziyannis et al Gastroenterology 2012, 143, 629–636.e1; Jeng et al Gastroenterology 2012, 143, 629–636.e1; Papatheoridis et al Antivir. Ther. 2018, 25, 25; Liu et al Hepatology 2019, 70, 1045–1055; Hall et al Viruses 2020 Aug 25;12(9):934;. This could be discussed in brief. 12) The paragraph opening the Hepatitis C section, detailing its historical discovery, could be shortened to a sentence or two. At present it seems unnecessarily long and hagiographic.

13) It is stated "When cured patients eventually are re-infected with HCV, it is still not clear if they will need to be DAA re-treated or if they could spontaneously control HCV infection since their immunity will be restored after a successful DAA treatment". I am unaware of any international guidelines, let along empirical evidence, that suggests that reinfected patients could "spontaneously control HCV infection". All guidelines advocate for retreatment of this patient population to reduce further morbidity, transmission and mortality (especially as many HCV patients may be re-infected with different genotypes). The authors cite an article by Maticic et al after this sentence. However, the article does not mention anything about this... 14) The authors state "transplanting organs from HCV-infected donors into infected or uninfected recipients is now a reality." However I think this paragraph presents view of this situation that is a bit too premature and optimistic. AASLD 2020 guidelines by Ghany et al state "Although early outcome data are encouraging, the overall experience is limited, and many ethical issues and scientific questions remain, such as avoidance of selection bias, the optimal timing of DAA therapy, detailed evaluation of drug–drug interactions between DAAs and immunosuppressants, and long - term graft and patient outcomes... there are no data on possible long - term hepatic and extrahepatic adverse effects associated with HCV exposure, even among those cured of the infection." As such, transplanting livers from HCV-infected donors into uninfected recipients requires special approval from

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governing bodies in the USA and in nearly all countries around the world. It is by no means a mainstream reality. 15) The authors describe that "DAA therapy reports informed a potential high risk of HCC occurrence and recurrence after treatment". However this paragraph should be deemphasised. As the authors state, "it is likely that the impact of DAAs on HCC risk may be an old tale"- this is truly the case, expert opinion and large prospective studies/meta-analyses show that the previous fears raised by the articles of Reig et al and Conti et al from around 2016 are unfounded; and were likely affected by selection bias of older, more cirrhotic patients compared to previous IFN-based studies. See studies by Guarino et al, Liver Cancer International, July 2020, 1:1 pp 12-2; Waziry et al J Hepatol 2017;67:1204-12; Saraiya et al Aliment Pharmacol Ther 2018;48:127-37; Ioannou et al J Hepatol 2018, 68, 25–32. Essentially, I believe that this matter is no longer under debate and doesn't need to be highlighted in this review article. The implications of those previous fears (making clinicians reluctant to offer HCV treatment to those with previous HCC/ those at perceived high HCC risk) are clinically detrimental to the patient population at large. 16) The hepatitis E section has no paragraph about treatment of hepatitis E. While the vast majority of cases are of course treated conservatively, there are worthwhile discussions to be had about the role of ribavirin or IFN treatment in certain scenarios, especially post transplant (see Shrestha et al Euroasian J Hepatogastroenterol. 2017 Jan-Jun; 7(1): 73–77; Goel et al Expert Rev Gastroenterol Hepatol. 2016 Sep;10(9):1065-74., Lhomme et al J Clin Med. 2020 Feb; 9(2): 331; Horvatits et al Viruses. 2019 Jul; 11(7): 617.)

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63182

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Reviewer's code: 03646555
Position: Peer Reviewer
Academic degree: FRACP, MBBS
Professional title: Attending Doctor, Lecturer, Staff Physician
Reviewer's Country/Territory: Australia
Author's Country/Territory: Argentina

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Reviewer accepted review: 2021-04-18 08:25
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Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

To the authors Thank you very much for taking most of my suggestions on board. I am

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really honoured to have been involved in such an substantial piece of work. Where you have argued against my suggestions, your reasoning was very clear and sensible, and I do agree with your positions. I would please ask for a bit more clarification in the revised manuscript of the following two paragraphs which remain a little bit confusing to the casual reader, incorporating the excellent responses that you have given me: 1) "Three circulation patterns have historically been described for HAV: a) in high endemicity areas from low- and middle-income countries, where the incidence varies from low to high, there is a peak age of infection in early childhood, the transmission pattern is person-to-person, and outbreaks are uncommon; b) in moderate endemicity areas, from middle-income countries (regions where sanitary conditions are variable), the incidence is high, the peak age of infection is in the late childhood/adolescence or in young adults, the transmission pattern is also from person-to-person, food and water, and therefore outbreaks are common; and c) in low endemicity areas from high income-countries, the incidence is low, the peak age of infection is in young adulthood, the transmission pattern is from person-to-person, and also by food and water; and outbreaks are common[3]." Perhaps it could be (my suggested additions in CAPITAL LETTERS): "Three circulation patterns have historically been described for HAV: a) in high endemicity areas from low- and middle-income countries, where the incidence varies from low to high OVER TIME AND BETWEEN DIFFERENT REGIONS, there is a peak age of infection in early childhood WHICH IS FREQUENTLY ASYMPTOMATIC, the transmission pattern is person-to-person, and outbreaks are uncommon DUE TO HIGH RATES OF IMMUNITY FROM PREVIOUS CHILDHOOD INFECTION; b) in moderate endemicity areas, from middle-income countries (regions where sanitary conditions are variable), the incidence is high, the peak age of infection is in the late childhood/adolescence or in young adults WHICH IS FREQUENTLY SYMPTOMATIC, the transmission pattern is also from person-to-person, food and water, and therefore

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outbreaks are common DUE TO LOW RATES OF IMMUNITY FROM PREVIOUS CHILDHOOD INFECTION; and c) in low endemicity areas from high income-countries, the incidence is low, the peak age of infection is in young adulthood WHICH IS FREQUENTLY SYMPTOMATIC, the transmission pattern is from person-to-person, and also by food and water; and outbreaks are common DUE TO LOW RATES OF IMMUNITY FROM PREVIOUS CHILDHOOD INFECTION[3]. 2) "Because of HAV pediatric immunization, as well as the improvement of socio-economic, hygienic and sanitation measures, young adults are now becoming more susceptible to HAV infections, so in areas of low and middle-endemicity, the prevalence of symptomatic cases in this age group has increased[6]." Perhaps it could be (my suggested additions in CAPITAL LETTERS): "RECENT improvement of socio-economic, hygienic and sanitation measures MAY TRANSLATE INTO AN INCREASE IN THE NUMBER OF ADULTS WHO HAVE NEVER BEEN INFECTED IN CHILDHOOD AND THEREFORE LACK IMMUNITY. FURTHERMORE, DESPITE PEDIATRIC IMMUNIZATION PROGRAMS, MANY YOUNG ADULTS MAY HAVE BEEN ABOVE THE CUT-OFF AGES TO BE INCLUDED WHEN SUCH SOCIAL PROGRAMS WERE INTRODUCED. Therefore, young adults are now becoming more susceptible to HAV infections in areas of low and middle-endemicity, and the prevalence of symptomatic cases in this age group has increased[6]."