Fourth, since the reported rates of virological relapsers or clinical relapsers are comparable between Asian and European studies, there seems insufficient scientific evidence to support the suggestion that consolidation therapy >3 years is better than the shorter but still >1 year consolidation in reducing relapse rates. Nevertheless, we did notice that consolidation therapy >2 years led to a lower off-TDF clinical relapse rate,[5] but not in off-ETV patients (Jeng WJ, *et al.* Hepatology 2019;70:296a-297a). In addition, neither TDF therapy nor duration of consolidation therapy were significant factors for HBsAg loss in our large study.[6] Finally, 2 studies (206 *vs.* 381 and 72 *vs.* 158 patients, respectively) with 5–8-year follow-up duration in pretherapy cirrhotic patients have shown that the incidence of hepatocellular carcinoma (HCC) is not higher in patients who stopped ETV compared to those who continued therapy.[2] Since HCC event rates are notoriously low, larger studies with longer follow-up are needed to ensure that this is not due to type II error.

In conclusion, we concur that the much increased off-therapy HBsAg loss rate is the main justification for finite NA therapy and that it is time to promote this strategy as a "firm recommendation" instead of an "option" in the guidelines of major liver associations. The high HBsAg loss rate of this strategy has also set the benchmark against which new drugs aimed at functional cure must be tested. The main challenge remaining for successful finite NA therapy relates to the timing of retreatment, which must not be too early (to allow for a sufficient immune response), nor too late (to ensure the safety of patients).[9] The finite NA therapy strategy in hepatitis B patients with cirrhosis has already been accepted by APASL guidelines, as reviewed elsewhere recently.[10] Whether the strategy is also feasible in Caucasian patients with cirrhosis awaits further studies from Western countries and/or in patients infected with HBV of genotype(s) other than B and C.

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Conflict of interest
The authors have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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Authors' contributions
Wen-Juei Jeng: Concept, manuscript drafting. Rong-Nan Chien: manuscript revision. Yun-Fan Liaw: Concept, manuscript revision.

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Wen-Juei Jeng[1,2,3]
Rong-Nan Chien[1,3]
Yun-Fan Liaw[1,3,*]
[1]*Liver Research Unit, Chang Gung Memorial Hospital, Taiwan*
[2]*Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou Medical Center, Taiwan*
[3]*College of Medicine, Chang Gung University, Taiwan*
[*]Corresponding author. Address: Liver Research Unit, Chang Gung Memorial Hospital, 199 Tung Hwa North Road, Taipei, 105, Taiwan; Tel.: 886-3-3281200 ext. 8120, fax: 886-3-3282824.
E-mail address: liveryfl@gmail.com (Y.-F. Liaw)

Reply to: Correspondence on 'the times they are a-changing - A refined proposal for finite HBV nucleos(t)ide analogue therapy.'

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To the Editor:
We would like to thank Wen-Juei Jeng and his colleagues for sharing their thoughts on this important topic and also for clarifying again the design of the Taiwanese nucleos(t)ide

analogue (NA) discontinuation trials.[1] All the issues raised are valid and highlight the need to further evaluate several important aspects of the finite NA strategy, from the duration of consolidation therapy to the predictors of treatment cessation and retreatment strategies.

In particular, we agree that induction of HBsAg loss, so-called functional cure, should be the main indication for considering a finite NA approach in HBeAg-negative disease. In this regard, however, the implications of numerous studies evaluating the finite approach in which the main endpoint was either the percentage of a virologic or clinical relapse are limited because, as also pointed out by Jeng and colleagues, relapse is not only almost universal but also an integral part of the stop-to-cure approach, and the ultimate trigger for HBsAg loss.[2]

In addition, the results of the Asian real-world studies are affected to some extent by the fact that early virologic and biochemical relapse episodes may have been missed, because HBV DNA and ALT levels were monitored less frequently after stopping NA treatment than in the prospective randomised controlled trials, and because no clear predefined rules for starting retreatment were applied. These factors are important both for the general assessment of the outcome after discontinuation of NAs and in particular for the question of long-term HBsAg response, since the timing of re-therapy also influences the chance of a functional cure.

We also agree that the lower the HBsAg level at the end of treatment, the greater the chance of getting rid of HBsAg after stopping NAs, and that an HBsAg level of <100 IU/ml should be a strong indicator to give stopping NA a chance. However, in our view and based on the experience from our prospective FINITE study, in which none of the patients who lost their HBsAg had an HBsAg level below 100 IU/ml,[3] we should aim for a less stringent HBsAg threshold to give more patients a chance to achieve a functional cure. As far as the indication to stop NA before HBsAg loss in patients with cirrhosis is concerned, we think that this population should be handled with special care given the effectiveness and safety of the current strategy based on long-term administration of potent NAs. In our opinion, prematurely stopping NAs before HBsAg loss in patients with cirrhosis is not “ready for prime time” which means it should not be pursued in clinical practice, outside a clinical trial, given the risk of a clinical decompensation following NA withdrawal.

Masaru Enomoto and colleagues addressed the topic of end-of-treatment predictors and the costs of NA withdrawal.[4] The combination of low HBsAg and HBcrAg levels could be useful to identify a subgroup of patients at low risk of off-treatment relapse but this was not confirmed in the CREATE study. In this study, HBcrAg levels at end-of-treatment in the Asian population did not predict virological response or HBsAg loss but only ALT flares.[5] Moreover, as mentioned in our Expert Opinion, we believe that the endpoint of NA discontinuation before HBsAg loss should be functional cure, as virologic relapses are nearly universal and clinical relapses also do not exclude the possibility of achieving a functional cure. Cost could be an argument either in favor or against stopping NA therapy, according to local reimbursement rules. The possible role of the “stop-to-cure” strategy in resource-limited countries where HBV is prevalent deserves attention: in Africa for example, the cost of diagnostics is currently higher than the cost of antiviral drugs,[6] speaking in favor of long-term continuous therapy with limited monitoring.

The relationship between post-therapy ALT flares and HBsAg loss rates was discussed by George Papatheodoridis and colleagues.[7] We agree that this relationship deserves further studies as many HBeAg-negative patients may achieve functional cure without any significant off-therapy ALT flare or even significant HBV DNA rebound. End-of-treatment or early off-therapy predictors may be instrumental to identify these patients as early as possible. As already demonstrated several years ago in HBeAg-negative patients treated with IFNα, two different pathways to HBsAg loss were observed: some patients achieved functional cure after a significant ALT flare occurring within the first 6 months off therapy, while others became HBsAg negative without any major biochemical or virological event. While the current model of NA discontinuation before HBsAg loss seems to parallel that observed in IFN-treated patients, it is unknown if the molecular and immunological mechanisms behind these observations are also similar. The need for strict monitoring, which adds significant complexity and cost to the finite NA strategy, is indeed time related, being mainly concentrated in the first 12 months off therapy. However, in our opinion, this strategy remains difficult to adopt in non-expert liver centers or outside well designed and carefully performed clinical studies given the complicated dynamics of the different viral and non-viral biomarkers and the need to identify the best time to restart a NA – not too early to hamper any possible beneficial ALT flare but not too late to prevent any unfavorable outcome.

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Authors’ contributions

TB and PL both drafted the concept of this expert opinion article and wrote the manuscript.

Supplementary data

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Pietro Lampertico[1,2]
Thomas Berg[3,*]

[1]*Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy*
[2]*CRC "A. M. and A. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy*
[3]*Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany*
[*]Corresponding author. Address: Division of Hepatology, Department of Medicine II, LEIPZIG UNIVERSITY MEDICAL CENTER, Liebigstraße 20, Haus 4, 04103 Leipzig, Germany; Tel.: +49 341 97 12330, fax: +49 341 97 12339.
E-mail address: thomas.berg@medizin.uni-leipzig.de (T. Berg)

Multiple investigations for a very common disorder: Finding the right balance in NAFLD

To the Editor:

Liebe *et al.*'s excellent and comprehensive review of secondary causes for non-alcoholic fatty liver disease (NAFLD) raises important questions for the diagnostician.[1] How far do we go to find unusual conditions when the data available points to a very common one. As the American physician Theodore Woodward said in the 1940s, 'When you hear hoofbeats behind you, don't expect to see a zebra'.

Clinicians, especially trainees, are hard-wired to prioritise safety, and if there is a likelihood of an unusual diagnosis, they are likely to test for it. This tendency feeds into the phenomenon of over-diagnosis, as articulated by Iona Heath who wrote 'So doctors, perhaps especially young doctors, are learning to be afraid of uncertainty. We order ever more tests to try, often in vain, to be sure about what we are seeing.'.[2] Excessive testing to facilitate unusual diagnoses can lead to unintended patient harm as indeterminate or false positive results lead to patient anxiety, unnecessary tests, procedures and treatments and can distract from the most important.[3]

NAFLD is already associated with over-diagnosis, made all the more important as there is currently no highly effective, widely available medical therapy.[4] The risks of over-diagnosis may be physical, psychological, or economic.[5–7]

In terms of this review, greater awareness of secondary causes is of course desirable. Yet, discretion should be exercised in 'chasing down' these causes. For instance, triggering investigations into lysosomal acid lipase deficiency on the basis of splenic and liver enlargement may not be justified for a condition that affects between 1:40,000–300,000 in those presenting in childhood or adulthood.[8] The same argument applies to Wilson's disease, especially in the older population.

The authors admit that 'The majority of NAFLD cases are observed as a constituent of the metabolic syndrome, caused by excess nutrition', but in clinical practice there are often grey areas. Elements of the metabolic syndrome may appear slightly incomplete or borderline, there may be mild gastrointestinal symptoms on review of systems, or vague references may be made to other family members with liver disease. It is very easy in these situations to spread a wide net. We calculate that in our hospital it would cost at least €200 to complete the easily available blood tests shown on the investigation algorithm, rising to over €1,500 per patient if endoscopy, slit lamp and breath tests were arranged. Invasive procedures like endoscopy can be associated with significant risks and should be used judiciously. Given the high population prevalence of 'simple' NAFLD, there is potential for large scale expenditure and elongation of diagnostic pathways unless clinicians exercise caution in this area.

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