Hepatology International (2019) 13:665–673
https://doi.org/10.1007/s12072-019-09989-6

REVIEW ARTICLE

Finite nucleos(t)ide analog therapy in HBeAg-negative chronic hepatitis B: an emerging paradigm shift

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Received: 11 July 2019 / Accepted: 3 September 2019 / Published online: 26 September 2019

Abstract

Potent nucleos(t)ide analogs (NUC), such as entecavir and tenofovir disoproxil fumarate, are able to suppress HBV DNA to undetectable level. These agents have no direct action on cccDNA, which is a very stable template for HBV production, hence long-term or even life-long NUC therapy is required in HBeAg-negative patients to maintain HBV suppression and to achieve the ultimate goal of HBsAg loss. However, there are concerns of indefinite or life-long NUC therapy, including drug resistance, financial burden, adherence and willingness for indefinite long-term NUC therapy. Patients lost to follow-up and hence, not monitored may risk severe relapse that may deteriorate to hepatic decompensation or even hepatic failure. This Review integrated the cumulated evidence and assessed the strategy of finite NUC therapy in HBeAg-negative patients which was first tried in early 2000s. Earlier Asian findings that 2-year NUC therapy is feasible and safe have founded APASL stopping rule for patients on NUC therapy over 2–3 years since 2008. Subsequent studies have supported the strategy of finite NUC therapy, which has finally been accepted as an option by American and European liver associations since 2016. More recent studies have further shown greatly increased HBsAg loss rate (up to 5-year 39%) after stopping NUC therapy. The cumulated evidence has shown that the paradigm shift from indefinite long-term therapy to finite NUC therapy in HBeAg-negative patients is emerging. More studies are needed to fine-tuning the strategy including research for the optimal duration of consolidation therapy, timing to stop and to start re-treatment.

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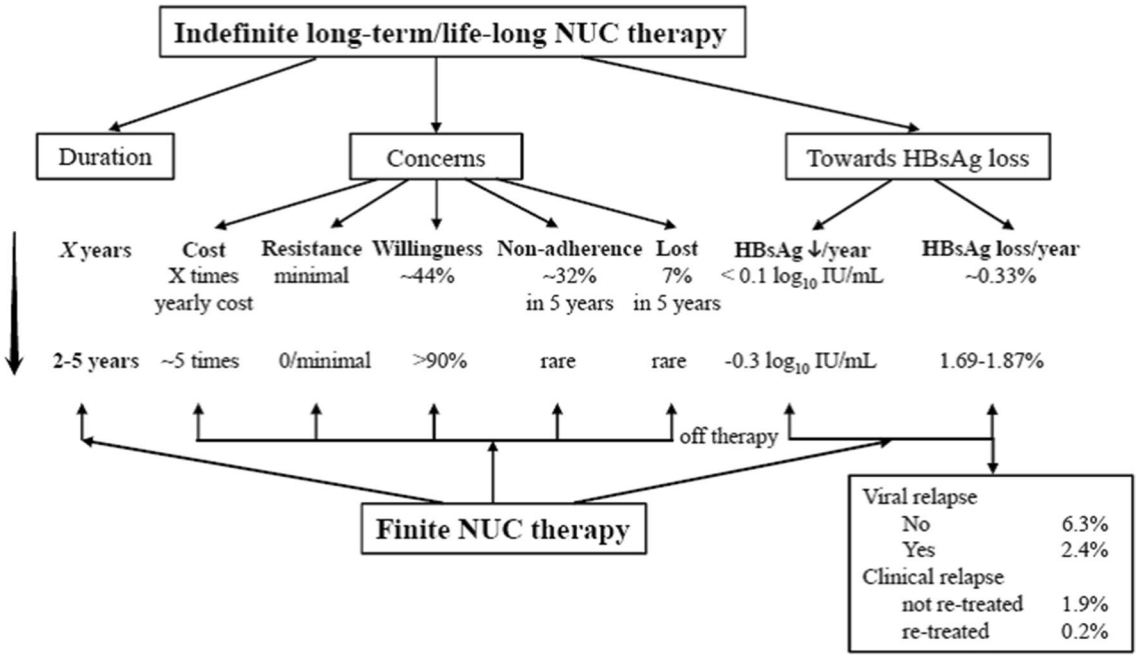
Graphic abstract



Keywords Clinical relapse · Entecavir · Hepatitis flare · Hepatic decompenation · Sustained remission · Tenofovir

Abbreviations

ADV	Adefovir
ALT	Alanine aminotransferase
APASL	Asian-Pacific Association for the Study of the Liver
CR	Clinical relapse
ETV	Entecavir
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
INR	International normalized ratio
LAM	Lamivudine
NUC	Nucleos(t)ide analogs
qHBsAg	HBsAg quantity
TDF	Tenofovir disoproxil fumarate
ULN	Upper limit of normal
VR	Virologic relapse

Introduction

Chronic hepatitis B virus (HBV) infection is a global health issue with potential adverse sequelae including hepatic decompensation, cirrhosis and/or hepatocellular carcinoma (HCC) [1]. The advance in antiviral therapy has much improved the outcomes of chronic HBV infection [2]. Currently, both pegylated interferon and nucleos(t)ide analog (NUC), including entecavir (ETV), tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide, are preferred agents for antiviral therapy [3–5]. Actually, > 90% of the patients were treated with NUC(s). "HBsAg loss" has been set as the "ideal" end point of NUC therapy in hepatitis B e antigen (HBeAg)-negative patients. However, NUCs are able to suppress HBV DNA profoundly, but have no direct action on cccDNA, a very stable template for HBV production [6]. As such, it was estimated that NUC therapy for several decades is required to achieve HBsAg loss [7]. Hence, long-term or even life-long NUC therapy is required in the vast majority of patients.

Concerns of indefinite/life-long NUC therapy

Cost and drug-resistance issues

During lamivudine (LAM), adefovir (ADV) or telbivudine therapy, resistance mutation(s) may emerge [2] and cause hepatitis, hepatitis flare, even life-threatening hepatic decompensation [8]. In addition, recourse-limited countries such as those in Asia could not afford the financial burden of long-term NUC therapy [9]. For these reasons, Asian-Pacific

HBV experts proposed to stop NUC therapy with "the decision to stop NUC therapy should be determined on clinical response and severity of underlying liver disease" in earlier guidelines of Asian-Pacific Association for the Study of the Liver (APASL) prior to 2005 [10].

Adherence, willingness and other additional concerns

Whereas drug resistance is no more a concern during ETV or TDF monotherapy, compliance and adherence issues are emerging concerns [11]. A systematic review with meta-analysis involving 23,823 patients in 30 studies showed an overall adherence of 74.6%, much lower than the optimal adherence of 95% [12]. Another study in 894 patients with 5.2 ± 2.5 year, ETV therapy further showed poor adherence (< 70%) in 10.5%, moderate adherence (70–90%) in 20.5% and such patients showed significantly increased incidence of HCC, cirrhotic complications and mortality at a dose-dependent manner [13]. Even in rich and well-developed regions, a survey in 421 Singapore patients showed that only 43.5% were willing to receive life-long NUC therapy, down to 25.3% if they had to pay 10 US dollars per day [14]; a real-world 7-year ETV study also showed that 22% of 222 Hong Kong patients were unwilling to commit or had financial difficulty to continue therapy [15]. More seriously, a 5-year ETV study showed that 7.3% of 658 patients (Asians: 83.3%) stopped therapy by themselves or lost to follow-up [16]. Conceivably, patients defaulted to follow-up, and hence were not monitored, may risk severe clinical relapse, even hepatic failure and death [17]. It can be anticipated that the above-mentioned concerns will be minimized if the treatment duration is shortened to a finite period of 2–3 years.

Besides, the safety issues of NUC therapy beyond 10 years are unknown and is also one of the concerns.

Earlier studies on finite NUC therapy leading to a stopping rule

Considering resistance and cost issues, one study showed a relapse rate of 50% in 37 HBeAg-negative Canadian Chinese patients after cessation of 2-year LAM therapy with undetectable HBV DNA on three occasions > 3 months apart [18]; a Taiwan study of 69 patients with pre-therapy alanine aminotransferase (ALT) > 5X upper limit of normal (ULN) showed a rate of 52% after cessation of 6–12 months LAM therapy [19]; and another study of 50 Hong Kong patients showed a rate of 46% after cessation of 2-year LAM therapy with maintained normal ALT and HBV DNA $< 2 \times 10^3$ IU/mL [20].

Based on these encouraging and safe results, year 2008 APASL guidelines recommended that "cessation of NUC therapy can be considered after demonstration of undetectable HBV DNA on three occasions 6 months apart" [21]. Subsequent studies using more stringent stopping criteria (> 2 years therapy with HBV DNA undetectable > 18 months) showed that 50.8% of 61 LAM-treated patients and 61% of 145 ADV-treated patients relapsed, respectively, and were generally safe [22, 23]. With these, the recommendation was updated in the 2012 guidelines: "NUC therapy > 2 years with demonstration of undetectable HBV DNA on three occasions each 6 months apart" [24], which has been known as "APASL stopping rule".

Finite NUC therapy with proper monitoring is feasible and safe

Using the "APASL stopping rule" or more stringent criteria, several studies involving a large number of patients treated with ETV or TDF were conducted, almost all from Asia. The reported 1-year incidence of virologic relapse (VR, HBV DNA > 2000 IU/mL) and 1-year clinical relapse (CR: VR + ALT > 2X ULN) varied from 50 to 68% and 28 to 52%, respectively, across different study populations [25–31].

Studies have shown the lower the EOT HBsAg quantity (qHBsAg), the lower the CR rate will be [30–32]. Most recent larger data (Fig. 1) showed that CR rate was significantly lower off-ETV than off-TDF (1-year 41 vs 62%; 2-year: 57 vs 69%; both $p < 0.001$) and that CR rate decreased with decreasing EOT qHBsAg at a level-dependent manner to 27, 39 and 50% ($p < 0.001$) in those with EOT < 100, < 200, and < 500 IU/mL, respectively, at year 2 (Jeng WJ and Liaw YF 2019 unpublished data). A systematic review involving 1732 HBeAg-negative patients suggested that NUC cessation can be considered if qHBsAg had declined to < 200 IU/mL [33]. Conceivably, more studies from different countries, in patients with different HBV genotypes and in therapy with different NUCs are required to find an optimal qHBsAg level for stopping NUC.

Of note, clinical relapses after stopping LAM, ADV and TDF occur mostly within 6 months in contrast to > 6 months off-ETV [26–30], as shown in Fig. 1a. More importantly, up to 53% and 77% of the clinical relapses after stopping ETV and TDF, respectively, showed ALT > 5X ULN [26, 28] and 3–11% of these relapses showed increased bilirubin > 2 mg/dL [26]. Prolonged prothrombin time or international normalized ratio (INR) > 1.5 was rare nearly 0 in non-cirrhotics [26, 28, 32], but 5-year rate ~ 3% in cirrhotics [32] tended to be more severe off-TDF. Overall, the collective rates were VR < 70%, CR < 50%, re-treatment < 40% and hepatic decompensation < 1% [33, 34]. The mortality is rare and was observed only in < 1% of 308 patients with cirrhosis [32].

The general conclusion of these results is that finite NUC therapy in HBV suppressed HBeAg-negative patients

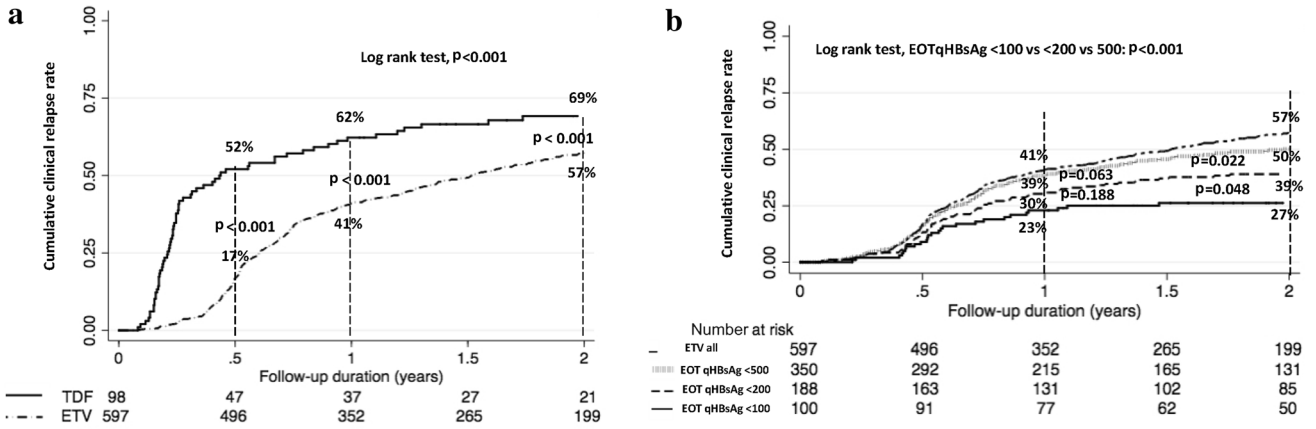


Fig. 1 Clinical relapse after cessation of entecavir (ETV) and tenofovir (TDF). **a** The clinical relapses occur significantly more frequently and much earlier after cessation of TDF than after ETV. **b** The off-ETV rate was decreased in patients with lower HBsAg quantity (qHBsAg) at end of therapy (EOT) at a level-dependent manner

is feasible and safe if proper monitoring schedule is provided and adhered. Even in cirrhotic patients, off-NUC hepatic decompensation rate was low and not higher than that during continuing NUC therapy [13, 16, 35, 36], especially in patients with suboptimal adherence < 70% [13], as shown in Fig. 2. The liver-related mortality of < 1% in 308 patients who stopped NUC therapy [32] is even lower than those continued ETV therapy with poor adherence [13]. Of note, a study of 263 HBeAg-negative patients with hepatitis flare complicated with hepatic decompensation showed that cessation of NUC therapy after restoration of compensated liver function was also safe under adequate monitoring with timely re-treatment [37]. Studies in HBeAg-negative patients with cirrhosis also showed that the HCC incidence after cessation of ETV therapy by APASL stopping rule was not higher than in those continued ETV therapy [35, 36]. These results suggest that finite NUC therapy is also feasible and reasonably safe in patients with cirrhosis and those with hepatic decompensation precipitated by hepatitis flare.

As evidence is accumulating, finite NUC therapy has finally been accepted as an option for HBeAg-negative patients by American (AASLD) guidelines since 2016 [4]. The 2017 European (EASL) guidelines have also suggested that NUC may be discontinued under close off-NUC monitoring in non-cirrhotic patients with ≥ 3 years on-therapy HBV suppression [5]. These guidelines still exclude patients with cirrhosis and those with hepatic decompensation for finite NUC therapy.

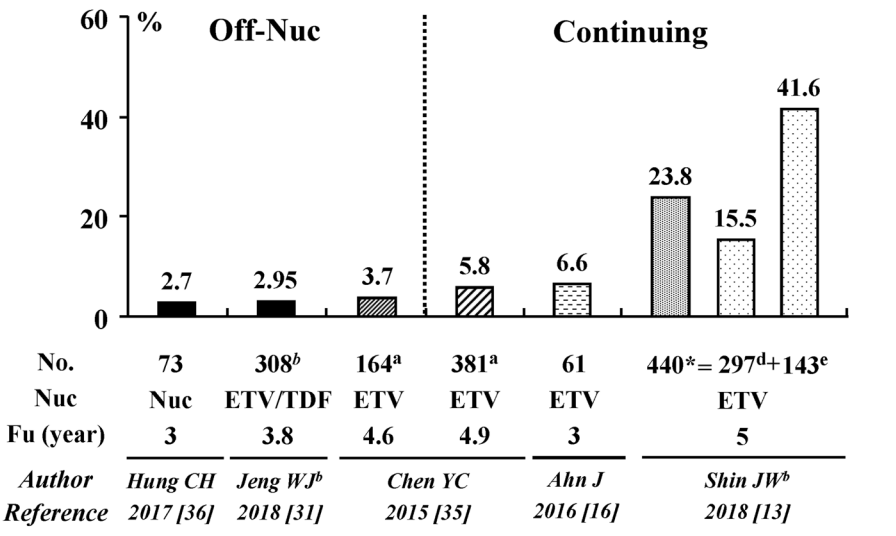


Fig. 2 Off nucleos(t)ide analog (NUC) hepatic decompensation in patients with cirrhosis was at least not more frequent in those discontinued than those continuing NUC therapy, especially those with poor adherence during long-term NUC therapy

*a. Same study; b. Cumulative rate; c. 40% Ishak F4; * Adherence: overall: 89.1%; d. ≥ 90%; e.<90%*

Additional benefit of finite NUC therapy

HBsAg loss rate much increased after cessation of NUC therapy

In HBeAg-negative patients, undetectable HBV DNA can be achieved in > 95% of the patients, but qHBsAg decline was small during ETV or TDF therapy [38, 39]. As expected, HBsAg loss is very rare, reported to be 0.33% per year during 6-year ETV therapy in 5409 mostly genotype C HBV-infected patients [40], 0.15% per year in 1075 genotype B or C HBV-infected patients treated with ETV or TDF for 3 years [32] and only 1 of 375 mostly genotype D HBV-infected patients treated with TDF for 7 years [41].

Unexpectedly, a study involving 53 Hong Kong patients showed a 5-year HBsAg loss rate of 23% after cessation of 38 months of LAM therapy [42]. A small study of 33 Greek patients further showed a much higher HBsAg loss rate (5-year 39%) after cessation of 4–5 year ADV therapy [43]. Shortly thereafter, studies involving Caucasian patients appeared. An US study of 33 patients with 5.3 years (mean) NUC therapy showed a safe biochemical relapse rate of 48%, and ultimately 52% remained treatment-free during 36 months (median) of off-NUC follow-up [44]; a German study of 15 patients showed a 1-year clinical relapse rate of 47% and a 4-year HBsAg loss rate of 20% after stopping NUC therapy with effective HBV suppression > 3 years [45] and a study of 57 Greek patients with NUC therapy ≥ 4 years and HBV DNA undetectable ≥ 3 years showed an off-NUC 1-year HBsAg loss rate of 16% [46]. More importantly, a randomized control trial, albeit small (21:21), further proved that HBsAg loss rate was much higher (3 years: 19 vs 0%) in patients who had stopped a > 4-year course of TDF therapy [47]. The HBsAg loss rate in studies involving Asian patients was much lower [31, 32, 48], as shown in Table 1. Perhaps, HBV genotype (D vs B or C) and the duration of HBV infection (age of infection) are factors for the remarkable difference in off-NUC HBsAg loss rate between the West and the East.

Factors for off-NUC HBsAg loss

Earlier studies in HBeAg-negative patients showed that patients with EOT qHBsAg ≤ 100 IU/mL were significantly (~ 15-fold, $p = 0.016$) more likely to achieve HBsAg loss [31, 42]. It was also shown that patients with qHBsAg reduction > 1 $\log_{10}$ from start to EOT had a fourfold HBsAg loss rate [42]. A recent large study of 691 patients (308 with cirrhosis) showed a 6-year off-NUC HBsAg loss rate of 13% and that EOT qHBsAg level < 100 IU/mL, qHBsAg reduction from start to EOT > 1 $\log_{10}$ IU/mL and no-retreatment were three independent factors for off-NUC HBsAg loss; the 5-year rate was 33% ($p < 0.001$) in 114 patients with EOT qHBsAg < 100 IU/mL [31]. Another study in 263 non-cirrhotic patients showed a 5-year off-NUC HBsAg loss rate of 20.8%, increased to > 40% in 87 patients with EOT < 200 IU/mL [30].

"No-retreatment" was first found to be the strongest factor for off-ADV HBsAg loss in the Greek ADV study [43]. Studies afterward all showed much higher HBsAg loss rate in patients with CR who remained "no-retreatment" than in those who received re-treatment [31, 32, 48, 49], as shown in Table 2. The large study of 691 patients further showed that patients with off-therapy sustained remission had a highest 6-year HBsAg loss rate (36%), followed by patients with CR, but had remained no re-treatment (19%) and lowest (1%) in patients with CR who had received re-treatment [32]. Immunologic studies have shown that the host immune response prior to EOT or upon off-NUC virologic or clinical relapse is the pathobiological basis for subsequent sustained response prior to HBsAg loss [45, 50–52], and that un-necessary or too early re-treatment may prevent further immune response to facilitate further HBsAg decline towards HBsAg loss [45].

Table 1 HBsAg loss increased after stopping NUC therapy

Source [Reference]		No.	Nuc	HBsAg loss
Hadziyannis	Greece [43]	33	ADV 4–5 yr	39%/5 yr
Siederdissen	Germany [45]	15	NUC > 3 yr	20%/4 yr
Berg	Europe [47]	21/21	TDF > 4 yr	19%/3 yr
Papatheodoridis	Greece [46]	57	ETV/TDF 5 yr	16%/1 yr
Chan	Hong Kong [42]	53	LAM 3 yr	23%/5 yr
Chi	Asian 80% [31]	59	NUC 5 yr	14%/3 yr
Jeng	Taiwan [32]	383 (CHB) 308 (LC)	ETV/TDF 3 yr	16%/6 yr 9%/6 yr
Chen	Taiwan [48]	234	ETV 3 yr	13%/5 yr

ETV entecavir, *Fu* follow-up, *TDF* tenofovir, *ADV* adefovir, *CHB* chronic hepatitis B, *ETV* entecavir, *LAM* lamividine, *LC* liver cirrhosis, *NUC* nucleos(t)ide analogs, *TDF* tenofovir, *yr* year

Table 2 Higher HBsAg loss rate in patients with non-retreated off-NUC relapse

Source	HBsAg loss non-retreated vs retreated	Reference
Hadziyannis	5 yr: 12/18 (66.7%) vs 1/15 (6.7%); $p=0.027$	[43]
Chi	3 yr: 9/33 (27.3%) vs 0/26 (0%)*	[31]
Berg	3 yr: 4/13 (31%) vs 0/8 (0%)*	[49]
Jeng	6 yr: 19%/150 vs 1%/269 (HR: 8.4; $p<0.01$)	[32]
Chen	5 yr: 18%/27 vs 0%/111 (HR: 18.6; $p<0.001$)	[48]

NUC nucleos(t)ide analog, *HR* hazard ratio

*p value of comparison not reported

Management after cessation of NUC therapy

Proper monitoring is mandatory

Since clinical relapse may occur in ~ 50% of the patients who stopped NUC therapy and some relapses may facilitate HBsAg decline towards HBsAg loss, whereas some severe relapses may deteriorate to life-threatening decompensation; it is mandatory to monitor the patients properly. The recommended monitoring plan for all patients includes ALT every 1–1.5 month in the first 3 months, then every 3 months along with HBV DNA assay every 3 months in the first year, more frequently in case of virologic relapse or clinical relapse and every 6–12 months afterward if needed [3, 24, 32]. Patients with cirrhosis may follow the same off-NUC monitoring plan, but more frequently if serum HBV DNA level is increasing, even have not reached the level of virologic relapse. More importantly, it has long been recommended that patients with increasing ALT or ALT > 5X ULN should have weekly–biweekly tests of serum ALT, bilirubin and prothrombin time for timely re-treatment [21, 24]. In addition, the cost of qHBsAg assay is much cheaper than that of HBV DNA assay. As discussed below, it can be recommended to assay qHBsAg every 3–6 months and more frequently in cases of clinical relapse, such as 2–4 weeks when ALT is increasing or > 5X ULN for re-treatment decision.

Re-treatment decision

It has been accepted that the indications of off-NUC re-treatment are similar to those for treatment-naïve patients [3–5]. In principle, off-therapy patients with persistent (> 3 months) mild-to-moderate hepatitis activity are candidates for re-treatment. Of note, the re-treatment decision for patients with off-NUC hepatitis with ALT > 5X ULN is more complex, because hepatitis flare may be followed by spontaneous remission or, on the contrary, end up with persistent/intermittent hepatitis activity or hepatitis flare even hepatic decompensation. Therefore, re-treatment decision is crucial. Ideally, the optimal timing of re-treatment is not too soon to allow further immune response that may facilitate qHBsAg decline towards HBsAg loss and, more importantly, not too late to prevent adverse outcomes such as hepatic decompensation [32, 45, 46]. Patients presenting with increasing serum bilirubin > 2 mg/dL may reflect impending decompensation (INR is still normal) or overt hepatic decompensation (INR > 1.5) require immediate re-treatment.

Consistent with the HBsAg kinetics observed in the natural course of hepatitis B flare [53], a proof-of-concept study has suggested that re-treatment is not necessary or can be held in patients showing successive qHBsAg decline when ALT is still rising with normal serum bilirubin and INR. This pattern of combined HBsAg/ALT kinetics reflects successful immune clearance of a "beneficial" flare (Fig. 3a). In contrast, re-treatment is required in patients showing stable or increasing qHBsAg prior to and/or after the peak of ALT during hepatitis flare (Fig. 3b). This pattern of combined HBsAg/ALT kinetics reflects failed or ineffective immune clearance of a "bad" flare [54]. The results of a most recent study have confirmed that re-treatment is not necessary in 24 patients with decreasing qHBsAg during clinical relapse, with or without hepatitis flare, as they all finally achieved low qHBsAg levels or even HBsAg loss upon further follow-up [55]. As such, a "stop-and-watch" strategy requires more frequent qHBsAg assay, which is much less expensive than HBV DNA assay and hence, much more affordable [56]. More studies are required to support these recent findings.

Conclusions and perspective

The cumulated data in the past decade have supported the evolving idea of finite NUC therapy in HBeAg-negative patients to a mature level sufficient for paradigm shift. Starting with APASL [21, 24], now AASLD and EASL guidelines [4, 5] have also included finite NUC therapy as an option for HBeAg-negative patients. More recent findings of a much increased off-NUC HBsAg loss rate may further suggest that finite NUC therapy can be considered as a "firm recommendation" rather than only "an option" for HBeAg-negative patients. Given the positive evidence derived from Asian studies in hundreds of patients with hepatic decompensation [36], thousands of patients with cirrhosis [32, 35, 37] and high cirrhotic complications in patients with poor adherence during long-term continuing ETV therapy [13], finite NUC therapy for patients with pre-therapy hepatic decompensation or liver cirrhosis have also been accepted by APASL guidelines [3, 24], but not yet by AASLD and EASL [4, 5] though ~ 20% of the patients were cirrhotics in at least two studies from Western countries [16, 31]. Obviously, more studies are

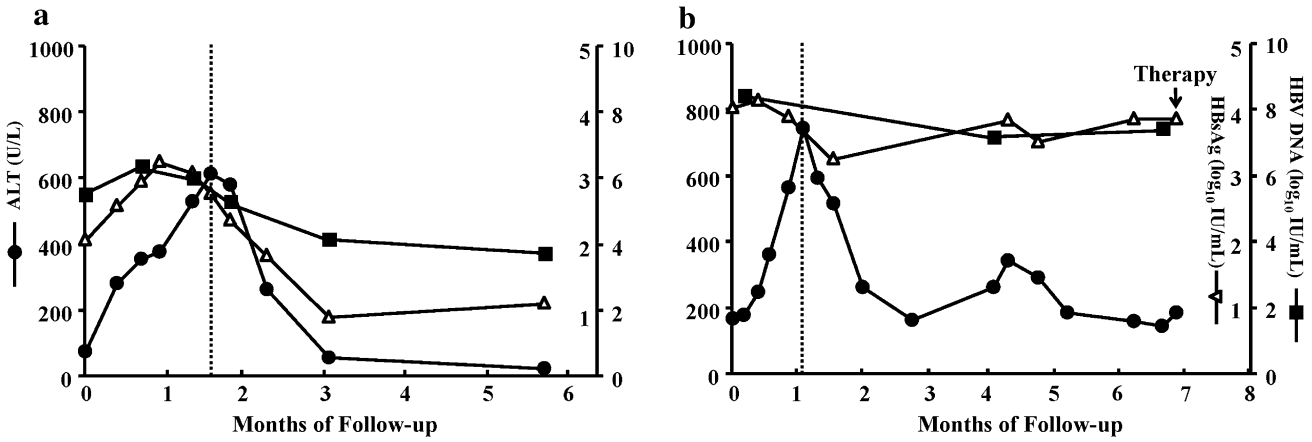


Fig. 3 Combined HBsAg/ALT kinetics during hepatitis flares in HBeAg-negative patients (**a**). "Beneficial flare": qHBsAg starts to decline prior to the peak of ALT, and decrease further successively in patients with "effective immune clearance" followed by subsiding hepatitis that antiviral therapy is necessary or can be held; (**b**). "Bad flare": qHBsAg remains high or increase further in patients with "ineffective immune clearance" hence, requires earlier therapy. Vertical dotted lines indicate the peak of ALT flare

needed in Caucasian patients and those infected with HBV other than genotype B or C to test these issues. In any case, careful off-NUC monitoring is mandatory to detect and manage clinical relapse in time. In addition to the monitoring plan of APALS guidelines [3, 24], assays of qHBsAg at EOT, every 3–6 months after EOT and more frequently, once virologic relapse or ALT elevation has emerged, are useful for optimal re-treatment decision or prediction of near-term prognosis, including HBsAg loss [56].

In conclusion, with all concerns minimized and HBsAg loss rate much increased, it can be recommended to stop NUC therapy in HBeAg-negative patients by APASL stopping rule. Proper off-NUC monitoring is mandatory and careful re-treatment decision may ensure safety and increase HBsAg loss rate, which will be a benchmark to evaluate the efficacy of the emerging new drugs or strategies aiming functional cure or HBsAg loss.

Acknowledgements The author thanks Ms. Su-Chiung Chu for assistance through the study and in preparing the manuscript and figures, Dr. Wen-Juei Jeng for providing Fig. 1, Ms. Li-Hua Lu for laboratory work and Ms. Chiou-Huei Lin for database maintenance.

Funding The author has been supported by grants from the Chang Gung Medical Research Program (CMRPG1G0061-3) and the Prosperous Foundation, Taipei, Taiwan.

Compliance with ethical standards

Conflict of interest No relevant conflict of interest.

Human or animal rights This article is a Review, not a direct original study involving human or animal subjects.

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