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# The Long Game: A Functional Cure Is Possible with Nucleoside Analogues and the Tincture of Time

**Nicholas Noverati [1], Vivian Yan [2], Jay W. Jun [2], Dina Halegoua-DeMarzio [3] and Hie-Won Hann [3,*]**

[1] Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA 19107, USA; nicholas.noverati@jefferson.edu
[2] Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA 19107, USA; vivian.yan@students.jefferson.edu (V.Y.); jay.jun@students.jefferson.edu (J.W.J.)
[3] Division of Gastroenterology and Hepatology, Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA 19107, USA; dina.halegoua-demarzio@jefferson.edu
* Correspondence: hie-won.hann@jefferson.edu

**Abstract:** Chronic hepatitis B is still prevalent globally. Many patients are treated for many years with nucleos(t)ide analogues to prevent the virus from actively replicating. However, although it typically requires consecutive treatment for more than 10 years, patients can achieve a functional cure from this virus. This case series presents details of functional cures in patients who received varying nucleos(t)ide therapies for an average of 15.3 years before losses of hepatitis B surface antigen and viral load were observed. It is imperative to understand that abbreviating therapy once a functional cure is achieved may be a possibility in treating patients in order to limit the associated costs and side effects of an otherwise lifelong therapy until other cure drugs are approved.

**Keywords:** chronic hepatitis B; functional cure; host response



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## 1. Introduction

The hepatitis B virus (HBV) still affects close to 296 million individuals globally, contributing to 50% of all cases of hepatocellular carcinoma (HCC). Many individuals develop chronic hepatitis B after being infected at birth and remaining asymptomatic for many years [1–3].

In light of the serious complications of HBV infection, treatment is paramount. Current therapies include interferon and nucleoside analogues. However, these medicines are thought to only keep the virus "at bay" and to not completely cure an individual from the virus.

Currently, an HBV cure can be categorized as functional and complete, with the differences exemplified by serologies, as shown in Table 1.

**Table 1.** Definitions.

| | HBsAg | Anti-HBs | Viremia | cccDNA |
|---|---|---|---|---|
| **Functional Cure** | - | + | - | + |
| **Complete Cure** | - | + | - | - |

Being totally cured of HBV infection means that no virus remains in the body, and in the liver, that is able to replicate and produce disease. For this to occur, covalently closed circular DNA (cccDNA), the template for virus replication, must be eradicated from hepatocytes so as to prevent them from producing more virus [4–9].

Certain markers can be used to assess whether a "functional" cure occurs while being treated for hepatitis B. Hepatitis B surface antigen (HBsAg), for example, is thought to mirror the presence of cccDNA, and viral load is a direct measure of circulating virus.

When these markers are both negative, a patient can be deemed "functionally" cured. However, this has been shown to occur at a very low rate in patients treated with antivirals, somewhere between 2% and 10%, typically after many years (upwards of >10) of therapy, and possibly even lower [10–12]. This has shifted attention to the need for cure drugs that can achieve this outcome in more effective ways [13,14].

Nucleos(t)ide analogues (NAs) remain the most well-tolerated and easily prescribed options, with tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) and entecavir (ETV) being first-line choices [10]. However, in earlier stages of anti-HBV treatment, lamivudine (approved in 1998) and adefovir (approved in 2002) were the only treatments of choice until 2008, when TDF was approved. A higher dose (150 mg) of lamivudine was used as an off-label treatment for hepatitis B patients until the 100 mg dose of lamivudine was approved in 1998. For those with low baseline HBV DNA, this higher dose of lamivudine, 150 mg per day, was noted to result in low or no lamivudine resistance compared with the 100 mg dose of lamivudine [15,16]. Although tenofovir and entecavir are more potent drugs compared to other NAs, they have still not been as well documented in establishing a functional cure, especially in the short term [11]. This is in part because cccDNA remains in hepatocytes even at DNA levels that are undetectable by the current approved clinical assays. If HBsAg remains, this may also indicate that integrated viral DNA remains, which has been shown to produce some HBsAg as well.

This case series presents a cohort of patients who were treated with antiviral drugs for many years and were observed to lose both HBsAg and DNA and were thus deemed functionally cured. This case series serves to demonstrate that a functional cure is possible even with the present nucleos(t)ides, although typically at a cost of >10 years of therapy in our cohort.

## 2. Case Series

Included in this series are 17 patients that have achieved a functional cure on nucleoside analogue therapies and 3 patients who achieved a functional cure without therapy. Tables 2 and 3 display their basic characteristics, as well as more specific data, including treatment details and serologies. Most patients appeared to have been infected with HBV at birth from their HBV-carrying mother. Table 4 provides a more extensive outline of the patients' family histories. All patients were Asian-Americans (most Korean-Americans) and had no other significant comorbidities, including no concomitant liver disease or risk factors for hepatitis B progression. The average length of treatment prior to the documented loss of HBsAg was 15.3 years. Further, all patients are currently healthy, with no signs or symptoms of cirrhosis. All have had routine 6-month screenings for cirrhosis and HCC, which have been negative.

As shown in Table 3, some patients switched from one drug to another. This was usually related to various clinical studies they were enrolled in and not due to medication intolerances. This also occurred over many years of therapy, as the table outlines, which also means different therapies became available as the years went on.

Of note, there are three patients who achieved a spontaneous functional cure without treatment (patients #1, #2, and #20). Patient #1 was infected perinatally from her mother, and patient #2 had an unknown transmission as she was separated from her birth parents as an infant.

**Table 2.** Basic patient characteristics.

| Patient | Current Age | Sex | Age at Dx | Maternal or Paternal Family History (HBV) |
|---|---|---|---|---|
| 1 | 44 | M | 12 | Maternal |
| 2 | 48 | F | 12 | Unknown |
| 3 | 54 | M | 33 | None |
| 4 | 74 | F | 36 | None |
| 5 | 66 | M | 42 | Unknown |
| 6 | 66 | M | 34 | None |
| 7 | 72 | F | 46 | None |
| 8 | 78 | F | 44 | Both |
| 9 | 59 | M | 29 | Maternal |
| 10 | 65 | M | 40 | None |
| 11 | 61 | M | 16 | Maternal |
| 12 | 66 | M | 43 | Unknown |
| 13 | 69 | F | 30 | Maternal |
| 14 | 58 | F | 33 | Maternal |
| 15 | 51 | M | 19 | Maternal |
| 16 | 56 | M | 23 | Maternal |
| 17 | 52 | M | 32 | Paternal |
| 18 | 61 | M | 16 | Maternal |
| 19 | 69 | M | 63 | None |
| 20 | 18 | M | 15 | Maternal |

**Table 3.** Details of patients who achieved a functional cure.

| Patient (Current Age) | Years of HBsAg+ | Time between DNA- and HBsAg Loss | Treatment (Year Began) | Length of Treatment (Years) | Time HBsAg- from Cessation of Treatment (Years) |
|---|---|---|---|---|---|
| 1 (44 years) | 30 | 10 months | None | n/a | n/a |
| 2 (48 years) | 20 | 4 years | None | n/a | n/a |
| 3 (54 years) | 10 | 3 years 3 months | LAM (2004), TDF (2009) | 8 | 10 |
| 4 (74 years) | 35 | 2 years 3 months | LAM (2004), TDF (2011), TAF (2017) | 14 | 1 |
| 5 (66 years) | 20 | 9 years 4 months | TLB (2008), ETV (2008), TAF (n/a), TDF (n/a) | 18 | 1 |
| 6 (66 years) | 20 | 3 years 7 months | IFN (n/a) LAM (n/a), TDF (n/a), ADV (n/a) | 20 | 13 |
| 7 (72 years) | 22 | 18 years | LAM (2003), TDF (2016) | 19 | 1 |
| 8 (78 years) | 22 | 5 years | LAM (2002) | 3 | 14 |
| 9 (59 years) | 30 | 11 years | LAM (2000), TDF (2011) | 30 | 1 |
| 10 (65 years) | 25 | 14 years | LAM (2002), ADV (2008), TDF (2017), LAM (2020), TDF (2020) | 19 | 1 |
| 11 (61 years) | 45 | 9 years | LAM (2009), REALM ETV (2009) | 13 | 1 |
| 12 (66 years) | 23 | 10 years | TDF (2012), LAM | 10 | 1 |
| 13 (69 years) | 39 | 13 years | LAM (2009) | 19 | 1 |
| 14 (58 years) | 24 | 1 year 6 months | LAM (n/a), ADV (n/a), TDF (n/a) | 12 | 1 |
| 15 (51 years) | 32 | 12 years | LAM (2009), TLB (2009), TDF (2009), TAF (2018) | 18 | 1 |
| 16 (56 years) | 33 | 17 years | LAM (1999), LAM (2002), LAM-r (2003), TDF (2004), TAF (2021) | 23 | 1 |
| 17 (52 years) | 20 | 15 years | LAM (2006), TDF (2021) | 12 | 1 |
| 18 (61 years) | 45 | 10 years 4 months | LAM (2006), RTV, TAF (n/a), ETV (n/a) | 16 | 1 |
| 19 (69 years) | n/a | 5 years | TDF (n/a), TAF (n/a) | 6 | 1 |
| 20 (18 years) | 3 | 2 years | None | n/a | n/a |

n/a: not available; IFN: interferon; LAM: lamivudine, here mostly at the dose of 150 mg/day; TLB: telbivudine; ADV: adefovir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; ETV: entecavir.

**Table 4.** Details of patients' family histories.

| Patient (Current Age) | Details of Family History |
|---|---|
| 1 (44 years) | Mother and older brother are HBsAg (+) but are not on anti-HBV therapy. |
| 2 (48 years) | Unknown |
| 3 (54 years) | Unknown |
| 4 (74 years) | Unknown |
| 5 (66 years) | Younger brother has CHB and is on therapy. |
| 6 (66 years) | Unknown |
| 7 (72 years) | Older brother has HCC. Maternal uncle has CHB and is on therapy. |
| 8 (78 years) | Mother and father have cirrhosis. Younger brother and sister have CHB and are on therapy. |
| 9 (59 years) | Mother, older brother, and sister and younger brother are HBsAg (+) and is not on therapy. |
| 10 (65 years) | Unknown |
| 11 (61 years) | Older brother has HCC. Mother has cirrhosis. Older brother has CHB and is on therapy. |
| 12 (66 years) | Unknown |
| 13 (69 years) | Mother and older brother have HCC. Older sister has cirrhosis. Two older brothers and three older sisters have CHB and are on therapy. |
| 14 (58 years) | One older brother, one older sister, and one younger brother are HBsAg (+) and are not on anti-HBV therapy. |
| 15 (51 years) | Two maternal aunts have HCC. One younger sister, one younger brother, and three maternal aunts all have CHB and are on therapy. |
| 16 (56 years) | Father, younger brother, and sister have HBsAg (+) and are not on therapy. |
| 17 (52 years) | Unknown |
| 18 (51 years) | Unknown |
| 19 (69 years) | Unknown |
| 20 (18 years) | Mother and two sisters are HBsAg (+). |

## 3. Discussion and Conclusions

Treating hepatitis B is an important task for many clinicians, even in the United States. It is imperative when treating to understand what options there are currently and what treatment goals can be realistically accomplished.

As mentioned previously, nucleoside analogues remain the most well-tolerated and easily prescribed options for patients, with TDF, TAF, and ETV being first-line options. As supported by our findings, it may be reasonable to stop antiviral therapies in patients that have both an undetectable HBV DNA level and are negative for HBsAg (<0.05 IU/mL). These negative serologies and titers are surrogate markers for a lack of viral cccDNA within hepatocytes, thus implying a functional cure. The choice to discontinue therapy has been supported by studies that have shown that stopping drugs when a patient has been HBeAg-negative and HBV DNA-negative for 12 months leads to a 50% relapse at 1 year [17] and thus a better strategy is to also ensure the loss of HBsAg, which is suggested by the American Association for the Study of Liver Diseases (AASLD) [18,19]. Another study suggested that the adaptive immune system in particular may play a role in patients that lose HBsAg on chronic antiviral therapy [20]. Regardless of the mechanism, the rates of functional cure may be low, but it is possible [19].

Although some clinicians may be wary to discontinue treatment in patients, it is also prudent to consider the long-term side effects and costs associated with taking a medication for life. Thus, our data and the data of others continue to support that it can be safe to discontinue treatment with appropriate longitudinal follow-up [16]. Based on the International, Multicenter, Multiethnic Cohort (RETRACT-B Study) by Hirode et al., there have been proposals to discontinue NAs when HBsAg levels are lower than 100 IU/mL for

Asians and <1000 IU/mL for non-Asian hepatitis B patients [11,21]. Our cases with HBsAg loss indicate that the patients' HBsAg levels are <0.05 IU/mL.

The unique perspective of the authors at this tertiary care center is the extensive panel of Asian-American hepatitis B-positive patients that have received follow-ups in our department for decades. Many patients continue to receive follow-ups from various locations in the United States. This has allowed us to observe, over the course of many years, patients on antiviral therapy and their outcomes. As shown here, a functional cure is possible after many years of potent NA therapy alone, even in patients who were infected perinatally. Further, our lab's interpretation of a negative HBsAg level is equivalent to an absolute value of <0.05 IU/mL, which strengthens our confidence in this cohort of patients being truly negative. Although our mean time to the loss of HBsAg was 15.3 years of treatment with NAs, many patients may have actually been HBsAg negative before it was first documented, in part due to our own assumptions that it would be unlikely. Therefore, the true mean time to HBsAg loss could be shorter. In addition, our longitudinal patient relationship allows us to observe family histories in detail. As evidenced in Table 4, even patients with a functional cure have family members with very different outcomes, some even with late-stage complications such as cirrhosis and hepatocellular carcinoma. This, in light of the context of family members likely having the same virus subtype and no other significant liver-related medical history, stresses the vagaries that can be observed within hosts. Some hosts have much more favorable outcomes that may be dependent on non-traditional risk factors such as stress, or differences in immune function and its role in controlling the infection.

One of the weaknesses of this case series is the small sample size, although there are likely more patients on our practice's panel with similar findings not included here. Also, the time since HBsAg loss and the time off antiviral therapy are short for some patients who were more recently discovered to have lost HBsAg. Thus, it may be reasonable to question whether they will have sustained remissions. In contrast, we did include some patients that have sustained HBsAg-negative statuses for over a decade.

In light of shifting research and the drug development of combination therapies to achieve a functional cure, as well as drug options for a complete HBV cure in the future [22–24], we present here the fact that a functional cure can indeed be achieved through NA treatment alone [5,6,8,9]. Potential downsides to this choice of therapy include the amount of time and the commitment to therapy needed to achieve this goal. Further, this extends to the financial implications of such a course of treatment, especially in countries outside the United States. Newer drugs to achieve functional cures or complete cures are likely to be even more expensive. More research is needed for combination therapies for an HBV cure and their associated outcomes in different patient groups. In the meantime, we should try to achieve a functional cure with the available therapies within the shortest duration of treatment.

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