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Functional cure induced by tenofovir alafenamide plus peginterferon-alpha-2b in young children with chronic hepatitis B: a case series study

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Abstract

Background and Aims Data on the safety and effectiveness of tenofovir alafenamide (TAF) plus peginterferon-alpha (Peg-IFN-α) in children with chronic hepatitis B (CHB) are lacking. The current study aimed to present the characteristics of four pediatric CHB patients who obtained a functional cure by using TAF and Peg-IFN-α.

Methods In this case series study initiated in May 2019, ten children who had no clinical symptoms or signs received response-guided (HBV DNA undetectable, hepatitis B e antigen [HBeAg] loss or seroconversion, and hepatitis B surface antigen [HBsAg] loss or seroconversion) and functional cure-targeted (HBsAg loss or seroconversion) TAF (25 mg/d, orally) plus Peg-IFN-α-2b (180 μg/1.73m^2, subcutaneously, once weekly) in combination (9/10) or sequential (1/10) therapy. The safety and effectiveness of these treatments were monitored.

Results As of April 2024, four out of ten children obtained a functional cure after a mean of 31.5 months of treatment, and the other six children are still undergoing treatment. These four cured children, aged 2, 4, 8, and 6 years, were all HBeAg-positive and had alanine aminotransferase levels of 80, 47, 114, and 40 U/L; HBV DNA levels of 71200000, 93000000, 8220, and 96700000 IU/mL; and HBsAg levels of 39442.8, 15431.2, 22, and 33013.1 IU/mL, respectively. During treatment, all the children (10/10) experienced mild or moderate adverse events, including flu-like symptoms, anorexia, fatigue, and cytopenia. Notably, growth retardation (8/10) was the most significant adverse event; and it occurred in three cured children (3/4) treated with combination therapy and was present to a low degree in the other cured child (1/4) treated with sequential therapy. Fortunately, all three cured children recovered to or exceeded the normal growth levels at 9 months posttreatment.

Conclusions TAF plus Peg-IFN-α-2b therapy is potentially safe and effective for pediatric CHB patients, which may provide important insights for future clinical practice and study designs targeting functional cures for children with CHB.

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Keywords Children, Chronic hepatitis B, Functional cure, Peginterferon alpha, Tenofovir alafenamide

Introduction

Chronic hepatitis B virus (HBV) infection is a global public health burden that affects 257.5 million individuals worldwide [1]. Although perinatal transmission has significantly decreased since the implementation of maternal antiviral prophylaxis and infant vaccination [2, 3], almost 2 million new infections have occurred annually through perinatal and horizontal transmission in children aged 5 years or younger [4].

There is an unmet need in real-life clinical practice. On the one hand, many children continue to be at risk of progressive liver disease due to active hepatitis [5]; however, less attention has been given to this topic, and limited antiviral options have been approved for younger children with chronic hepatitis B (CHB). Moreover, most hepatologists have adopted a conservative attitude toward antiviral treatment for CHB children [4, 6], which has resulted in few concerns about functional cures. On the other hand, discrimination against chronic HBV infection is severe in China [7], and most families are eager to cure their children in an easy way so as not to interfere with their schooling and work.

In this case series study, we report four functionally cured CHB children treated with two first-line antivirals, tenofovir alafenamide (TAF, which theoretically does not need dosage adjustment because of its favorable safety profile and similar high genetic barrier to resistance compared with tenofovir disoproxil fumarate [TDF]) plus peginterferon-alpha-2b (Peg-IFN-α-2b, the only available Peg-IFN-α in our hospital and even in most areas of China), which has not been evaluated or reported previously in young CHB children.

Patients and methods

Patients

From May 2019 to August 2023, a total of 10 children (all of whom were less than 8 years old) visited and were diagnosed with treatment-naïve and asymptomatic hepatitis B e antigen (HBeAg)-positive CHB in our center; moreover, their parents strongly demanded a functional cure and could not accept the cumbersome oral antiviral drug (entecavir and TDF) dosing adjustments or frequent regular interferon injections. As of April 2024, four children aged 2, 4, 8, and 6 years who were enrolled from May 2019 to November 2021 and treated with TAF plus Peg-IFN-α-2b have achieved functional cure. Here, we mainly report the management process of four cured children.

Clinical procedures

After careful discussion by the expert group and approval by the Medical Management Department of the hospital, we decided to administer response-guided and functional cure-targeted TAF (25 mg/d, orally, once daily) plus Peg-IFN-α-2b (180 μg/1.73 m^2, subcutaneously, once weekly) therapy to the 10 children. In detail, children with strong immune clearance features (high [abnormal] alanine aminotransferase [ALT] levels with or without relatively low levels of virological markers, i.e., HBV DNA, HBeAg, and hepatitis B surface antigen [HBsAg]) received initial combination therapy, and children with weak immune clearance features (low [normal] ALT levels with or without relatively high levels of virological markers [HBV DNA, HBeAg, and HBsAg]) received TAF monotherapy first and then received Peg-IFN-α-2b add-on therapy sequentially at specific time points in the future.

Definition of functional cure

The definition of a functional cure for CHB is seroclearance of HBsAg, i.e., loss of detectable serum HBsAg by the assays as described as following with or without seroconversion to hepatitis B surface antibody (HBsAb) [8]. Certainly, before or simultaneously with the seroclearance of HBsAg, HBV DNA and HBeAg should also become undetectable or undergo seroclearance.

Definition of response-guided treatment

Commonly, there are three virologic steps for the functional cure of HBeAg-positive CHB, i.e., undetectable HBV DNA, HBeAg loss or seroconversion, and HBsAg loss or seroconversion, although these steps may not occurr sequentially. Therefore, response-guided therapy and functional cure-targeted treatment are aimed at these three steps. In fact, prior to the start of this study, we did not specifically define this response-guided therapy quantitatively. Generally, on the basis of good adherence and tolerance, if a child's HBV DNA level continues to decrease to an undetectable level, treatment will continue to achieve this goal. Similarly, if a child's HBeAg continues to decrease to a negative level, treatment will continue to achieve this goal. Again, if a child's HBsAg continues to decrease to a negative level, treatment will continue to achieve this goal. In contrast, if a child's HBV DNA, HBeAg, or HBsAg do not exhibit an obvious decrease at two follow-up timepoints with an interval of 3 months, combination therapy will be discontinued, or only TAF will be retained to continue monotherapy.

Management of the side effects of hemocytopenia

During treatment, when the neutrophil count is $\leq 0.75\times10^9$/L, the platelet count is $<50\times10^9$/L, and/or the ALT level is > 5 times the upper limit of normal (ULN, 40 U/L), the interferon dose should be reduced; 1 to 2 weeks later, these parameters should be retested; if recovery occurs, increase to the original dose. When the neutrophil count is $\leq 0.5\times10^9$/L, the platelet count is $<25\times10^9$/L, and/or the ALT concentration is > 10 ULN, interferon should be suspended [6]. For patients with significantly decreased blood cell counts, granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor may be used; additionally, for patients with significantly increased ALT levels, hepatoprotective drugs (glutathione tablets) may be used [6].

Laboratory assessments and growth evaluations

Serum HBV markers were tested by using the Abbott ARCHITECT Alinity i Reagent Kit (Abbott Ireland Diagnostics Division, Finisklin Bussiness Park, Sligo, Ireland), with a lower limit of quantification [LLOQ] of 0.05 IU/mL for HBsAg (< 0.05 IU/mL indicating a negative result or HBsAg loss), a normal range of 0–10 mIU/mL for HBsAb (> 10 mIU/mL indicating a positive result), and a normal range of 0–0.18 IU/mL for HBeAg (< 0.18 IU/mL indicating a negative result or HBeAg loss). The serum HBV DNA levels (the LLOQ was 10 IU/mL) were measured by using an Abbott Real Time HBV Assay (Abbott Molecular Inc., Des Plaines, IL, USA). The upper limit of normal for ALT was defined as 40 U/L [9]. The growth conditions (weight and height) were referred to as "Height and weight standardized growth charts for Chinese children and adolescents aged 0 to 18 years" [10].

Results

Baseline characteristics

Table 1 presents the detailed characteristics of the four cured children before treatment initiation. The baseline characteristics of the other six children who were still undergoing treatment and follow-up testing are presented in Table 2. The four cured children, aged 2, 4, 8, and 6 years, were infected with HBV through mother-to-child transmission, were asymptomatic and HBeAg-positive, and had alanine aminotransferase levels of 80, 47, 114, and 40 U/L, HBV DNA levels of 71200,000, 93000,000, 8220, and 96700000 IU/mL, and HBsAg levels of 39442.8, 15431.2, 22, and 33013.1 IU/mL, respectively. Three children (Nos. 1–3,

Table 1 Baseline characteristics of the four functionally cured children with chronic hepatitis B

Characteristics	No.1	No.2	No.3	No.4
Gender	Male	Female	Male	Male
Age, years (y) + months (m)	2y + 5 m	4y + 0 m	8y + 3 m	6y + 4 m
Transmission route	MTCT	MTCT	MTCT	MTCT
Hepatitis B surface antigen, IU/mL	39,442.8	15431.2	22	33013.1
Hepatitis B e antigen, PEIU/mL	448.6	502	172.5	519.6
HBV DNA, IU/mL	71200000	93000000	8220	96700000
Alanine aminotransferase (0–40 U/L)	80	47	114	40
Aspartate aminotransferase (0–40 U/L)	58	53	72	68
Total bilirubin (0–17.1 μmol/L)	8.4	10.1	4.6	9.3
Alpha fetoprotein (0–9 ng/mL)	2.6	3.6	3.6	2
White blood cell count ($\times10^9$/L)	6.3	9.3	5	6.2
Neutrophil count ($\times10^9$/L)	1.3	4.5	1.6	1.9
Hemoglobin (≥ 110 g/L)	117	137	119	134
Platelets (100–300 $\times10^9$/L)	203	237	258	212
Systemic disorders	No	No	No	No
Other viral infections	No	No	No	No
Other liver diseases	No	No	No	No
Treatment regimen	TAF + Peg-IFN-α	TAF + Peg-IFN-α	TAF + Peg-IFN-α	TAF monotherapy and TAF + Peg-IFN-α
Treatment duration	Response-guided therapy	Response-guided therapy	Response-guided therapy	Response-guided therapy

Abbreviations: *HBV* Hepatitis B virus, *m* months, *MTCT* Mother-to-child transmission, *Peg-IFN-α* Pegylated interferon alpha, *TAF* Tenofovir alafenamide fumarate, *y* years

Table 2 Characteristics of the six children with chronic hepatitis B who have not yet been functionally cured

Parameters	No.5	No.6	No.7	No.8	No.9	No.10
Baseline characteristics						
Gender	Female	Male	Male	Female	Male	Male
Age, years (y) + months (m)	2y + 2 m	2y + 10 m	4y + 1 m	5y + 5 m	6y + 3 m	6y + 9 m
Transmission route	MTCT	MTCT	MTCT	MTCT	MTCT	MTCT
Hepatitis B surface antigen, IU/mL	2311.7	68,989	9218	38,916	10,943.6	87,527.4
Hepatitis B e antigen, PEIU/mL	85.6	511.4	466	141.4	244.1	251.8
HBV DNA, IU/mL	2830000	536000000	26000000	280000000	12200000	200000000
Alanine aminotransferase (0–40 U/L)	46	69	56	94	49	61
Aspartate aminotransferase (0–40 U/L)	33	41	34	96	44	34
Total bilirubin (0–17.1 μmol/L)	6	4.8	6.5	10.4	5.7	10.3
Alpha fetoprotein (0–9 ng/mL)	3.6	1.0	2.8	1.8	1.8	1.2
White blood cell count ($\times 10^9$/L)	7.2	7.5	10	7.2	5.2	8.3
Neutrophil count ($\times 10^9$/L)	2.1	3.3	5.8	4.1	3.0	4.0
Hemoglobin (≥ 110 g/L)	117	122	131	129	125	134
Platelets (100–300 $\times 10^9$/L)	342	299	334	276	230	332
Systemic disorders	No	No	No	No	No	No
Other viral infections	No	No	No	No	No	No
Other liver diseases	No	No	No	No	No	No
Treatment regimen	TAF + Peg-IFN-α	TAF + Peg-IFN-α	TAF + Peg-IFN-α	TAF + Peg-IFN-α	TAF + Peg-IFN-α	TAF + Peg-IFN-α
Treatment duration (ongoing)	15	18	21	9	9	6
HBV DNA undetectable	Yes	Yes	Yes	Yes	Yes	Yes
Time-taken, months	12	12	6	6	3	6
Hepatitis B e antigen loss	Yes	No	No	No	No	No
Time-taken, months	3	-	-	-	-	-
Latest level, PEIU/mL	0.06	0.7	121.7	15.6	56.1	16.3
Hepatitis B e antibody positivity	Yes	No	No	No	No	No
Time-taken, months	1	-	-	-	-	-
Hepatitis B surface antigen loss	No	No	Yes	No	Yes	No
Time-taken, months	-	-	21	-	9	-
Latest level, IU/mL	8.3	6.6	0.04	14529.2	0.02	418
Hepatitis B surface antibody positivity	Yes	No	Yes	No	Yes	No
Time-taken, months	15	-	15	-	9	-
Latest level, IU/mL	35.9	-	67.8	-	261.5	-
Adverse events						
Fever	Yes	Yes	Yes	Yes	Yes	Yes
Muscle pain	Yes	Yes	Yes	Yes	Yes	Yes
Anorexia	Yes	Yes	Yes	Yes	Yes	Yes
Fatigue	Yes	Yes	Yes	Yes	Yes	Yes
Nausea	No	No	Yes	No	Yes	No
Rash	Yes	No	No	No	No	No
Growth retardation	Yes	Yes	Yes	Yes	No	No
Laboratory abnormalities						
Cytopenia	Yes	Yes	Yes	Yes	Yes	Yes
Alanine aminotransferase elevation	Yes	Yes	Yes	Yes	Yes	Yes
Thyroid dysfunction	No	No	No	No	No	No
Hyperbilirubinemia	No	No	No	No	No	No

Abbreviations: *HBV* Hepatitis B virus, *m* months, *MTCT* Mother-to-child transmission, *Peg-IFN-α* Pegylated interferon alpha, *TAF* Tenofovir alafenamide fumarate, *y* years

Table 1) with strong immune clearance features received initial TAF plus Peg-IFN-α-2b combination therapy, and one child (No. 4, Table 1) with weak immune clearance features received TAF and Peg-IFN-α-2b sequential therapy.

Effectiveness

As of April 2024, four out of ten children obtained a functional cure after a mean of 31.5 months of treatment (ranging from 18 to 42 months), and the detailed viral dynamics are presented in Fig. 1. HBV DNA was undetectable in three children (Nos. 1–3) after 3 to 6 months of TAF and Peg-IFN-α-2b combination therapy. Notably, child No. 1 received TAF monotherapy for 15 to 24 months due to the infeasibility of regular follow-up due to the coronavirus disease 2019 (COVID-19) lockdown in his hometown. Unfortunately, child No. 4 was not able to undergo regular monitoring during the first 21 months of TAF monotherapy because of the COVID-19 lockdown in his hometown, and undetectable HBV DNA and HBeAg seroconversion were both detected at 21 months of treatment (Fig. 1). Moreover, HBeAg seroclearance was detected in the other three children (Nos. 1–3) after 24, 18, and 30 months of TAF and Peg-IFN-α-2b combination therapy; however, persistent HBeAg seroconversion was detected only in child No. 2 (Fig. 1). For the functional cure, it is interesting that child No. 3 had the lowest level of HBsAg (22 IU/mL) but the longest treatment duration. Notably, HBsAg seroconversion occurred in children Nos. 1, 2, and 3, with HBsAb levels of 991.1, 53.5, and 29.4 mIU/mL, respectively, at posttreatment month 9, and child No. 4 did not achieve HBsAg seroconversion but maintained the HBsAg seroclearance at posttreatment month 9.

Safety profiles

During treatment, all four cured children experienced mild or moderate adverse events, including flu-like symptoms, anorexia, and fatigue (Table 3), and laboratory abnormalities, including elevated ALT levels (Fig. 2), neutropenia (Fig. 3), and thrombopenia (Fig. 4). However, none of the children presented elevated total bilirubin or abnormal thyroid function parameters. Notably, children Nos.1–3, who received long-term initial combination therapy, exhibited growth retardation, and child No. 4, who received sequential therapy (only one year of Peg-IFN-α-2b treatment), was less affected by growth retardation (Figs. 5 and 6).

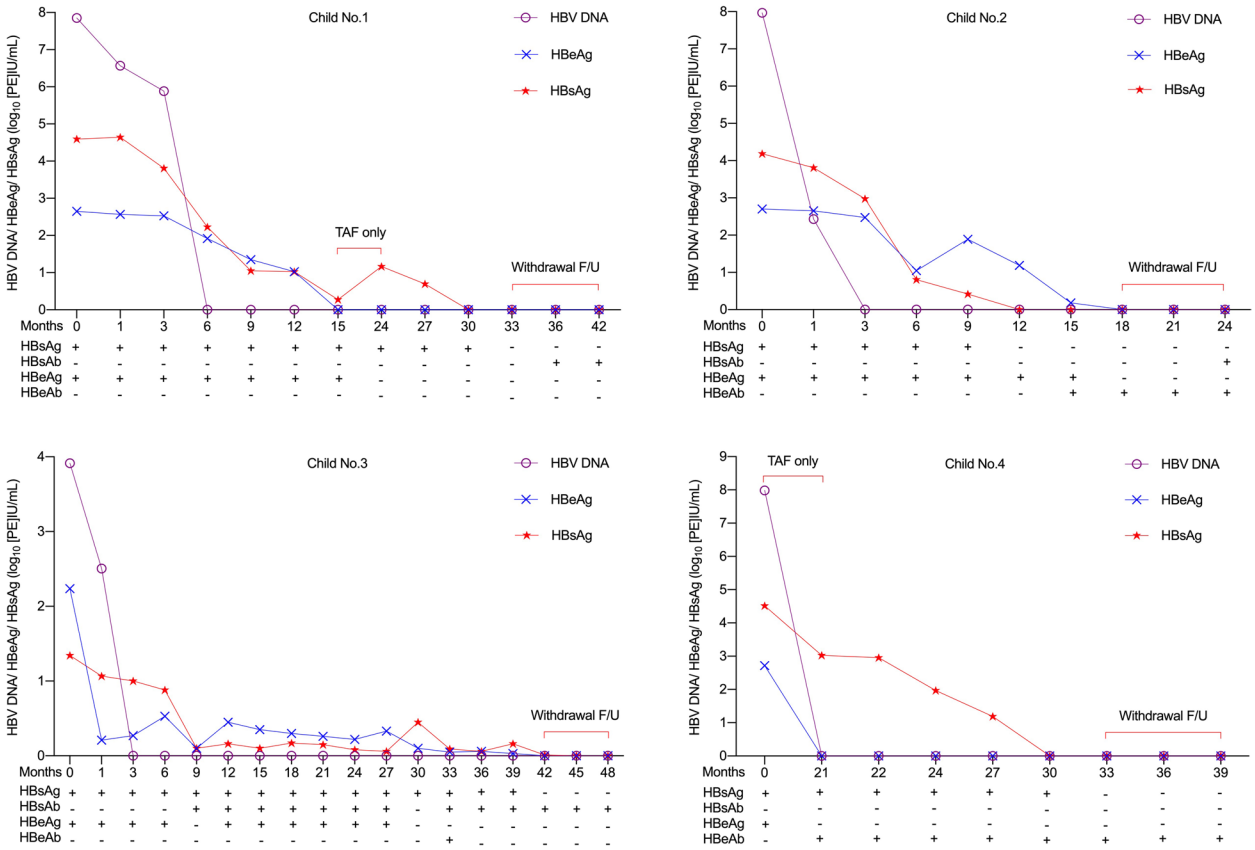

Fig. 1 Hepatitis B viral dynamics during treatment and follow-up. Abbreviations: F/U, follow-up; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; TAF, tenofovir alafenamide

Table 3 Adverse events and laboratory abnormalities during treatment

Adverse events[†]	No.1	No.2	No.3	No.4
Fever	Yes	Yes	Yes	Yes
Muscle pain	Yes	Yes	Yes	Yes
Anorexia	Yes	Yes	Yes	Yes
Fatigue	Yes	Yes	Yes	Yes
Growth retardation	Yes	Yes	Yes	No
Nausea	No	Yes	No	No
Vomiting	No	Yes	No	No
Insomnia	No	No	Yes	No
Headache	No	No	Yes	No
Rash	No	No	No	No
Dizziness	No	No	No	No
Leukopenia	Yes	Yes	Yes	Yes
Neutropenia	Yes	Yes	Yes	Yes
Anemia	Yes	Yes	Yes	Yes
Thrombopenia	Yes	Yes	Yes	Yes
Thyroid dysfunction	No	No	No	No
Hyperbilirubinemia	No	No	No	No

Infants' growth during posttreatment follow-up

Interestingly, by 9 months post-treatment, all three cured children were catching up with or even exceeding the expected growth parameters (Figs. 5 and 6). Unexpectedly, child No. 3 grew 17 cm after 9 months of drug withdrawal (Fig. 6). Notably, although child No. 4, who received sequential therapy, had normal growth parameters during treatment, the baseline gap between the actual and expected growth parameters was obviously larger than that at treatment discontinuation, indicating that only one year of Peg-IFN-α-2b add-on treatment may still slightly influence a child's growth (Figs. 5 and 6).

Discussion

Many studies have reported the safety and efficacy (effectiveness) of Peg-IFN-α therapy in CHB children [4, 11–16]; however, data on the use of Peg-IFN-α plus TAF combination therapy are limited or even lacking. This study is the first to demonstrate the generally favorable safety and effectiveness of TAF plus Peg-IFN-α-2b combination therapy in children with CHB, and reversible growth retardation is the most significant adverse event. These findings may provide important insight for future clinical practice and study designs targeting functional cures for children with CHB.

The functional cure rate of CHB in children is obviously different from that in adults. A previous study indicated that sequential combination treatment with lamivudine and interferon can lead to remarkable HBsAg loss in children with chronic HBV infection and immune-tolerant characteristics [17]. Recently, a randomized trial revealed that peg-interferon and TDF combination therapy followed by protocolized TDF withdrawal led to earlier

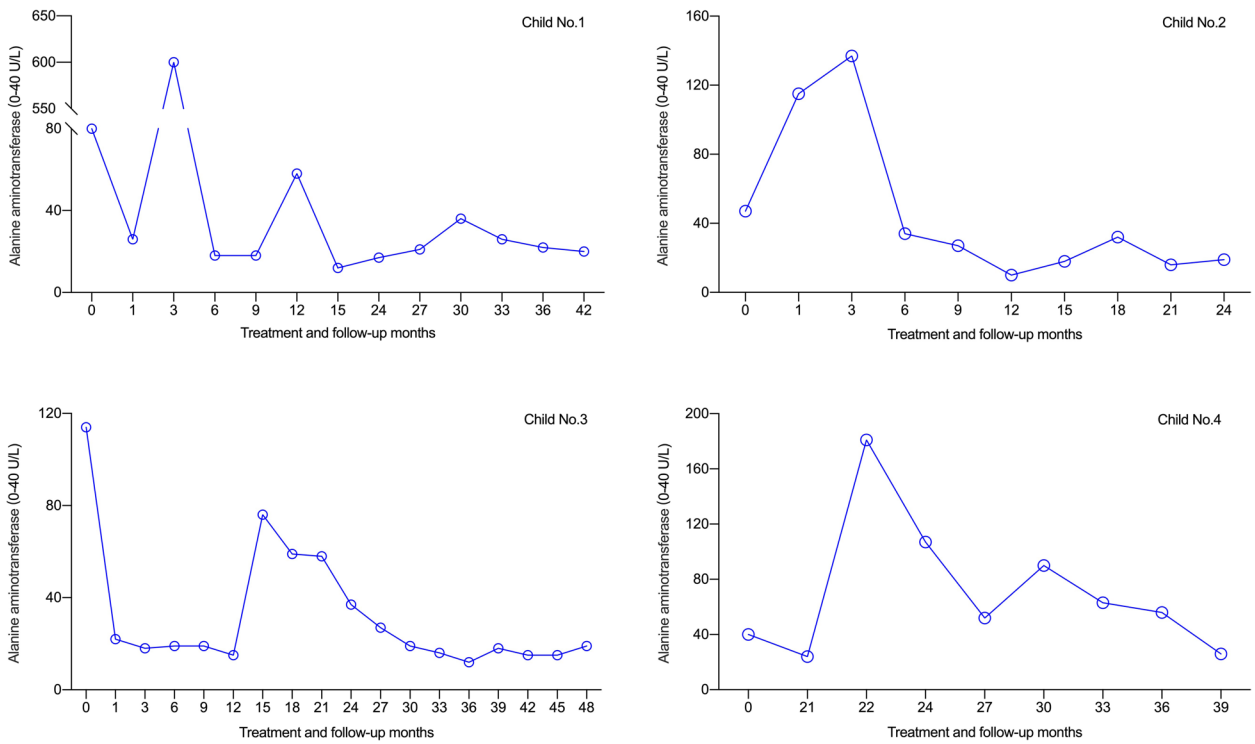

Fig. 2 Changes in alanine aminotransferase levels during treatment and follow-up

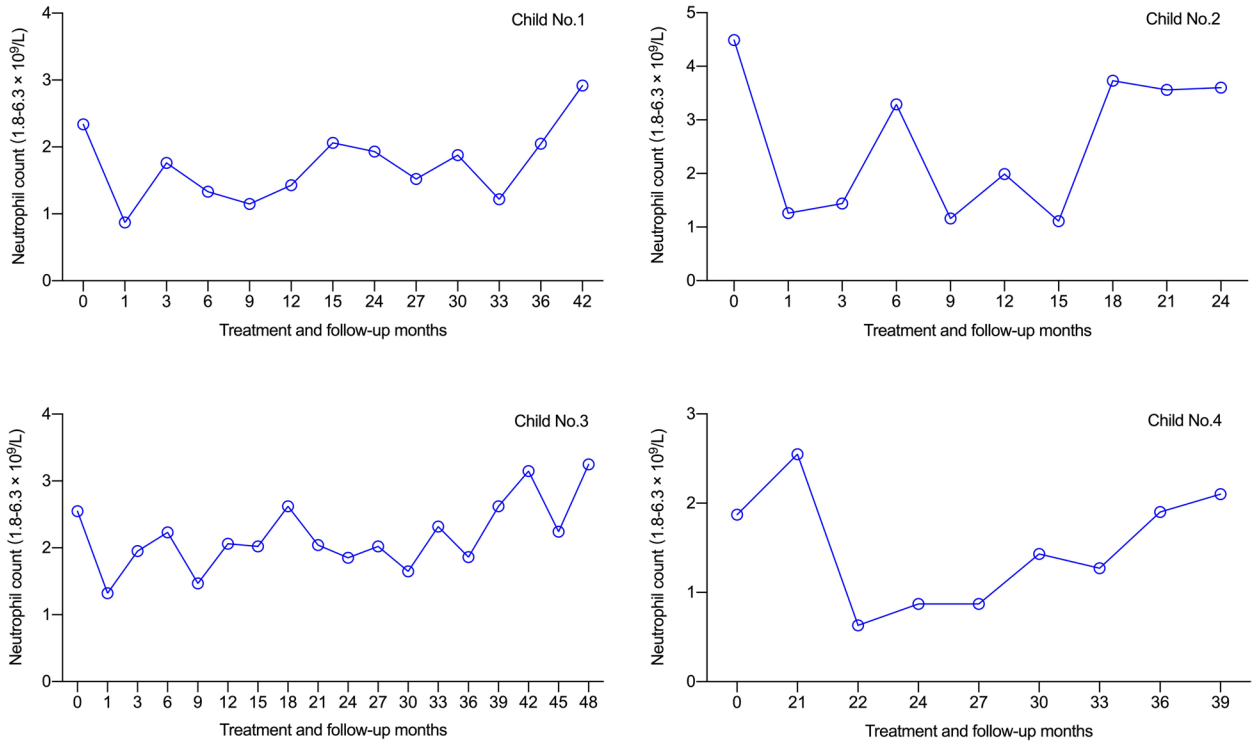

Fig. 3 Changes in neutrophil count during treatment and follow-up

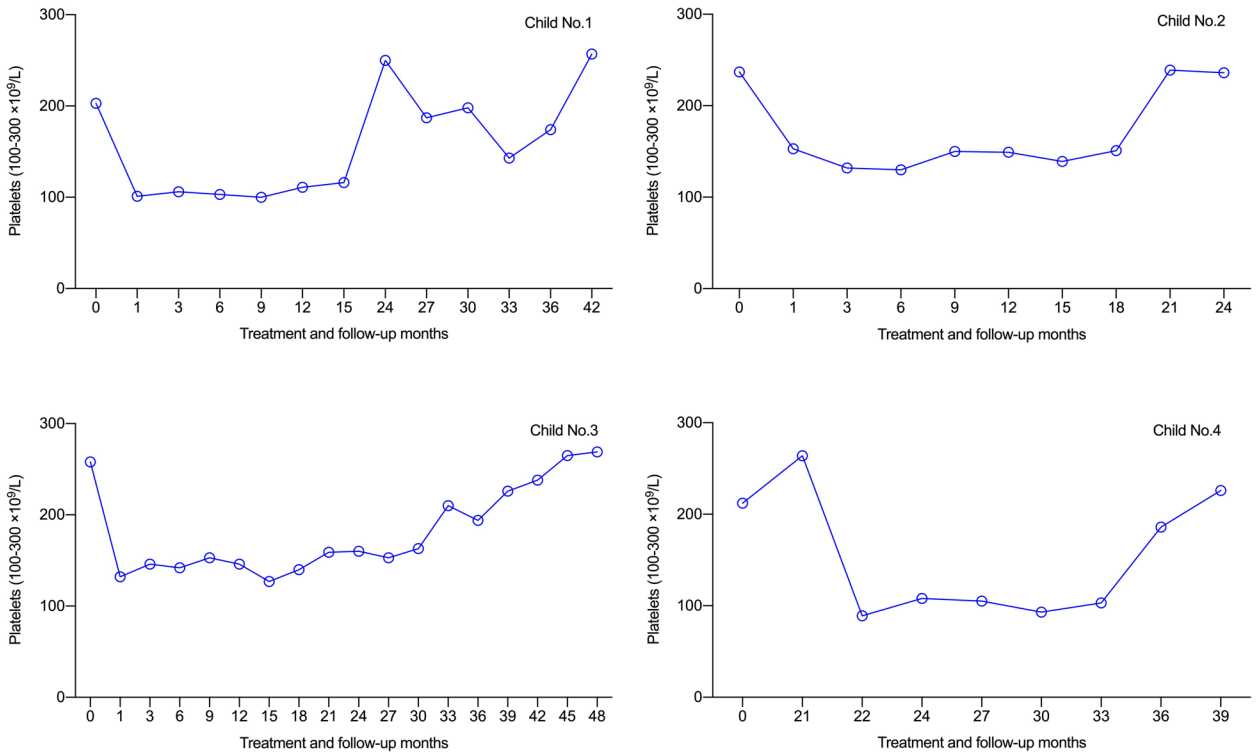

Fig. 4 Changes in platelet count during treatment and follow-up

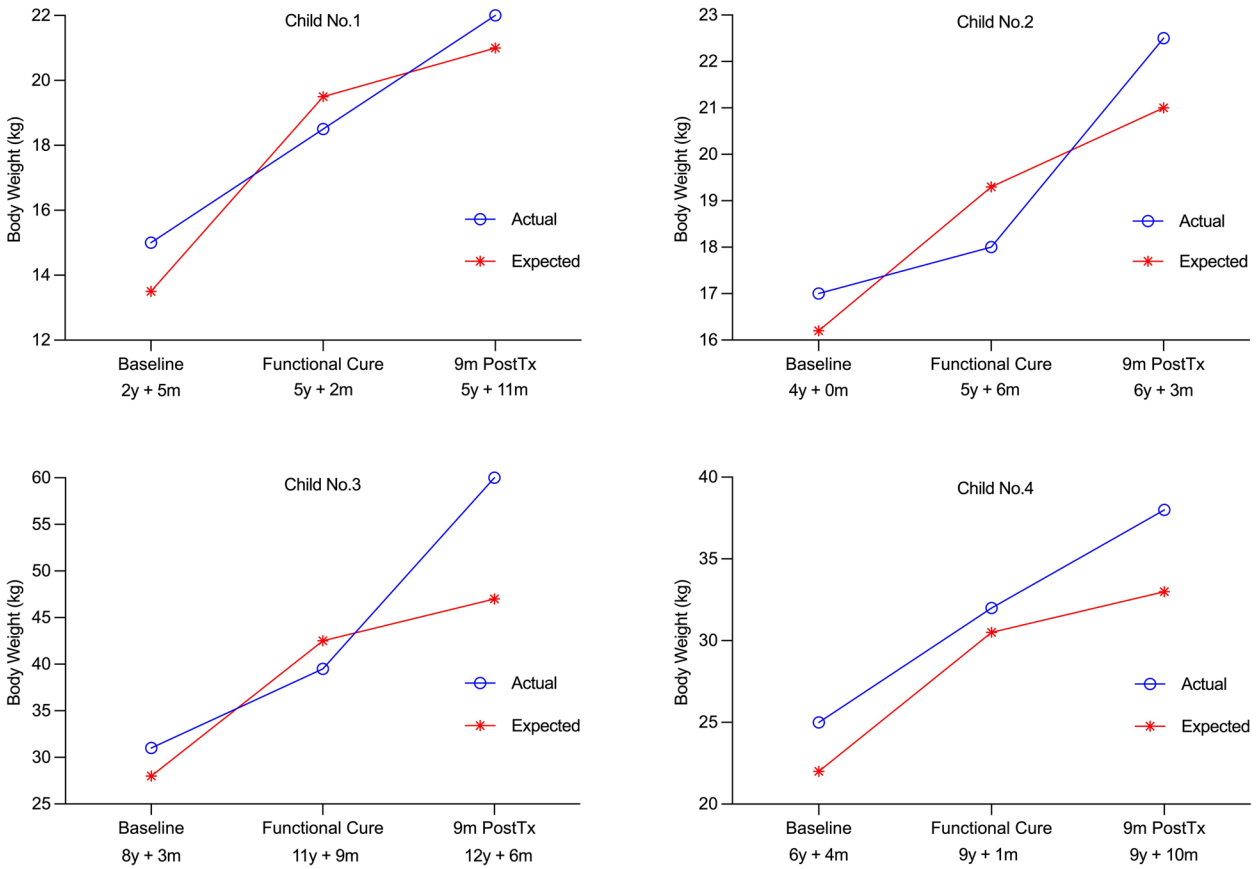

Fig. 5 Children's body weight at baseline, functional cure, and 9 months posttreatment. Abbreviations: m, months; PostTx, posttreatment; y, years

but not greater HBsAg clearance [18]. Our recent study showed that, compared with those aged 7 years and older, children aged between 1 and 7 years with active CHB can attain a high rate of functional cure through antiviral therapy (nucleos[t]ide analog monotherapy or combination therapy with regular interferon-α), which suggests that early antiviral treatment is beneficial for children with CHB [19].

Currently, the first-line anti-HBV drugs used include entecavir, TDF, TAF, and interferon [6]. Previous studies have indicated that TAF is noninferior to TDF in adult CHB patients and has improved bone and renal effects [20, 21]. Furthermore, our previous studies demonstrated the favorable safety and effectiveness of short-term TAF therapy to prevent mother-to-child transmission in pregnant women with chronic HBV infection and high HBV DNA levels and long-term TAF therapy to treat pregnant women with active CHB [2, 3]. However, data on the safety and effectiveness of TAF in CHB patients (especially those younger than 6 years) are lacking, as are data on TAF and interferon combination therapy.

Notably, entecavir and TDF require dose adjustment for children, and regular interferon necessitates frequent injection, which results in strong rejection by parents. The TAF concentration is less than 1/10 of the TDF concentration and has a high genetic resistance barrier similar to that of TDF [22, 23]. Moreover, a previous study indicated that antiviral monotherapy with Peg-IFN α-2a in children with CHB is well tolerated and effective [24]. Currently, Peg-IFN-α-2b (PegBeron) is the only available Peg-IFN-α in China [25]. Therefore, after providing written informed consent, the expert group decided to administer the TAF plus Peg-IFN-α-2b combination or sequential therapy to meet their parents' needs.

During long-term treatment, growth retardation was the most significant adverse event. We speculate that this is mainly caused by long-term Peg-IFN-α-2b injection rather than TAF. Fortunately, this adverse event was reversible after 9 months of treatment discontinuation. Notably, the reversible nature of the growth retardation that occurred in children Nos. 1–3 was impressive, especially for child No. 3. During the 9 months posttreatment, child No. 3's growth was so remarkable that his family, neighbors, teachers, and physicians were all astonished. These findings may greatly alleviate concerns in future clinical practice and research.

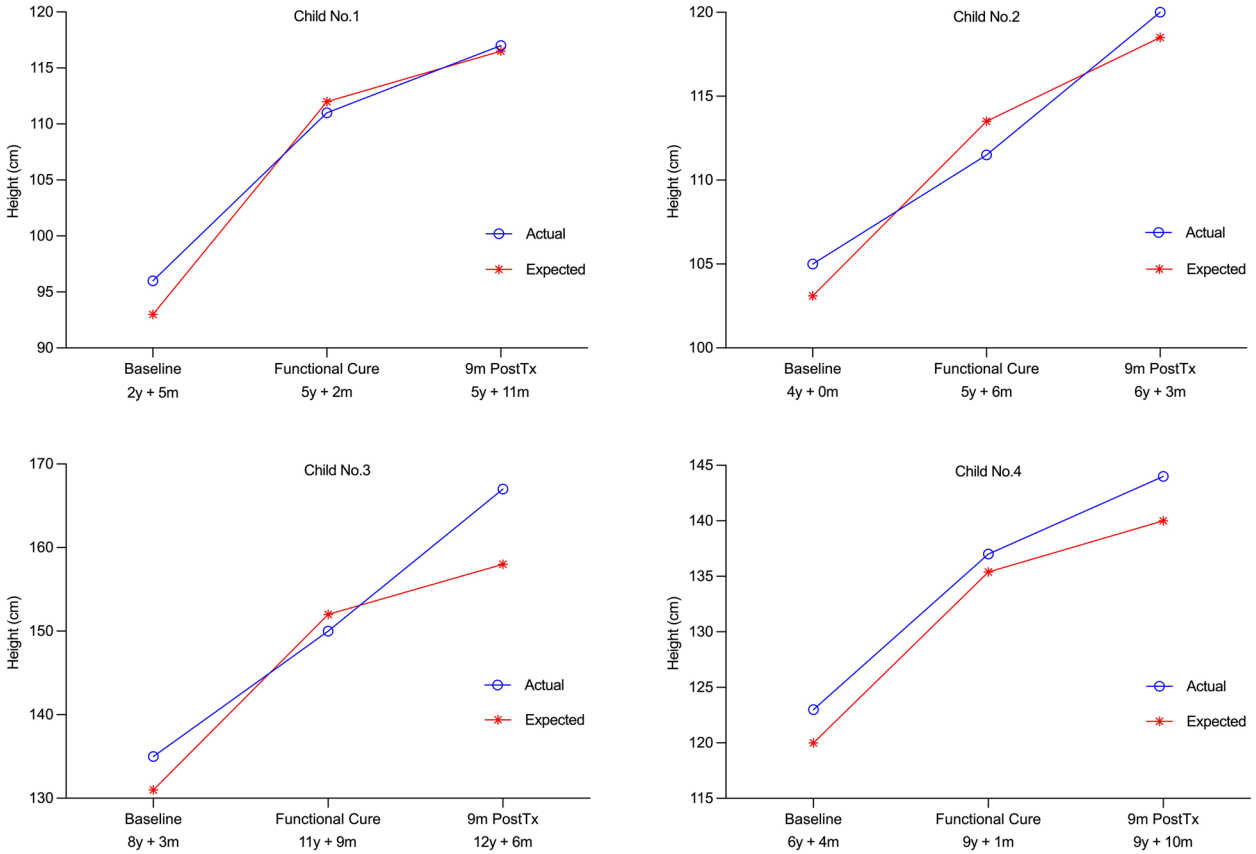

Fig. 6 Children's height at baseline, functional cure, and 9 months posttreatment. Abbreviations: m, months; PostTx, posttreatment; y, years

Initial combination and sequential therapies are two common treatment strategies for functional cure. In this study, Child No. 4, who received sequential therapy (shorter Peg-IFN-α-2b treatment duration), exhibited less Peg-IFN-α-2b–induced growth retardation, which may provide critical insight into management strategy selection or study design for the future treatment of CHB. Therefore, TAF monotherapy can be used first to achieve the first goal of undetectable HBV DNA. TAF monotherapy or TAF plus Peg-IFN-α-2b combination therapy can then be selected based on the decreasing trend in HBeAg to achieve the second goal of HBeAg loss or seroconversion. Finally, TAF plus Peg-IFN-α-2b combination therapy or even Peg-IFN-α-2b monotherapy can eventually be selected based on the decreasing trend in HBsAg to achieve the final goal of HBsAg loss or seroconversion.

Currently, the achievement of a functional cure in children with CHB does not have a fixed mode or standard of care. Response-guided and functional cure-targeted therapy may be an important mode of treatment, as mentioned above. This means that the treatment plan needs to be adjusted according to the response during treatment, and whether the drug should be stopped if "a standard or prespecified course is completed and there is an obvious response but no functional cure" has become a problem worth considering. In this study, we reported only four children who were cured; the other six children who responded favorably to treatment have not yet been cured, and it is not even possible to predict whether or when they will be cured in the future. Therefore, on the basis of safety, "determining the functional cure goal without determining a clear course of treatment" has become an important strategy for the functional cure of CHB patients in China, including children, which can also be interpreted as a "response-guided and functional cure-targeted strategy", as described in the Methods section of this study.

In conclusion, although this study had a small sample size, the findings clearly demonstrated the potential for a functional cure of children with CHB treated with TAF plus Peg-IFN-α-2b, as well as the reversibility of growth retardation, which may provide important clues and may change clinical practice or thinking in the future.

Abbreviations

ALT	Alanine aminotransferase
CHB	Chronic hepatitis B
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
LLOQ	Lower limit of quantification
Peg-IFN-α-2b	Peginterferon-alpha-2b
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate

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Authors' contributions
Q.L.Z., F.S.W., and Z.J.Y. contributed to the conception and design of this study. Q.L.Z., R.Y.C., X.Y.L., and Y.J. P. contributed to the data collection and interpretation. S.H. and W.Z.L. contributed to the statistical analysis. Q.-L. Z. contributed to the drafting and revision of this manuscript. F.S.W. and Z.J.Y. contributed to the critical revision of the manuscript for important intellectual content. All authors approved the final version of this manuscript. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Availability of data and materials
Availability of data and materials. All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from the parents before the initiation of the treatment. This study was approved by the ethics committee of The First Affiliated Hospital of Zhengzhou University.

Consent for publication
Written informed consent for publication was obtained from all the parents of the children.

Competing interests
The authors declare no competing interests.

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