Real-world effectiveness of initial antiviral regimens in children with chronic hepatitis B: an age-stratified cohort study

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Summary

Background Interferons (IFN-α) and nucleos(t)ide analogues (NAs) are currently the primary treatment options for children with chronic hepatitis B (CHB), but the efficacy of different initial antiviral regimens in children with different ages remains unclear.

Methods This study included 483 treatment-naïve children with CHB who received initial antiviral therapy at Hunan Children's Hospital between June 2015 and November 2023. According to the initial 24-week regimens, patients were divided into (Peg) IFN-α monotherapy, NAs monotherapy, and combination therapy groups, and stratified by age of treatment initiation (1–7 years vs. ≥ 7 years). The study outcome was HBsAg loss. Propensity score matching (PSM) was used to adjust for confounding factors, and a sensitivity analysis was performed to assess the robustness of the results.

Findings Of the 483 subjects, 294 (60.87%) were male, with a median age of 5 years. Median (interquartile range) follow-up duration was 90 (53, 156) weeks. 158 (32.71%), 56 (11.59%), and 269 (55.69%) participants were assigned to (Peg) IFN-α monotherapy, NAs monotherapy, and combination therapy groups, respectively. After adjusting for other covariates, HBsAg loss rates were comparable in the (Peg) IFN-α monotherapy group and the combination treatment group in children aged 1–7 years ((Peg) IFN-α: Reference group, NAs: HR (95% CI) 0.47 (0.23–0.96), Combination: 1.31 (0.94–1.82)); while HBsAg loss rate was significantly higher in the combination treatment group compared to the other two groups in children aged ≥7 years group (NAs: 0.70 (0.23–2.19), Combination: 3.02 (1.42–6.45)). PSM and sensitivity analyses observed similar findings.

Interpretation Initial combination therapy had a significant advantage over HBsAg loss in CHB children. In children aged 1–7 years, (Peg) IFN-α monotherapy and combination therapy achieved comparable efficacy; in children aged ≥7 years, combination therapy was more advantageous. Antiviral therapy for children with CHB should be individualized according to the age at treatment initiation to optimize clinical benefit.

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Keywords: Antiviral therapy; Chronic hepatitis B; Interferons; Nucleoside analogs; Combination therapy

Introduction

Hepatitis B virus (HBV) infection continues to pose a major global public health challenge. As of 2019, It is estimated that about 296 million individuals worldwide were living with chronic hepatitis B (CHB).[1] HBV infection mainly occurs in perinatal and infant period, with a chronicity rate reaching up to 90%.[2] The global prevalence of hepatitis B surface antigen (HBsAg) in children younger than 5 years was reported to be 0.7% in 2022, corresponding to 5.6 million children with HBV infection.[3] Although the majority of children with CHB exhibit relatively mild liver damage, 3%–5% and 0.01%~0.03% of cases may progress to cirrhosis or hepatocellular carcinoma before adulthood, respectively.[4] HBsAg loss is considered an ideal treatment endpoint for achieving functional cure of CHB, which is significantly correlated with a reduced risk of long-term liver complications in patients.[5–7]

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Research in context

Evidence before this study

We searched PubMed using the terms "chronic hepatitis B", "children", "interferon", "nucleos(t)ide analogues", and "HBsAg loss" for articles published up to March 2025. Although interferons (especially Peg-IFN-α) and nucleos(t)ide analogues (NAs) are both recommended for treatment among children with CHB, existing studies mainly focus on single-drug regimens and have limited data comparing initial antiviral strategies. Age at treatment initiation has been increasingly recognized as an important factor affecting treatment response in pediatric HBV infection, but no consensus exists on age-specific initial antiviral regimen selection.

Added value of this study

This study provides comprehensive comparative data on initial antiviral strategies for pediatric CHB patients. It evaluates three regimens—(Peg) IFN-α monotherapy, NAs monotherapy, and combination therapy—in treatment-naïve children and conducts subgroup analyses by age. The findings show that combination therapy significantly outperforms monotherapy in children aged ≥7 years, while (Peg) IFN-α monotherapy and combination therapy achieve comparable HBsAg loss rates in children aged 1–7 years.

Implications of all the available evidence

Our findings support the use of age-specific treatment strategies in pediatric CHB. For younger children (1–7 years), (Peg) IFN-α monotherapy remains an effective option; for older children (≥7 years), initiating combination therapy may offer superior clinical benefit in promoting HBsAg loss. These results provide valuable evidence for individualized antiviral treatment decisions in clinical practice and future guideline development.

Currently, antiviral drugs for CHB mainly included interferons (IFNs, e.g., IFN-α, pegylated interferon alpha (Peg IFN-α)) and nucleos(t)ide analogues (NAs, e.g., lamivudine (LAM), entecavir (ETV), and tenofovir disoproxil fumarate (TDF)).[5–7] Accumulated evidence showed that antiviral therapy could significantly improve clinical outcomes in children with CHB, promoting HBsAg loss, HBV DNA suppression, alanine aminotransferase (ALT) normalization, and hepatitis B e antigen (HBeAg) seroconversion.[8–11] Notably, compared with adults, children demonstrate a higher rate of functional cure after a finite-course antiviral therapy, with approximately 50% achieving HBsAg loss.[12]

Notably, there remains no consensus on the optimal antiviral regimen for CHB in children. Antiviral treatment regimens are diverse in clinical context, including (Peg) IFN-α monotherapy, NAs monotherapy, combination therapy (IFN plus NAs), and sequential therapy. However, studies specifically focusing on comparison of various treatment regimens in children with CHB remain limited, and considerable heterogeneity exists in the choice of treatment regimens.[13–15]

Age at treatment initiation is an important factor affecting the efficacy of antiviral therapy in pediatric CHB. Our previous findings suggest that earlier initiation of antiviral therapy is linked to a greater possibility of HBsAg loss.[16] Similarly, Zhang et al. conducted a 36-month study of active CHB children and showed that children aged 1–6 years exhibited a significantly higher cumulative incidence of HBsAg loss (50.78%) than those aged 7–16 years (12.93%),[17] further emphasizing the importance of treatment initiation age. Thus, it is necessary to determine the optimal antiviral regimen for children at different ages. However, high-quality evidence regarding the impact of various initial antiviral regimens on HBsAg loss remains limited, particularly in children from different age groups. Therefore, we explored the association between initial antiviral regimens and HBsAg loss in children stratified by age at treatment initiation, aiming to provide evidence for optimizing individualized treatment strategies in pediatric CHB.

Methods

Study population

This study retrospectively included treatment-naïve CHB children (1–17 years old) who received initial antiviral therapy for at least 6 months at Hunan Children's Hospital between June 2015 and November 2023. All patients had confirmed HBsAg positivity for more than 6 months prior to treatment and maintained a consistent treatment regimen during the first 24 weeks, without discontinuation or regimen change. Exclusion criteria included: nonalcoholic fatty liver disease or other chronic liver diseases; co-infection with hepatitis C, hepatitis D, HIV, Epstein–Barr virus, or cytomegalovirus; concurrent malignant tumors; and incomplete key clinical data. Demographic, biochemical, and virological data were collected at baseline and every 3–6 months during the treatment period.

Ethics approval

In accordance with the ethical guidelines of the Declaration of Helsinki, this study protocol was approved by the Ethics Committee of Hunan Children's Hospital. As this was a retrospective study, the requirement for informed consent was waived.

Antiviral regimens

Before the release of the Chinese guidelines (2022 version), all included patients met the treatment

indication of persistent or recurrent elevation of ALT, or advanced liver disease.[18,19] After the 2022 guideline update, children in the immune-tolerant phase (aged <7 years or with inflammation grade 1) were also considered eligible for antiviral therapy.[7]

In this study, the actual antiviral treatment drugs for children were selected according to the guidelines available at the time of patient enrollment.[7,19–22] In order to unify the classification and analysis of antiviral treatment drugs, we retrospectively sorted out the drugs involved in the study with reference to the "Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2022 version)[7]" and the "Consensus on Clinical Antiviral Treatment of Chronic Hepatitis B in Children (2024 version)[22]". During the study period, several guidelines and consensus statements were published, and updates in recommended drugs and age indications were added in the Supplementary Methods.

According to the above guidelines, IFN-α is recommended for children with CHB aged ≥1 year, while Peg IFN-α is indicated for those aged 3 years or older. In this study, NAs included LAM, ETV, and TDF. LAM was prescribed for children under 2 years old. For children aged ≥2 years, ETV was used as the first-line medication, with TDF reserved for those with antiviral resistance.

IFN-α was administered at a dose of 6 million IU/m^2 body surface area (BSA) three times a week for 24–48 weeks. Peg IFN-α was given at 104 μg/m^2 BSA once weekly for 48 weeks. NAs were dosed by body weight: LAM at 4 mg/kg/day, ETV at 0.015 mg/kg/day (maximum 0.5 mg/day), and TDF at 8 mg/kg/day (maximum 300 mg/day).

The initial antiviral regimen was determined based on baseline clinical features, potential drug-related side effects, and guardian preference. In clinical practice, (Peg) IFN-α-based therapy was generally recommended.[18,23] Combination therapy was preferred for patients with higher baseline HBV DNA and HBsAg levels. Children initially received NAs monotherapy when their guardians refused (Peg) IFN-α treatment due to continuous injection or potential side effects. During treatment, therapy adjustments were made according to on-treatment response. For children initially treated with (Peg) IFN-α monotherapy, an age-appropriate NA was recommended as alternative treatment to those who had a decline in serum HBV DNA of <2 $\log_{10}$ IU/mL after 24 weeks of treatment; NA add-on strategy was adopted to those who had a decline in serum HBsAg of >1 $\log_{10}$ IU/mL after 24 weeks of treatment; otherwise, (Peg) IFN-α monotherapy was continued to 48 weeks, which can be extended according to the condition, but the continuous treatment course should not exceed 96 weeks.[19,21,24] For children initially treated with NAs monotherapy, (Peg) IFN-α was added as sequential combination therapy after 24 weeks of NAs monotherapy, with guardian consent; otherwise, NAs monotherapy was continued. For patients with a poor antiviral response (defined as serum HBV DNA >2000 IU/mL after 48 weeks of NAs monotherapy), (Peg) IFN-α could be added with guardian approval. If guardians continued to decline (Peg) IFN-α, treatment was either switched to or combined with another age-appropriate NA.[20,22,25]

Patients were grouped according to the initial 24-week antiviral regimens into three groups: (1) initial (Peg) IFN-α monotherapy, (2) initial NAs monotherapy, and (3) initial combination therapy. Based on treatment adjustments during follow-up, patients were further divided into subgroups: continuous monotherapy, sequential therapy (e.g., IFN followed by NAs or vice versa), and combination therapy.

Outcomes and follow-up evaluation

The endpoint outcome of this study was HBsAg loss, defined as achieving an HBsAg level below 0.05 IU/mL. The index date was defined as the date of initiation of antiviral treatment. The follow-up duration for each patient was calculated from the index date to the date of HBsAg loss, treatment discontinuation, or the last follow-up (March 31, 2025).

Safety evaluation

Safety was assessed during the initial 24 weeks of antiviral therapy. Adverse events, including clinical symptoms and laboratory abnormalities, were documented at each follow-up visit. Adverse events were categorized by treatment regimen: (Peg) IFN-α monotherapy, NAs monotherapy, and combination therapy.

Laboratory and histological assessments

Quantitative HBsAg levels were measured using an electrochemiluminescence assay on the cobas e 601 analyzer (Roche Diagnostics, Germany), with a quantification range of 0.05–52,000 IU/mL. Serum HBV DNA was quantified using a quantitative fluorescence PCR assay kit (Sansure Biotech, China) on the ABI 7500 Real-Time PCR System (Life Technologies, USA), with a quantification range of 20–5.0 × 10^9 IU/mL.

Liver histopathological assessments were performed blinded by two experienced hepatologists and biopsy specimens were independently reviewed. Histological changes were quantified using the internationally recognized Scheuer scoring system, which grades fibrosis (stage 0–4) and inflammatory activity (grade 0–4), respectively. Informed consent was obtained from all guardians prior to liver biopsy.

Statistical analysis

Continuous variables were described as mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for skewed data. Categorical variables were presented as frequencies and

percentages. Group comparisons for continuous variables were performed using analysis of variance (ANOVA) or the Kruskal–Wallis test, depending on data distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The cumulative incidence of HBsAg loss was estimated using Kaplan–Meier curves, and differences between treatment groups were assessed with the log-rank test. Associations between initial antiviral regimens and HBsAg loss were evaluated using Cox proportional hazards models. Children who experienced serious adverse drug reactions or discontinued antiviral therapy for other reasons were included in the analysis and censored at the time of treatment discontinuation. To control for potential confounders, propensity score matching (PSM) was conducted based on baseline covariates identified through multivariable logistic regression. A 1:1:1 nearest-neighbor matching algorithm with a caliper of 0.05 standard deviations of the estimated propensity score was applied across the three treatment groups. Furthermore, we performed sensitivity analyses in the subgroups of patients who maintained their initial treatment regimen throughout the study (i.e., continuous monotherapy and combination therapy) to avoid the effect of possible treatment adjustments (e.g., adding or adjusting medication after 24 weeks) during the follow-up period. All statistical analyses were performed using R software (version 4.3.2), with a two-sided significance level of $\alpha = 0.05$.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Baseline characteristics

A total of 501 treatment-naive children with CHB were initially identified. 18 children were excluded due to other significant comorbidities (e.g., Epstein–Barr virus, cytomegalovirus, leukemia, or non-alcoholic fatty liver disease, n = 6), and incomplete key clinical data (n = 12).

Finally, 483 children were included in the analysis. Based on their initial 24-week antiviral regimen, patients were categorized into three groups: initial (Peg) IFN-α monotherapy (n = 158), initial NAs monotherapy (n = 56), and initial combination therapy (n = 269). Group allocation process is detailed in the treatment flowchart (Fig. 1).

Table 1 presents the baseline demographic, virological, and liver histological characteristics of the cohort. The median age at enrollment was 5 years. Most children were infected with HBV genotype B (65.01%), and the age of treatment initiation was 1–7 years (61.08%). Histological assessments revealed that 41.82% had mild hepatic inflammation (grade <2) and 57.56% had mild fibrosis (stage <2). Children in the initial (Peg) IFN-α monotherapy group were younger than those in the NAs and combination therapy groups (median age: 3 vs. 7 and 5 years, respectively; $p < 0.001$). A significant difference in gender distribution was observed among the groups ($p = 0.017$), with a higher proportion of males in the initial (Peg) IFN-α monotherapy group. The combination therapy group exhibited lower baseline ALT levels ($p = 0.001$), but higher qHBsAg levels ($p < 0.001$), HBV DNA levels ($p = 0.021$), and a higher proportion of HBeAg positivity ($p = 0.012$).

According to our previous study,[16] the age of treatment initiation was critical for HBsAg loss in

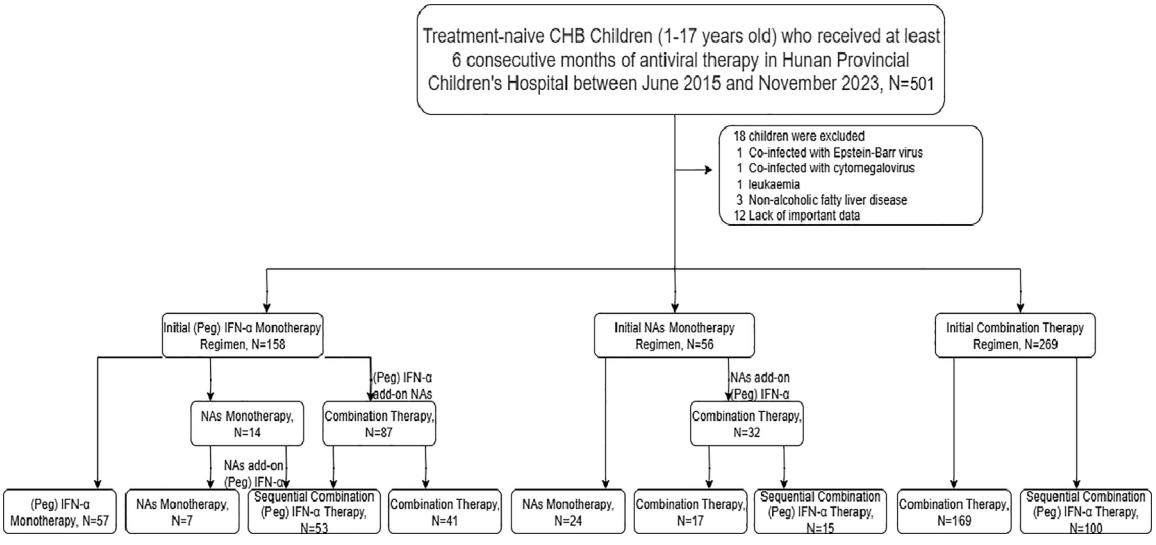

Fig. 1: Flowchart of patient selection and treatment allocation.

CHB children. The incidence of HBsAg loss in patients aged 1–7 years is much higher than that in patients aged ≥7 years (55.1% vs 17.0%). Table S1 summarizes the baseline characteristics of CHB patients stratified by age at treatment initiation. Except for the initial antiviral regimen, baseline antibody against hepatitis B surface antigen (HBsAb) and HBV genotype, no significant differences were found in other variables between the 1–7 years group and the ≥7 years group.

Incidence of HBsAg loss by initial therapy and age

As shown in Fig. 2, the overall incidence of HBsAg loss varied significantly across the three initial treatment regimens ($p < 0.001$), with the highest incidence observed in the (Peg) IFN-α monotherapy group (58.2%), followed by combination therapy (47.6%) and NAs monotherapy (28.6%). In children aged 1–7 years, the difference remained significant ($p = 0.008$), with HBsAg loss rates of 70.7%, 58.6%, and 40.7%, respectively. However, in children aged ≥7 years, no signifi-

Variables	Total (n = 483)	Initial (Peg) IFN-α monotherapy (n = 158)	Initial NAs monotherapy (n = 56)	Initial combination therapy (n = 269)	*p*-value
Age, years	5 (3, 9)	3 (2, 7)	7 (4, 10)	5 (3, 9)	<0.001
1~7	295 (61.08)	116 (73.42)	27 (48.21)	152 (56.51)	
≥7	188 (38.92)	42 (26.58)	29 (51.79)	117 (43.49)	
Gender					0.017
Male	294 (60.87)	107 (67.72)	26 (46.43)	161 (59.85)	
Female	189 (39.13)	51 (32.28)	30 (53.57)	108 (40.15)	
Follow-up time	90 (53, 156)	103 (51.25, 192.75)	112.5 (71.75, 178)	84 (52, 138)	0.006
Maternal HBV infection					0.012
Yes	394 (81.57)	133 (84.18)	38 (67.86)	223 (82.9)	
No	22 (4.55)	10 (6.33)	4 (7.14)	8 (2.97)	
Missing	67 (13.87)	15 (9.49)	14 (25)	38 (14.13)	
ALT, IU/L	40.8 (23.35, 74.65)	51.95 (28.83, 89.02)	37.15 (21.33, 80.18)	34.9 (22.2, 62.8)	0.001
qHBsAg, $\log_{10}$ IU/ml	4.25 (3.36, 4.71)	3.95 (3.16, 4.59)	3.6 (2.78, 4.69)	4.43 (3.67, 4.72)	<0.001
HBeAg					0.012
Positive	452 (93.58)	143 (90.51)	50 (89.29)	259 (96.28)	
Negative	31 (6.42)	15 (9.49)	6 (10.71)	10 (3.72)	
HBsAb, IU/L	2 (2, 9.16)	2 (2, 10.87)	2.98 (2, 13.15)	2 (2, 8.02)	0.316
HBsAb					0.048
Positive	110 (22.77)	44 (27.85)	16 (28.57)	50 (18.59)	
Negative	373 (77.23)	114 (72.15)	40 (71.43)	219 (81.41)	
HBV DNA, $\log_{10}$ IU/ml	6.98 (5.48, 7.94)	6.88 (5.95, 7.54)	6.38 (4.56, 7.91)	7.3 (5.31, 8.16)	0.021
FIB-4	0.14 (0.08, 0.23)	0.11 (0.06, 0.21)	0.19 (0.11, 0.33)	0.14 (0.09, 0.23)	<0.001
APRI	0.42 (0.29, 0.72)	0.51 (0.35, 0.85)	0.41 (0.29, 0.84)	0.37 (0.27, 0.64)	<0.001
Inflammation grade					0.002
<2	202 (41.82)	67 (42.41)	21 (37.5)	114 (42.38)	
≥2	137 (28.36)	60 (37.97)	12 (21.43)	65 (24.16)	
Undetected	144 (29.81)	31 (19.62)	23 (41.07)	90 (33.46)	
Fibrosis stage					0.009
<2	278 (57.56)	102 (64.56)	27 (48.21)	149 (55.39)	
≥2	61 (12.63)	25 (15.82)	6 (10.71)	30 (11.15)	
Undetected	144 (29.81)	31 (19.62)	23 (41.07)	90 (33.46)	
HBV genotype					<0.001
B genotype	314 (65.01)	86 (54.43)	33 (58.93)	195 (72.49)	
C genotype	68 (14.08)	16 (10.13)	6 (10.71)	46 (17.1)	
Undetected	101 (20.91)	56 (35.44)	17 (30.36)	28 (10.41)	

Note: Values are presented as median (IQR) for continuous variables and n (%) for categorical variables. *p* values were calculated using the Kruskal–Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Abbreviations: (Peg) IFN-α; (pegylated) interferon-α, NAs; nucleos(t)ide analogues, ALT; alanine aminotransferase, qHBsAg; quantitative hepatitis B surface antigen, HBeAg; hepatitis B e antigen, HBsAb; antibody against hepatitis B surface antigen, HBV; hepatitis B virus, FIB-4; Fibrosis-4 Index, APRI; aspartate aminotransferase-to-platelet ratio index.

Table 1: **Baseline characteristics according to the initial 24-week antiviral regimen among children with CHB.**

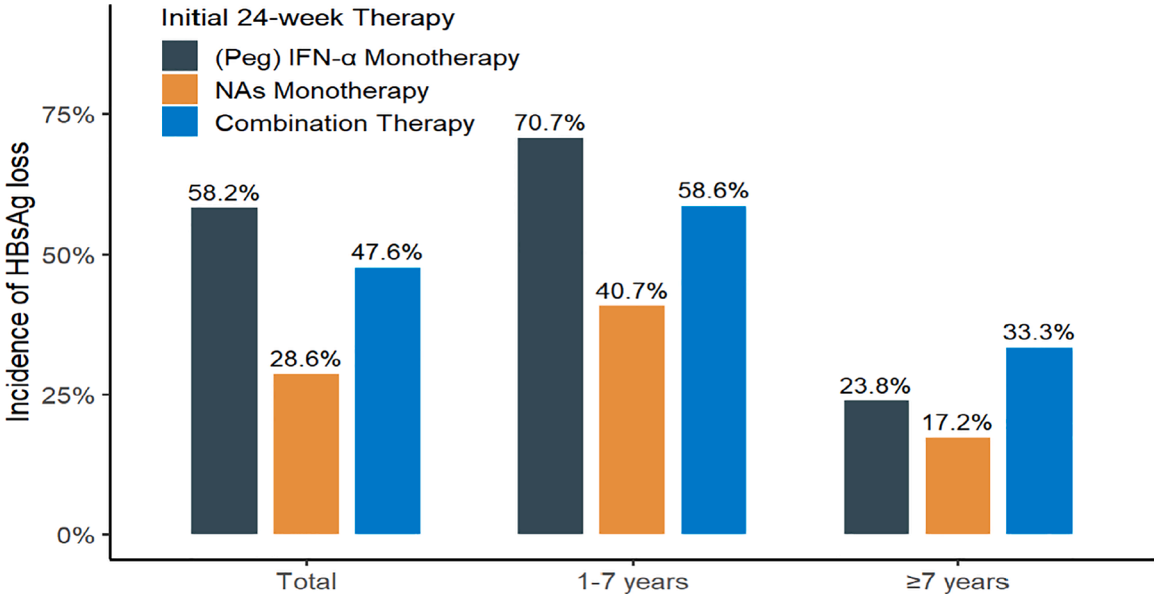

Fig. 2: Incidence of HBsAg loss according to initial 24-week antiviral therapy stratified by the age of treatment initiation.

cant difference was found among the three regimens, and the incidence of HBsAg loss was relatively low across all antiviral regimens.

Initial antiviral regimen and HBsAg loss

The cumulative incidence of HBsAg loss varied according to initial antiviral regimen (Fig. 3A). Patients receiving combination therapy or (Peg) IFN-α monotherapy had a higher cumulative incidence of HBsAg loss, while the lowest in the NAs monotherapy group (log-rank p = 0.0088). Unadjusted Cox regression showed that the initial antiviral regimen was associated with the occurrence of HBsAg loss (Initial NAs: HR (95% CI) 0.51 (0.30–0.86), Initial Combination: 1.13 (0.85–1.49)) (Table 2). After adjustment for age, sex, maternal infection status, AlT, qHBsAg, HBeAg, HBsAb, and HBV DNA, initial combination therapy was significantly associated with an increased likelihood of HBsAg loss compared with (Peg) IFN-α monotherapy (HR = 1.54, 95% CI: 1.15–2.06), whereas NAs monotherapy was linked to a lower likelihood of HBsAg loss (HR = 0.51, 95% CI: 0.29–0.91). Given that the missing rate of inflammatory grade, fibrosis stage, and HBV genotype exceeds 20%, these variables were excluded from the multivariate Cox regression analysis shown in Table 2 to minimize potential bias. However, we performed a supplementary analysis of these variables (Table S2) and the results were consistent with Table 2.

Subgroup analysis according to age

Age-stratified analyses revealed different patterns. Among patients aged 1–7 years (Fig. 3B), the cumulative incidence of HBsAg loss was comparable among three therapy groups (log-rank p = 0.23). However, the results of multivariate Cox regression suggested that compared to initial (Peg) IFN-α monotherapy, patients receiving combination therapy group had comparable probability to achieve HBsAg loss, while NAs monotherapy was strongly linked to a lower likelihood of HBsAg loss (HR = 0.47, 95% CI: 0.23–0.96).

In contrast, among children aged ≥7 years (Fig. 3C), combination therapy showed a significantly higher cumulative incidence of HBsAg loss compared to both monotherapy groups (log-rank p = 0.011). Multivariate Cox regression revealed that patients receiving initial combination group were 3.02 times probability to achieve HBsAg loss (HR = 3.02, 95% CI: 1.42–6.45), whereas no statistically significant difference was found between the two monotherapy groups.

Propensity score matching and sensitivity analysis

To minimize the impact of baseline imbalance, we performed PSM based on key covariates including age, sex, ALT, qHBsAg, HBV DNA, and HBV genotype. Although some covariates were not completely balanced, the comparability of the matched cohort was improved (Table S3). In the sub-cohorts, results were generally consistent with the original analysis (Figure S1, Table S4). Among children aged 1–7 years, initial (Peg) IFN-α monotherapy and combination therapy showed comparable efficacy (Initial NAs: 0.41 (0.18–0.95); Initial Combination: 0.93 (0.47–1.83); Ref: Initial (Peg) IFN-α); whereas in those aged ≥7 years, combination therapy was the most effective (Initial

NAs: 1.13 (0.17–7.72); Initial Combination: 9.05 (1.48–55.16); Ref: Initial (Peg) IFN-α).

In addition, in patients who maintained their initial antiviral regimen throughout the follow-up period (Table S5), we performed sensitivity analyses to avoid the impact of treatment adjustments during the follow-up period on outcomes. The results were broadly consistent with the overall cohorts: the cumulative incidence of HBsAg loss was similar between initial (Peg) IFN-α monotherapy and combination therapy in the 1–7 years subgroups, while the combination therapy was more effective in children aged ≥7 years (Figure S2, Table S6).

Furthermore, for patients who changed their initial antiviral regimen during the entire follow-up period (Table S7), we conducted a sensitivity analysis. The results showed that there was no statistically significant difference in the loss of HBsAg among the three initial antiviral regimens in both the overall cohort and subgroups (Table S8).

Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2022 version) expanded the treatment indications for children in the immune-tolerant (IT) phase: for children with age of >7 years and positive HBV DNA and ALT < ULN, liver histology assessment is required (If the liver histology grade is G ≥ 1, antiviral therapy should be initiated). For children aged 1–7 years, antiviral treatment may be considered even in the absence of liver pathology results, provided there is thorough discussion and informed consent. Based on this update, we administered antiviral therapy to the children who were in the IT phase but met the above treatment criteria (4.1%, 20/483). To avoid potential bias in this group of patients to the overall analysis, we excluded them from a subsequent sensitivity analysis, and the results showed that the conclusions remained robust (Table S9, Table S10).

Safety evaluation

During the initial 24 weeks of antiviral therapy, adverse events were observed primarily in patients receiving (Peg) IFN-α monotherapy or combination therapy, while no adverse events were reported in the NAs monotherapy group (Table S11). The most frequent adverse event was fever (28.99%, 140/483), with the highest incidence in the combination group (37.55%, 101/269), followed by (Peg) IFN-α monotherapy group (24.68%, 39/158). Neutropenia occurred in 89 cases (18.43%), mainly in the combination therapy group (26.77%, 72/269) and (Peg) IFN-α monotherapy group (10.76%, 17/158). Anorexia, cough, and persistent exacerbations were also frequently observed, especially in the combination group. Other adverse effects, such as dizziness, headache, alopecia, hypodynamia, and gastrointestinal symptoms, were predominantly mild and self-limited. Adverse events in most cases can be controlled through symptomatic treatment or dose

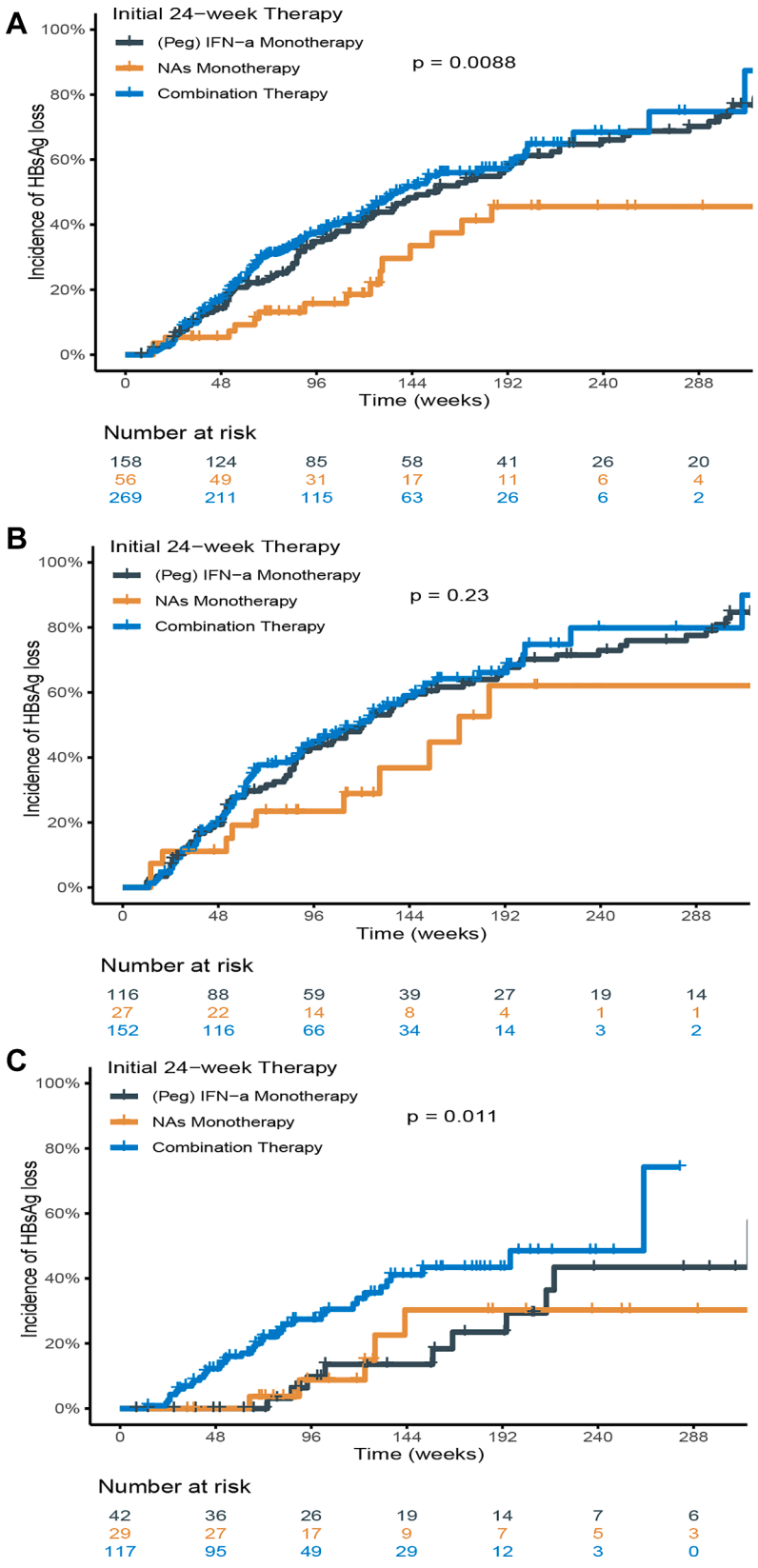

Fig. 3: Kaplan–Meier curves for cumulative incidence of HBsAg loss according to initial 24-week antiviral regimen in (A) the overall population, (B) children aged 1–7 years, and (C) children aged ≥7 years.

Variables	Total				1–7				≥7			
	Univariate COX		Multivariate COX		Univariate COX		Multivariate COX		Univariate COX		Multivariate COX	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.89 (0.85–0.92)	<0.001	0.88 (0.84–0.92)	<0.001	0.95 (0.86–1.04)	0.270	0.92 (0.82–1.02)	0.097	0.87 (0.75–0.99)	0.037	0.81 (0.69–0.95)	0.011
Male	0.68 (0.53–0.88)	0.004	0.66 (0.51–0.86)	0.002	0.80 (0.59–1.07)	0.128	0.77 (0.56–1.04)	0.089	0.48 (0.28–0.83)	0.008	0.37 (0.21–0.68)	0.001
Maternal HBV infection (+)	1.08 (0.59–1.99)	0.810	0.57 (0.30–1.06)	0.077	1.26 (0.52–3.09)	0.610	0.86 (0.34–2.14)	0.738	0.58 (0.25–1.39)	0.223	0.29 (0.11–0.74)	0.010
Initial (Peg) IFN-α	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Initial NAs	0.51 (0.30–0.86)	0.012	0.51 (0.29–0.91)	0.023	0.63 (0.34–1.19)	0.156	0.47 (0.23–0.96)	0.038	0.78 (0.26–2.27)	0.642	0.70 (0.23–2.19)	0.541
Initial combination	1.13 (0.85–1.49)	0.398	1.54 (1.15–2.06)	0.004	1.09 (0.80–1.48)	0.599	1.31 (0.94–1.82)	0.110	2.29 (1.11–4.73)	0.025	3.02 (1.42–6.45)	0.004
ALT	1.00 (1.00–1.00)	0.332	1.00 (1.00–1.00)	0.391	1.00 (1.00–1.00)	0.612	1.00 (1.00–1.00)	0.558	1.00 (1.00–1.00)	0.639	1.00 (1.00–1.00)	0.390
HBsAg	0.69 (0.61–0.79)	<0.001	0.65 (0.54–0.77)	<0.001	0.67 (0.57–0.77)	<0.001	0.69 (0.56–0.85)	<0.001	0.75 (0.57–0.98)	0.035	0.60 (0.42–0.86)	0.005
HBeAg(+)	1.35 (0.77–2.37)	0.296	1.43 (0.81–2.53)	0.221	1.18 (0.66–2.12)	0.583	1.31 (0.72–2.39)	0.378	3.65 (0.50–26.48)	0.201	1.51 (0.18–12.90)	0.705
HBsAb(+)	2.13 (1.61–2.81)	<0.001	1.67 (1.23–2.26)	<0.001	2.00 (1.47–2.74)	<0.001	1.63 (1.16–2.31)	0.005	1.94 (1.04–3.63)	0.038	2.50 (1.22–5.13)	0.013
HBV DNA	0.92 (0.86–0.99)	0.019	0.99 (0.91–1.09)	0.890	0.87 (0.80–0.94)	<0.001	0.94 (0.84–1.06)	0.302	1.00 (0.87–1.16)	0.935	1.13 (0.94–1.34)	0.207
G ≥ 2	0.98 (0.72–1.34)	0.912			0.98 (0.69–1.39)	0.905			0.98 (0.49–1.94)	0.950		
S ≥ 2	0.97 (0.65–1.44)	0.871			1.02 (0.64–1.62)	0.922			1.11 (0.48–2.56)	0.809		
B genotype	1.47 (0.98–2.21)	0.061			1.64 (1.03–2.61)	0.038			1.28 (0.53–3.07)	0.580		

Abbreviations: HR; hazard ratio, CI; confidence interval, Ref; reference group, (Peg) IFN-α; (pegylated) interferon-α, NAs; nucleos(t)ide analogues, ALT; alanine aminotransferase, HBsAg; hepatitis B surface antigen, HBeAg; hepatitis B e antigen, HBsAb; antibody against hepatitis B surface antigen, HBV; hepatitis B virus, G; inflammation grade, S; fibrosis stage.

Table 2: **Univariate and multivariate Cox regression analysis of initial antiviral regimen associated with HBsAg loss in the overall cohort and age-stratified subgroups.**

adjustment (Peg) IFN-α, and symptoms resolve spontaneously or with dose reduction. Only a few cases required intervention. During the follow-up period, 5 children discontinued due to serious adverse drug reactions, all of which occurred during (Peg) IFN-α treatment after 24 weeks. These included 2 cases of severe neutropenia (absolute neutrophil count $\leq 0.5 \times 10^9$/L), 1 case of thyroid dysfunction, 1 case of intolerable persistent headache, and 1 case of growth retardation.

Discussion

Our study explored the effectiveness of initial antiviral regimens on HBsAg loss in pediatric CHB across different treatment initiation age groups. We found that children treated with (Peg) IFN-α-based regimens had a higher likelihood of achieving HBsAg loss. In children aged 1–7 years, HBsAg loss rate of (Peg) IFN-α monotherapy was comparable to that of combination therapy; In children aged ≥7 years, combination therapy was significantly better than that of other regimens.

Previous studies have indicated that age at treatment initiation plays a crucial role in predicting HBsAg loss in children with CHB. A follow-up study of 372 untreated CHB children found that the cumulative incidence of HBsAg disappearance after 36 months of treatment in children aged 1–7 years was approximately four times higher than that of children aged ≥7 years (50.78% vs. 12.93%).[17] Wang et al.'s retrospective study showed that within 13 years of follow-up, patients aged 1–7 years had a much higher HBsAg loss rate than patients aged 8–17 years (71.40% vs. 39.0%) in children treated with IFN-α.[12] Similarly, our study found that 61.7% and 28.7% of CHB children achieved HBsAg loss in the 1–7 years and ≥7 years groups, respectively. Therefore, 7-years old at the time of treatment initiation may be a key age point, affecting the treatment response to different antiviral regimens.

Although some studies have argued that combination therapy can enhance the functional cure of CHB in children,[26,27] evidence in children aged 1–6 years indicates comparable efficacy between IFN-α monotherapy and combination therapy. A retrospective study of 95 HBeAg-positive CHB patients aged 1–6 years showed that combination therapy (IFN-α plus LAM) was not superior to IFN-α monotherapy in HBsAg negative rates at both 48 and 96 weeks.[13] In addition, Pan et al. observed similar results in a cohort of 236 CHB patients within the same age group.[28] Consistent with these findings, our study showed that (Peg) IFN-α monotherapy was comparable to combination therapy in patients aged 1–7 years, while the advantage of combination therapy was mainly reflected in children ≥7 years of age.

This age-stratified difference may be associated with the maturity of the immune system in children with

CHB. First, integrated HBV DNA is another important source of HBsAg in addition to covalently closed circular DNA (cccDNA) in patients with CHB, and its accumulation is strongly correlated with the time of infection.[29] Since most children are infected through mother-to-child transmission, younger children are infected for a shorter period of time, resulting in fewer HBV DNA integrations into the host genome.[30] Secondly, the smaller liver volume of young children means that the virus pool is limited.[31] Finally, the thymus is still developing in infancy, and younger children have a higher proportion of lymphocytes in peripheral blood and may have a stronger immune response.[32] Thus, in children aged 1–7 years, (Peg) IFN-α monotherapy may be sufficient to activate an adequate immune response regardless of use of NAs, whereas in children aged ≥7 years, NAs acting synergistically with (Peg) IFN-α (the former inhibiting viral replication and the latter enhancing immune clearance) may contribute more to HBsAg clearance.

This study also assessed safety during the initial 24 weeks. Compared with previous drug safety studies in children with CHB, the adverse events incidence of our study was relatively low, which may be related to the fact that safety evaluation in this study was based only on a 24-week follow-up period. However, the types of adverse events were basically consistent with previous studies,[8,26,33] mainly including mild fever, neutropenia, etc., almost all of which occurred in children treated with (Peg) IFN-α, and serious adverse events were extremely rare. We also documented serious adverse drug reactions that occurred after the initial 24-week treatment period and led to treatment discontinuation. Notably, a small number of serious adverse drug reactions were observed, resulting in discontinuation in 5 children. Although infrequent, these events highlight the need for careful monitoring during (Peg) IFN-α treatment, especially in the pediatric population. Overall, (Peg)IFN-α has shown an acceptable safety profile in the pediatric population.

In our study, we performed several sensitivity analyses to support the robustness of our findings. Interestingly, among patients who underwent antiviral regimen modifications during follow-up, no significant differences in HBsAg loss were observed across the initial treatment groups. However, these patients had a longer follow-up duration (median: 147 weeks) and may have received multiple individualized treatment adjustments based on their virological response. Over time, treatment strategies likely converged among the groups, thereby diluting the effect of the initial regimen. Therefore, this finding does not contradict our main conclusions, but rather reflects the impact of real-world adaptive treatment. It also underscores the importance of choosing an effective initial antiviral regimen—not only to reduce the need for frequent treatment modifications, but also to maximize the chance of achieving functional cure more rapidly.

Nevertheless, this study has several notable limitations. Firstly, the retrospective study design, which only included children with follow-up durations exceeding 24 weeks, may introduce selection bias. Secondly, adjustment of the antiviral regimen after 24 weeks of follow-up may have an impact on HBsAg loss, although we have validated the results by sensitivity analysis in patients with stable regimens. Thirdly, although this study found different optimal antiviral regimen for patients in different age treatment initiation groups, the immunological mechanisms behind it have not been explored in depth. Future studies should further clarify the differences in immune response, virus clearance and immune tolerance between different treatment initiation age groups.

In summary, our study found that the optimal initial antiviral regimen was different in children with different ages, suggesting that the starting age of treatment and treatment goal should be comprehensively considered when formulating treatment plans for pediatric patients. In children aged 1–7 years, (Peg) IFN-α monotherapy can achieve sufficient efficacy, while for children aged ≥7 years, combination therapy is more beneficial to HBsAg loss. These findings provide evidence for individualized treatment and new ideas for achieving functional cure of CHB in children.

Contributors

Sisi Li contributed to the study design, data analysis, and manuscript drafting. Meng Yang assisted with data analysis and contributed to manuscript revision. Ling Ye provided methodological support and participated in data interpretation. Yingping Gu and Yiying Kuang were responsible for data collection and management. Cai Gao and Huimin Lai contributed to data quality assurance. Songxu Peng conceptualized and supervised the study, provided administrative and technical support, and critically reviewed and edited the manuscript. Sisi Li and Songxu Peng have accessed and verified the data. All authors read and approved the final manuscript.

Data sharing statement

The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declaration of interests

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103478.

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