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Increased ATTENTION to Early Initiation of Antiviral Therapies in Chronic Hepatitis B Based on Viral Load

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This summary reviews Lim YS, Yu ML, Choi J, et al. Early antiviral treatment with tenofovir alafenamide to prevent serious clinical adverse events in adults with chronic hepatitis B and moderate or high viraemia (ATTENTION): Interim results from a randomised controlled trial. Lancet Gastroenterol Hepatol 2025; 10(4):295-305.

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STRUCTURED ABSTRACT

Question: Does early antiviral treatment with tenofovir alafenamide reduce liver-related serious adverse events in adults with non-cirrhotic chronic hepatitis B (CHB) and moderate or high viremia (serum HBV DNA ≥10,000 IU/mL), but normal or mildly elevated alanine aminotransferase (ALT) concentrations?

Design: A randomized controlled trial.

Setting: From February 8, 2019 to October 17, 2023, 22 centers in South Korea and Taiwan were included.

Patients: Adults aged 40-80 years with non-cirrhotic CHB, serum HBV DNA

concentrations between 4 $\log_{10}$ IU/mL and 8 $\log_{10}$ IU/mL, either HBeAg positive or HBeAg negative, and with normal ALT concentrations or lower than 70 U/L for males and 50 U/L for females. Key exclusion criteria included co-infection with hepatitis C or D, previous exposure to anti-HBV treatment, evidence of cirrhosis, hepatic decompensation, malignancy, or organ transplantation.

Intervention: Oral tenofovir alafenamide (25 mg daily) or no antiviral treatment (observation) for a median follow up time of 17.7 months.

Outcomes: The primary endpoint was a composite of the rate of hepatocellular carcinoma (HCC), hepatic decompensation, liver transplantation, or death from any cause. Secondary outcomes included the incidence of each individual component of the composite endpoint, achievement of viral response (i.e., undetectable serum HBV DNA [<10 IU/mL]), ALT normalization (defined as serum ALT ≤35 U/L for males or ≤25 U/L for females), and HBeAg seroconversion. In addition, virological, biochemical, and serological responses—including HBsAg seroclearance and HBeAg seroclearance in patients who were HBeAg positive at baseline—were assessed every 6 months at local laboratories.

Data Analysis: The statistical analysis plan included 2 interim analyses, scheduled at 4 years and 8 years after the enrollment of the first participant, with a final analysis planned at the 12-year mark, contingent upon the interim results. All analyses were performed on an intention-to-treat basis.

The cumulative incidence of the primary endpoint was estimated using Kaplan–Meier, with differences between treatment groups assessed via log-rank test. HRs for the primary outcome were derived from Cox proportional hazards regression models, considering the treatment group (tenofovir alafenamide vs observation) as the primary independent variable. To maintain a 2-sided type I error rate of 0.025—given the 2 planned interim analyses and a final analysis—the nominal significance level was determined using the O'Brien–Fleming spending function. Accordingly, stopping boundaries were set based on the timing of the interim analyses (e.g., at the first interim analysis, the stopping boundary for the log-rank test was $Z_1 = 4.17$, corresponding to a nominal α_1 of 0.00003), and 2-sided 97.5% CIs were reported for the primary outcome.

The secondary endpoints were analyzed with either the χ^2 test or Fisher's exact test, as appropriate, with treatment effects for binary outcomes estimated as risk

differences alongside 95% CIs, and prespecified subgroup analyses were conducted (including stratification by baseline HBeAg status, sex, and other criteria).

Funding: This study was funded by the late Kang Jeong-Ja, the Government of South Korea, and Gilead Sciences (which supplied tenofovir alafenamide), with funders having no role in study design, data collection, analysis, interpretation, or publication decisions.

Results: Overall, 798 individuals were screened and 734 were randomized (369 to the tenofovir alafenamide group and 365 to the observation group), with baseline characteristics well balanced between groups. The composite primary endpoint—comprising HCC, hepatic decompensation, liver transplantation, or death—occurred in 2 (1%) participants in the tenofovir alafenamide group (0.33 per 100 person-years) compared to 9 (2%) in the observation group (1.57 per 100 person-years), yielding a hazard ratio of 0.21 (97.5% CI 0.04–1.20; P=0.027). (**Table 1)** Notably, among participants with normal ALT concentrations at baseline, no primary endpoint events were observed in the tenofovir alafenamide group versus 4 events in the observation group, with similar trends evident when applying European and Asia-Pacific ALT criteria.

Secondary endpoints showed that significantly more participants in the tenofovir alafenamide group achieved virological response and ALT normalization (both P<0.0001) compared to those under observation, while HBeAg and HBsAg seroclearance rates were comparable between groups. Treatment adherence in the tenofovir alafenamide group was high (mean 98.4%), and the frequency of serious adverse events was similar between groups, with no new safety concerns identified during the follow-up period.

COMMENTARY

Why Is This Important?

Chronic HBV is a major global health concern, ranking as the third most common cause of cirrhosis and affecting nearly 300 million people worldwide, including approximately 2.4 million in the United States[1, 2] The cornerstone of management are antivirals such as tenofovir disoproxil fumarate, tenofovir alafenamide, and entecavir, which inhibit HBV polymerase activity to reduce viral replication.[2]

Although there is slight variation amongst the major international liver

societies regarding thresholds for treatment initiation, the common theme is that the main driver for HCC risk and disease progression (ie. development of fibrosis) is the viral load.[3-5] These findings have led to a growing consensus that treatment decisions should be driven primarily by HBV DNA levels, independent of ALT values.[5, 6]

To our knowledge, this is the first RCT to assess the efficacy of early antiviral treatment with tenofovir alafenamide in patients with non-cirrhotic chronic HBV and moderate to high viremia who do not meet current treatment criteria due to normal or only mildly elevated ALT levels. It challenges the conventional approach and suggests that treatment indications should be expand-

	Tenofovir alafenamide group (n=369)	Observation group (n=365)	Hazard ratio (97·5% CI)	p value
Composite primary endpoint				
Number (%)	2 (1%)	9 (2%)	0·21 (0·04 to 1·20)	0·027
Incidence rate per 100 person-years	0·33	1·57	..	..
Secondary endpoints				
Hepatocellular carcinoma	2 (1%)	7 (2%)	0·27 (0·04 to 1·62)	0·079
Hepatic decompensation	0	1 (<1%)	NE	0·31
Death	0	1 (<1%)	NE	0·29
Liver transplantation	0	0	NE	NE
Virological response*	295/325 (91%)	96/310 (31%)	59·8 (53·8 to 65·8)	<0·0001
Biochemical responses*				
Normal ALT†	261/325 (80%)	192/310 (62%)	18·4 (11·5 to 25·3)	<0·0001
ALT normalisation‡	124/171 (73%)	86/173 (50%)	22·8 (12·8 to 32·8)	<0·0001
Serological responses*				
HBsAg seroclearance	1/325 (<1%)	2/310 (1%)	−0·3 (−1·4 to 0·7)	0·62
HBeAg seroclearance	13/57 (23%)	8/45 (18%)	5·0 (−10·6 to 20·6)	0·53
HBeAg seroconversion	8/57 (14%)	6/45 (13%)	0·7 (−12·7 to 14·1)	0·92

Data are n/N (%) unless otherwise indicated. NE=not estimable. ALT=alanine aminotransferase. HBeAg=hepatitis B e antigen. HBsAg=hepatitis B surface antigen. *Participants who were followed up for at least 6 months were evaluated. †Normal ALT was defined as ≤25 U/L for females and ≤35 U/L for males. ‡Among participants with abnormal ALT concentrations at baseline.

Table 1. Primary and secondary efficacy endpoints.

ed based primarily on HBV DNA concentrations, considering patients with moderately high viremia, independent of the degree of fibrosis and ALT levels.

Expanding treatment criteria would increase the number of people eligible for therapy. For example, a recent study in South Korea showed that removing ALT restrictions for treatment in patients with viral loads of 2,000 IU/mL or higher increased eligibility from 25% to 54% of the CHB population, potentially reducing decompensated cirrhosis, HCC, and liver-related deaths by 68%, 33%, and 35%, respectively, by 2035.[7]

Key Study Findings

Patients treated with tenofovir alafenamide had a 79% lower risk of the overall composite primary endpoint (including HCC, hepatic decompensation, liver transplantation, or death) compared with patients in the observation group.

These findings suggest that antiviral therapy should be considered early on for individuals with non-cirrhotic chronic HBV and moderate to high viremia, even if ALT levels are not elevated, to prevent hepatocellular carcinoma and other serious liver-related events.

Caution

Although this study does show significant improvement in risk reduction of the composite endpoint with tenofovir alafenamide, we are only looking at 2 out of 369 participants who developed a liver-related endpoint in the treatment arm. Further, the median age in this study was 53 years, whereas in the US, due to the opioid crisis leading to rising cases of incident HBV in younger patients, this study may not be generalizable to our patients.

The median follow-up time of 17.7 months on average is relatively short for assessing outcomes such as HCC or death, however we do acknowledge that the trial is still ongoing and we look forward to long-term results.

The composite primary endpoint is almost entirely driven by HCC, with only one event each for hepatic decompensation and death, and no events for liver transplantation. Given this, it may be more accurate to say that the tenofovir alafenamide group could decrease the rate of HCC, while its impact on the other secondary endpoints remains questionable. In addition, 36% of patients in the observational group were eventually moved into the treatment arm as they met treatment criteria. This absolutely affected the incidence of the composite outcome in the observational arm.

Finally, the study evaluated only one agent, although other widely used agents, such as entecavir, have not yet been evaluated.

My Practice

Though in 2025 our armamentarium of antivirals is limited to drugs that are highly potent, efficacious and safe, they often can be cost-prohibitive. Though the thresholds are different, this study essentially aligns with the recent WHO guidelines which aim to eliminate hepatitis B as a major public health threat by 2030. They suggest treatment if the DNA is > 2,000 IU/mL and the ALT is above the upper limit of normal, thus treating before there is significant inflammation. In my practice, undoubtedly I utilize NILDA to risk-stratify patients first, obtain a full history, and understand their unique social determinants of health in a culturally competent manner to tailor my plan for them. If there is significant fibrosis, cirrhosis, co-infections, or a family history of HCC or cirrhosis, we opt for treatment (if they can follow-up and the medication is affordable). If there are multiple time points that demonstrate a rise in viral load, irrespective of ALT levels and fibrosis stage, I highly consider treatment initiation after a discussion with the patient and the individuals who identify as their support system.

CHB is arguably one of the most challenging topics for trainees to understand and master. Often, confusion can arise due to the varying guidelines put forth by the different international societies. As such, we must recall that guidelines are meant to guide us as clinicians, but at the end of the day, treatment decisions should be tailored to each individual patient based on shared decision making and by weighing the overall risks and benefits.

For Future Research

Future studies should aim to validate these findings in multi-center studies with diverse populations ideally with longer follow-up periods that allow for the development of more complications, making comparisons more meaningful. It would also be interesting to see more granularity in terms of patient reported outcomes such as the impact on quality of life after treatment with antivirals. Furthermore, in this study, tenofovir alafenamide was chosen. Given the frequently encountered concerns surrounding prescription drug coverage costs, the efficacy of alternatives such as entecavir or tenofovir disoproxil fumarate would add to this body of literature.

Conflict of Interest

The authors have no conflicts of interest to disclose.

Abbreviations

ALT, alanine aminotransferase; CHB, chronic hepatitis B; CI, confidence interval ; HBeAg, hepatitis B e-antigen; HBV, hepatits B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; NILDA, Non-Invasive Liver Disease Assessment; RCT, randomized controlled trial; WHO, World Health Organization.

Social Media

The authors of this summary are active on social media. Tag them on X to discuss their work.

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