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ORIGINAL ARTICLE

# Laboratory monitoring and antiviral treatment for chronic hepatitis B among routine care patients in the United States

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## Abstract

We investigated factors associated with rates of recommended monitoring of chronic hepatitis B (HBV) patients for viral DNA and alanine aminotransferase (ALT), and initiation of antiviral treatment among eligible patients, in a US cohort of patients under routine care. Patients were categorised by treatment indication: definite, equivocal or ineligible. Baseline covariates included demographics, clinical characteristics and specialist care status. 'Recommended monitoring' was defined ≥1 ALT or HBV DNA test per year. Logit models, univariate then multivariable, were used to evaluate factors associated with monitoring and treatment. Among 3,830 patients, treatment was received by 67.5% (788/1168 patients) in the 'definite' category, and 34.1% (208/610 patients) in the 'equivocal' category, of whom 109 moved up to 'definite' status at some point during follow-up. Sex, age and specialist care were independently associated with receipt of treatment in 'definite' patients. Routine monitoring rates were high prior to treatment in 'definite/ treated' patients (ALT: 77%; DNA: 85%) but declined afterwards (ALT 63%; DNA 36%). Rates of monitoring were lower in 'definite/ untreated' patients (ALT: 48%; DNA: 32%). Among 'equivocal/ treated' patients, lower age and comorbidity scores were associated with receipt of treatment; ALT monitoring rates were similar before and after treatment initiation (41% and 46%, respectively), while rates of DNA monitoring declined (55% and 29%). Monitoring among 'treatment ineligible' patients was similar to those in the 'equivocal' and untreated 'definite' groups. A large proportion of US HBV patients under routine care did not receive recommended annual laboratory monitoring, especially after initiation of antiviral treatment, and nearly one-third of patients with 'definite' indications for antiviral therapy remained untreated.

**KEYWORDS**
chronic hepatitis B (CHB), cirrhosis, hepatocellular carcinoma (HCC), liver fibrosis, screening

**Abbreviations:** AASLD, American Association for the Study of Liver Disease; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; BMI, body mass index; CHeCS, Chronic Hepatitis Cohort Study; EASL, European Association for the Study of the Liver; FIB4, fibrosis-4 index; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IU/mL, international units/millilitre; T2D, type 2 diabetes; ULN, upper limit of normal; VCTE, vibration controlled transient elastography.

  

## 1 | INTRODUCTION

Chronic hepatitis B virus (HBV) infection may progress to liver fibrosis and cirrhosis; however, with the emergence of effective treatments that provide long-term viral load suppression, progression of liver disease is no longer inevitable. A number of studies, including our own, have shown that antiviral treatment can prevent the development of cirrhosis and reduce the risk for hepatocellular carcinoma (HCC) and liver-related mortality.[1] Such benefits, however, are confined to patients who are provided appropriate treatment. Current guidelines for antiviral treatment recommend serial monitoring of HBV DNA and alanine aminotransferase (ALT) levels to characterise the phase of infection, as one-time measures are not sufficient. In general, patients with evidence of significant liver inflammation/fibrosis or active viral replication should receive antiviral treatment, whereas those with low-level viraemia or normal ALT may forego treatment but at least should be annually monitored. Patients may also fall into an equivocal treatment category if test results are discordant with regard to phase of disease.[2]

A previous study of HBV patients in the Chronic Hepatitis Cohort Study (CHeCS)—drawn from routine clinical care patients in the United States—found low rates of annual ALT and HBV DNA monitoring, even those with access to integrated healthcare.[3] Other studies have found similarly low rates of adequate monitoring, even in communities with high rates of chronic HBV.[4–7] We sought to update these data and evaluate whether appropriate monitoring varied by treatment indication (definite, equivocal and ineligible) and status (treated or untreated). We also investigated factors associated with receipt of antiviral treatment among patients who were classified in treatment definite and equivocal categories.

## 2 | METHODS

### 2.1 | Patient population

CHeCS is a retrospective/ prospective, observational study that includes patients from four large US health systems—Geisinger Clinic (Danville PA); Henry Ford Health System (Detroit MI); Kaiser Permanente Hawai'i (Honolulu HI) and Kaiser Permanente Northwest (Portland OR). CHeCS follows all guidelines of the US Department of Health and Human Services regarding protection of human subjects; study protocols were approved by the institutional review board at each participating site. The CHeCS study design has been previously described.[8] Briefly, electronic administrative data and electronic health records for patients ≥18 years who received health services at any study site from 1 January 2006 through 31 December 2017 were used to identify study candidates; eligibility was confirmed with medical chart abstraction. We excluded patients who were coinfected with hepatitis C or HIV. In addition, patients were excluded from the analytical cohort upon death.

**TABLE 1** Factors used in determination of antiviral treatment eligibility among patients with chronic hepatitis B viral infection (HBV) and available HBV DNA and ALT data

| |
|---|
| Treatment indication: Definite |
| Decompensated cirrhosis |
| Compensated cirrhosis + detectable HBV DNA |
| HBV DNA > 20,000 IU/ml + ALT >2xULN |
| HBV DNA > 2000 IU/ml + ALT > ULN + Significant fibrosis |
| HBV DNA > 2000 IU/ml + ALT > 2xULN + HBeAg neg |
| HBV DNA < 2000 + ALT > ULN + HBeAg neg + Significant fibrosis |
| Treatment indication: Indefinite |
| HBV DNA > 20,000 IU/ml + normal ALT |
| HBV DNA 2000–20,000 IU/ml + ALT > ULN + HBeAg pos/ unk + NO Significant fibrosis |
| Compensated cirrhosis + NO detectable HBV DNA |
| Treatment ineligible: |
| Does not meet any of the above criteria |

*Note:* Significant fibrosis: APRI > 1.5, FIB4 > 3.45, VCTE > 9.0 kPa or F3/F4 biopsy.

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; FIB4, fibrosis-4 index; HBeAg, hepatitis B e antigen; IU/mL, international units/ millilitre; ULN, upper limit of normal (as defined by the laboratory test used); VCTE, vibration-controlled transient elastography.

### 2.2 | Treatment indication

Using 2018 guidelines from the American Association for the Study of Liver Disease (AASLD)[2] and 2017 guidance from the European Association for Study of the Liver (EASL),[9] we categorised patients by treatment indication—definite, equivocal or ineligible (see Table 1). Patients with insufficient data to determine treatment eligibility category (i.e. non-cirrhotic patients with missing HBV DNA or ALT data, or compensated cirrhotic patients with missing HBV DNA data) were excluded, as were patients who were already on treatment and virally suppressed at the beginning of observation. Given the length of observation, treatment indication classification could change over the duration of the study (e.g. patients ineligible for treatment at the beginning of the study period might become eligible); as a result, patients could be classified in more than one treatment indication category.

### 2.3 | Data collection and analysis

Outcomes of interest were as follows: (1) rates of receipt of treatment within the 'definite' and 'equivocal' treatment indication categories; (2) factors associated with receipt of treatment and (3) proportions of patients who received ≥1 ALT and HBV DNA test per year within each treatment indication category; for treated patients, rates of ALT and HBV DNA testing were further broken down to before and after initiation of antiviral treatment. Univariate analysis (*t*-test for continuous

variables and chi-square test for categorical variables) followed by multivariate logistic regression analyses was used to investigate factors associated with receipt of treatment among patients with either 'definite' or 'equivocal' indications for antiviral therapy; significant ($p < .05$) covariates were retained for the multivariate model. For the analysis of factors associated with receipt of treatment, the index date for treated patients was defined as the date of first treatment initiation whereas the index date for patients who did not receive treatment was defined as the first date of the laboratory results used to define their treatment indication category. Patients with more than one treatment indication over the study period were assigned index dates for each category. The following variables (measured at index date) were included: demographics (age, sex, race, household income and health insurance); BMI; Charlson–Deyo comorbidity score[10]; fibrosis-4 (FIB4, a biomarker for liver fibrosis/ cirrhosis that has been previously validated in patients with HBV)[11]; type 2 diabetes (T2D); and access to specialist care (defined as an encounter with gastroenterology, hepatology or infectious disease departments).

## 3 | RESULTS

### 3.1 | Receipt of treatment status by treatment indication and patient monitoring

Among 5958 patients with confirmed chronic HBV infection, 1338 patients were excluded because they had insufficient data to determine treatment eligibility category; an additional 790 were excluded because they were already on treatment at the beginning of observation. This left 3830 patients in the final analysis cohort. Of these, 1,168 (30.5%) had 'definite' indications for treatment, of whom 788 (67.5%) received treatment; 610 (15.9%) had 'equivocal' indication for treatment, of whom 208 (34.1%) received treatment. Of these, 109 progressed to 'definite' status (thus also included in the 'definite' total, above). The remaining 2161 patients (56.4%) were classified as treatment 'ineligible', of whom only 5 (0.2%) received treatment.

Figure 1 summarises the sample categories and percentage of patients who received at least yearly ALT and HBV DNA level assessments within each treatment indication category. Among patients with 'definite' indication for treatment, 77% had at least one ALT level obtained per year before antiviral treatment was initiated; the rate dropped to 63% after treatment began. Similarly, 85% were at least annually tested for HBV DNA before treatment initiation, but the frequency decreased to 36% after treatment was started. Among patients with 'definite' indications for treatment but who did not initiate antiviral therapy, rates of annual ALT and HBV DNA testing were 48% and 32%, respectively.

Among patients with 'equivocal' indications for treatment who received therapy, 41% had at least annual ALT testing and 55% had at least annual HBV DNA assessments prior to treatment initiation; after treatment commenced, rates of ALT testing remained similar (46%) but HBV DNA testing declined to 29%. 'Equivocal' indication patients who did not initiate treatment had similar rates of annual ALT monitoring (43%) as those that were treated, but the percentage with annual HBV DNA assessment was 28%.

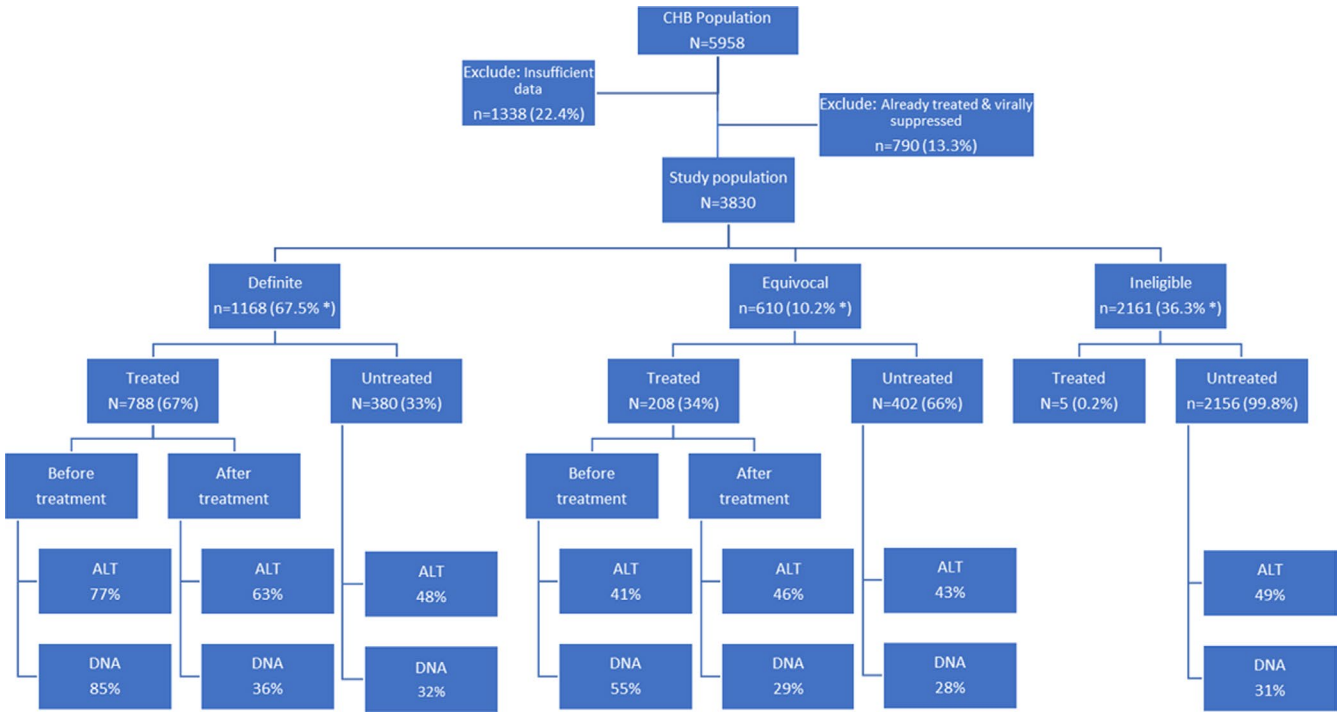


FIGURE 1 Distribution of chronic hepatitis B (CHB) patients by treatment indication and status, and rates of annual alanine aminotransferase (ALT) and viral DNA monitoring for each category. *The sum of percentages of Definite + Equivocal + Ineligible exceeds 100% because $n = 109$ patients were reclassified from equivocal to definite at some point during follow-up and are counted in both groups

Among 'ineligible' patients, 99.8% of whom did not initiate therapy, 49% had annual ALT monitoring and 31% had annual HBV DNA assessments.

### 3.2 | Factors associated with receipt of treatment among patients with 'definite' indications

Table 2A displays univariate comparisons for the 1,168 patients with 'definite' indications for treatment. Among these patients, demographic factors associated with higher rates of treatment included male sex, older age, Asian/Pacific Islander (AAPI) race and Medicare insurance. Clinical factors included higher FIB-4, presence of diabetes and receipt of care from a specialist.

Table 3A displays results from the multivariable analysis of factors associated with receipt of antiviral treatment among patients with definite indication for treatment. Only patient sex, age and access to specialist care remained significant in this analysis. Female patients were less likely to be treated than male patients (adjusted odds ratio (aOR) = 0.54, 95% confidence interval (CI) 0.41–0.70). Younger patients (<40 years old) were less likely to be treated than those 60 years or older (aOR = 0.46, 95% CI 0.31–0.67), and patients without care of a specialist were roughly 80% less likely to receive treatment (aOR = 0.20, 95% CI 0.12–0.34).

### 3.3 | Factors associated with receipt of treatment among patients with 'equivocal' indications

Table 2B shows univariate comparisons among the 610 patients with 'equivocal' indications for treatment. Demographic factors associated with initiation of treatment included younger age and Medicare insurance; significant clinical factors included higher FIB-4, presence of diabetes and higher Charlson–Deyo comorbidity score.

Table 3B displays the factors that were significantly associated with antiviral treatment in multivariable analysis among patients with 'equivocal' indication for treatment. Age and Charlson–Deyo comorbidity score were the only factors significantly associated with treatment initiation in this group. Younger patients were less likely to receive treatment than patients 60 years or older (<40 vs. ≥60: aOR = 0.36, 95% CI 0.21–0.62; 40–49 vs. ≥60: aOR = 0.46, 95% CI 0.28–0.75; 50–59 vs. ≥60: aOR = 0.55, 95% CI 0.34–0.88). Patients with fewer comorbidities (Charlson–Deyo comorbidity scores of 0 or 1) were less likely to be treated than those with scores of ≥3 (aOR = 0.26, 95% CI 0.12–0.56 and aOR = 0.32, 95% CI 0.13–0.79, respectively).

## 4 | DISCUSSION

In a large sample of patients with chronic HBV under routine clinical care, we observed low rates of treatment receipt—even among patients with definite indications for antiviral therapy—and variable rates of annual monitoring of HBV disease activity. Treatment was initiated for only 67% of patients classified as having 'definite' indications for antiviral therapy; factors associated with treatment receipt in this group included male sex, age ≥60 vs. <40 years old and access to a specialist. Although rates of recommended ALT and HBV DNA monitoring were high among these patients prior to treatment initiation (77% and 85%, respectively), they declined after treatment was begun (63% and 36%). This decline conflicts with guidelines that recommend at least annual monitoring of serum markers and viral load for patients on treatment.[2,9] Rates of annual ALT and HBV DNA testing among 'definite' patients who did not initiate treatment were even lower (48% and 32%, respectively).

Unsurprisingly, treatment was initiated for only 34% of patients with equivocal indications for antiviral therapy; older age and the presence of multiple comorbid conditions were the only factors significantly associated with receipt of treatment. Monitoring rates were also low for this group. Fewer than half of patients in the equivocal category underwent regular ALT testing, regardless of treatment status. HBV DNA testing rates were somewhat higher among treated patients prior to initiation of therapy (55%), but these rates declined after treatment (29%); likewise, DNA testing was infrequent among 'equivocal' patients who did not receive antiviral treatment (28%).

Interestingly, patients for whom treatment was not indicated (i.e. 'ineligible' category) underwent annual ALT and HBV DNA monitoring at similar rates to untreated patients in both the treatment 'definite' and 'equivocal' indication categories.

Our results are consistent with several analyses, including our own, that have found low rates of adequate ALT and viral DNA monitoring among patients with chronic HBV. Our own previous analysis found that older patients, men, those with Medicare insurance and those under the care of the specialist were more likely to receive regularly testing[3]; unsurprisingly, a number of these factors were also associated with receipt of treatment among patients in this updated analysis. These findings were also consistent with a recent review that categorised barriers to appropriate monitoring among patients with chronic HBV.[12] Although that manuscript encompassed a number of studies that were not methodologically comparable to this analysis, the authors reported a number of patient-level barriers (such as age and sex) and provider-level factors (such as access to specialist care) that are consistent with the factors associated with receipt of treatment among patients in our cohort with definite indication for antiviral therapy. They also reported that lack of patient knowledge regarding the need for frequent testing was common. Our analysis also found low rates of treatment and monitoring among patients whose treatment indication was equivocal; given that older age and the presence of multiple comorbidities were the only significant factors associated with receipt of treatment, it is possible that these patients have more frequent contact with healthcare providers and were more carefully monitored than patients who were younger and had fewer health conditions.

**TABLE 2** Univariate comparisons of characteristics among HBV patients with 'definite' (A) and 'equivocal' (B) indications for antiviral treatment

| | | A | | | B | | |
|---|---|---|---|---|---|---|---|
| **Treatment indication** | | **Definite (N = 1168)** | | | **Equivocal (N = 600)** | | |
| **Treatment status** | | **Untreated** | **Treated** | | **Untreated** | **Treated** | |
| **N** | | **380 (33%)** | **788 (67%)** | | **402 (66%)** | **208 (34%)** | |
| **Variable** | **Response** | | | ***p*-value** | | | ***p*-value** |
| Sex | Female | 185 (49%) | 267 (34%) | <.001 | 203 (50%) | 92 (44%) | .142 |
| | Male | 195 (51%) | 521 (66%) | | 199 (50%) | 116 (56%) | |
| Age category | <40 | 101 (27%) | 109 (14%) | <.001 | 107 (27%) | 34 (16%) | <.001 |
| | 40–<50 | 75 (20%) | 187 (24%) | | 114 (28%) | 43 (21%) | |
| | 50–<60 | 97 (26%) | 207 (26%) | | 105 (26%) | 53 (25%) | |
| | ≥60 | 107 (28%) | 285 (36%) | | 76 (19%) | 78 (38%) | |
| Race | AAPI | 202 (53%) | 489 (62%) | .005 | 262 (65%) | 131 (63%) | .347 |
| | Black | 48 (13%) | 84 (11%) | | 52 (13%) | 37 (18%) | |
| | White | 86 (23%) | 164 (21%) | | 58 (14%) | 29 (14%) | |
| | Unknown | 44 (12%) | 51 (6%) | | 30 (7%) | 11 (5%) | |
| Insurance status | Medicaid | 48 (13%) | 105 (13%) | .047 | 55 (14%) | 24 (12%) | <.001 |
| | Medicare | 88 (23%) | 233 (30%) | | 52 (13%) | 56 (27%) | |
| | Private | 244 (64%) | 450 (57%) | | 295 (73%) | 128 (62%) | |
| Household income | <$30K | 49 (13%) | 72 (9%) | .148 | 39 (10%) | 21 (10%) | .327 |
| | $30–49K | 103 (27%) | 213 (27%) | | 95 (24%) | 61 (29%) | |
| | ≥$50K | 227 (60%) | 494 (63%) | | 261 (66%) | 125 (60%) | |
| BMI | | 26.9 ± 6.1 | 26.7 ± 6.3 | .612 | 27.1 ± 6.1 | 26.7 ± 6.4 | .451 |
| Type 2 diabetes | Yes | 74 (19%) | 199 (25%) | .029 | 64 (16%) | 54 (26%) | .003 |
| | No | 306 (81%) | 589 (75%) | | 336 (84%) | 154 (74%) | |
| Fibrosis-4 | ≤1.21 | 183 (52%) | 322 (42%) | .006 | 270 (74%) | 128 (63%) | .029 |
| | 1.21–5.88 | 135 (38%) | 345 (45%) | | 91 (25%) | 69 (34%) | |
| | >5.88 | 34 (10%) | 100 (13%) | | 6 (2%) | 6 (3%) | |
| Charlson–Deyo comorbidity score | 0 | 300 (79%) | 601 (76%) | .438 | 346 (86%) | 150 (72%) | <.001 |
| | 1 | 40 (11%) | 82 (10%) | | 36 (9%) | 21 (10%) | |
| | 2 | 10 (3%) | 35 (4%) | | 9 (2%) | 13 (6%) | |
| | 3 | 30 (8%) | 70 (9%) | | 11 (3%) | 24 (12%) | |
| Seen by specialist | Yes | 331 (87%) | 761 (97%) | <.001 | 368 (92%) | 199 (96%) | .087 |
| | No | 49 (13%) | 27 (3%) | | 32 (8%) | 9 (4%) | |

There are a number of limitations for this study. Our study used electronic medical record data from four large US health systems; as a result, we do not have patient-reported data that would allow us to explore the impact of patient knowledge or attitudes towards treatment. Our analysis is also confined to patients with at least some contact with the medical system and may not be generalisable to other populations. Second, a large proportion of our original sample—1138 out of 5958 or 22%—were excluded because they could not be classified by treatment eligibility due to lack of available data; we are unable to ascertain whether these patients were receiving monitoring or care through another health system. Furthermore, the guidelines regarding management of patients with chronic HBV are complicated, reflecting the complex natural history of the infection over time and resulting in slightly different recommendations between professional organisations. As a result, our definition of treatment indication was necessarily streamlined to reflect only whether a patient had undergone ALT or HBV DNA testing at least once per year, although some guidelines recommend more frequent assessment during certain periods. Our results should, therefore, be interpreted whether patients have received at least the minimum, versus optimum, frequency of monitoring.

This analysis adds to a growing body of evidence that many chronic HBV patients in the US are receiving suboptimal screening

**TABLE 3** Multivariate logistic regression for receipt of antiviral therapy among HBV patients with 'definite' (A) and 'equivocal' (B) indications for treatment

| | Comparison | | | | Odds ratio | 95% CL | | *p*-value | |
|---|---|---|---|---|---|---|---|---|---|
| A | Sex | Female | vs. | Male | 0.54 | 0.41 | 0.70 | **<.001** | **<.001** |
| | Age | <40 | vs. | ≥60 | 0.46 | 0.31 | 0.67 | **<.001** | **<.001** |
| | | 40 < 50 | vs. | ≥60 | 0.95 | 0.66 | 1.37 | .786 | |
| | | 50 < 60 | vs. | ≥60 | 0.82 | 0.58 | 1.16 | .260 | |
| | Specialist Visit | No | vs. | Yes | 0.20 | 0.12 | 0.34 | **<.001** | **<.001** |
| B | Age | <40 | vs. | ≥60 | 0.36 | 0.21 | 0.62 | **<.001** | **<.001** |
| | | 40 < 50 | vs. | ≥60 | 0.46 | 0.28 | 0.75 | **.002** | |
| | | 50 < 60 | vs. | ≥60 | 0.55 | 0.34 | 0.88 | **.013** | |
| | Charlson-Deyo comorbidity score | 0 | vs. | ≥3 | 0.26 | 0.12 | 0.56 | **<.001** | **.002** |
| | | 1 | vs. | ≥3 | 0.32 | 0.13 | 0.79 | **.014** | |
| | | 2 | vs. | ≥3 | 0.61 | 0.20 | 1.92 | .401 | |

Abbreviation: CL, Wald confidence limit.

and treatment. Consistent with other studies, our data show that access to a specialist roughly doubles the likelihood of a patient who will receive treatment. Increasing specialist referral, therefore, is a natural starting point to improve retention of chronic HBV patients. One intervention successfully increased referral to hepatology by including 'sticky notes' in the electronic medical record. A note indicating that the patient had tested positive for HBV and requesting that they be referred for specialist care was 'pinned' at the top of the patient chart for one month, so it would be seen by any clinician accessing the record during that time. Rates of specialist referral increased from 28% to 78% after the implementation of this simple intervention.[13] Another study found that a seamless, direct electronic referral to hepatology for patients diagnosed with HBV during pregnancy—a point of universal screening in the US—significantly increased and accelerated linkage to care and treatment.[14]

Likewise, the higher rates of follow-up observed under specialist care suggest that provider familiarity with monitoring and treatment guidelines is an important factor in ensuring that patients receive appropriate care. Chronic HBV is a complex and variable disease; guidelines vary not only by stage of illness but between professional bodies and have evolved over time. Direct outreach to primary care providers via in-service training or continuing medical education could increase recognition of the need for regular monitoring and/or referral to hepatology in order to prevent long-term sequelae. For example, a large intervention directed at physicians found that attendance at a single educational lecture increased the proportion of doctors who would refer all HBV-positive patients to specialty care from 37% to 71%.[15]

Many of these interventions were targeted at the time of first positive test and did not address the large number of patients already living with a previous HBV diagnosis. However, especially for patients who are not referred to specialty care or for whom specialty care is inaccessible, primary care physicians may be the only contact a patient has with a health provider. Given the complexity of HBV treatment and monitoring guidelines, we suggest that health systems' leverage populated algorithms within the electronic medical record to identify patients with diagnosis codes related to HBV and generate prompts for recommended testing or treatment, with alerts at appropriate time intervals. Previous interventions have used both provider-level prompts and patient-level reminders; particularly, innovative methods have leveraged e-initiatives like automated text messaging or specialised apps to successfully link patients to follow-up care, with or without a liaison or navigator to facilitate appointment scheduling.[16–18]

Our study provides more evidence that rates of appropriate monitoring and antiviral treatment receipt—even among chronic HBV patients with definite indications for treatment—have stagnated during the last decade, hovering at roughly 50% or lower.[3–7,12] It is likely that efforts to improve these rates will require a multipronged approach, first by increasing provider and patient knowledge of the importance of specialist care and, second, by leveraging technology and the universal implementation of electronic medical record systems to streamline testing reminders and flag patients who require antiviral therapy. Implementation of such measures may be the most effective and efficient way to improve rates of necessary monitoring and treatment to prevent serious long-term sequelae of HBV.

## CONFLICT OF INTEREST

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