Open Forum Infectious Diseases

BRIEF REPORT

Infectious Diseases Society of America
HIV Medicine Association
OXFORD

Time to Initiation of Hepatitis B Treatment is Reduced With the Use of the Xpert HBV Viral Load Kit

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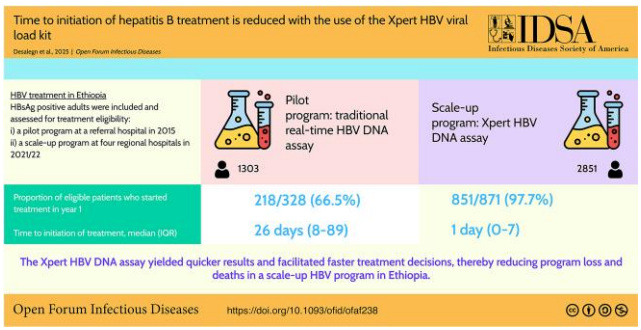
Timely initiation of hepatitis B virus treatment is essential for improving prognosis and outcomes. In Ethiopia, the use of the Xpert hepatitis B virus viral load kit significantly shortened the turnaround time compared to standard laboratory methods. By reducing the time to a treatment decision to 1 day, the Xpert kit allowed for quicker treatment initiation at lower costs, potentially saving lives that might otherwise be lost due to treatment delays.

Graphical Abstract



Received 20 November 2024; editorial decision 15 April 2025; accepted 16 April 2025; published online 18 April 2025

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https://doi.org/10.1093/ofid/ofaf238

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Keywords. antiviral therapy; hepatitis B; point-of-care; resource-limited settings; viral load.

BACKGROUND

In 2022, the World Health Organization (WHO) estimated that 254 million people were living with chronic hepatitis B (CHB), with 65% of cases located in the African and Western Pacific regions. Global studies indicate that 13.4% of individuals with CHB have been diagnosed and 2.6% receive treatment. In Africa, the situation is even more dire: an estimated 4.2% of people living with CHB are diagnosed and merely 0.2% receive treatment [1]. To achieve WHO's elimination targets of 90% testing and 80% treatment coverage, implementation of simplified screening and testing mechanisms will be essential [2].

International treatment guidelines, including the revised WHO 2024 guidelines, recommend measuring hepatitis B virus (HBV) viral load (VL) to determine treatment eligibility for individuals with CHB [3–5]. However, access to HBV VL testing remains severely limited in resource-constrained settings, particularly outside major cities. The lack of low-cost, simple, point-of-care laboratory assays has been identified as a significant barrier to expanding prevention, care, and treatment for people living with CHB in Africa [6].

In Ethiopia, our group set up a pilot CHB treatment program in 2015, using conventional polymerase chain reaction assays to monitor HBV VL. Later, we expanded with a scale-up program at 4 new sites outside the capital city, where the Xpert assay was used to measure HBV VL. In this study, we present a "real-life" comparison of the Xpert assay in the scale-up program and the Abbott assay in the pilot program, evaluating their impact on treatment initiation time and overall operational effectiveness.

METHODS

In 2015, we set up a pilot treatment program for CHB in Addis Ababa, Ethiopia ("the pilot program"), using available private and research laboratory facilities to measure HBV VL with the Abbott RealTi*m*e HBV VL assay (Abbott Molecular, IL, USA) [7]. In 2021 and 2022, we expanded this initiative by establishing a scale-up CHB treatment program at 4 sites outside the capital ("the scale-up program") and used the recently launched Xpert HBV viral load kit from Cepheid to measure HBV viral load (Cepheid, CA, USA) [8].

In both programs, adults (≥18 years of age) who tested positive for hepatitis B surface antigen (HBsAg) were referred from

surrounding blood banks, antenatal clinics, hospital wards, or other clinics/institutions. A confirmatory HBsAg rapid diagnostic test (Determine, Alere Inc., USA) was done at inclusion. Those with HIV or other diseases with a short life expectancy (such as disseminated malignancy) were excluded. The same diagnostic procedures were followed in both programs, except that fibrosis assessment was done with transient elastography (Fibroscan 402, Echosens, France) in the pilot program and with aspartate aminotransferase to platelet ratio index in the scale-up program. All participants consented to be included in the study after receiving information in their native language. The study was approved by the National Research Ethics Review Committee in Ethiopia (3.10/829/07) and the Regional Committees for Research Ethics in Norway (2014/1146).

The treatment eligibility criteria for the pilot program were based on the European Association for the Study of the Liver 2012 guidelines with some modifications as previously described [7]: (1) decompensated cirrhosis, (2) compensated cirrhosis, (3) liver stiffness >7.9 kPa and HBV VL >2000 IU/mL, (4) alanine aminotransferase > 2x upper limit of normal and HBV VL >2000 IU/mL, (5) a history of hepatocellular carcinoma in a first-degree relative and HBV VL >2000 IU/mL. Decompensated cirrhosis was diagnosed based on past or present evidence of ascites, bleeding esophageal varices, hepatic encephalopathy, or jaundice. Compensated cirrhosis was defined as liver stiffness >9.9 kPa.

For the scale-up program, the treatment eligibility criteria were based on data from the pilot program and emerging evidence from the Hepatitis B in Africa collaborative network [9]: (1) decompensated cirrhosis, (2) compensated cirrhosis, (3) alanine aminotransferase > upper limit of normal and HBV VL >2000 IU/mL, and (4) a history of hepatocellular carcinoma in a first-degree relative and HBV VL >2000 IU/mL. Decompensated cirrhosis was defined as described previously, whereas compensated cirrhosis was defined as aspartate aminotransferase to platelet ratio index ≥0.7.

In both programs, treatment for decompensated cirrhosis was initiated immediately. For other cases, treatment decisions were based on laboratory test results.

Time to initiation of treatment was defined as the interval between the date of inclusion and the date of the first provision of antiviral treatment. The Mann-Whitney *U* test was used to compare the median time to treatment initiation between the pilot and scale-up programs.

RESULTS

In the pilot program, 1303 individuals with CHB (40.9% women; median age, 31 years) were enrolled during the first year. Of these, 218 (16.7%) initiated antiviral treatment within the first 12 months of the program. In retrospect, upon reviewing all baseline laboratory results, it was determined that another 110 individuals (8.4%) met the treatment eligibility criteria at inclusion although it was not evident at the time since the HBV VL result was not available. The most common reasons for not starting therapy within the first 12 months of the program among these 110 individuals included awaiting laboratory results (n = 51), and loss to follow-up (n = 21) or death (n = 14; all but 2 were liver-related) while awaiting laboratory results (Figure 1).

In the scale-up program, 2851 individuals with CHB (45.9% women; median age, 30 years) were enrolled in the first year, of whom 851 (29.8%) were treatment eligible and started treatment within the first 12 months of the program. Another 20 individuals (0.7%) did not start treatment within this time frame despite being eligible; the reasons included awaiting laboratory

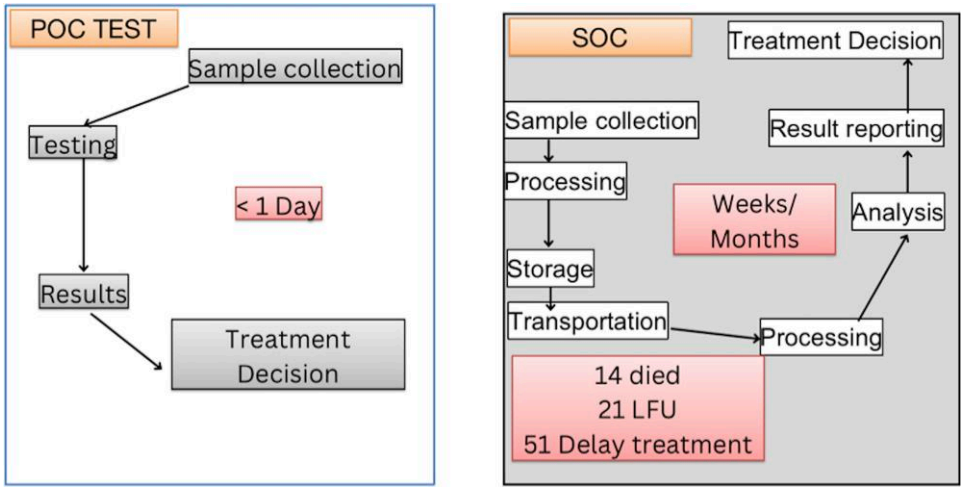

Figure 1. Comparison of turnaround time for point-of-care test versus standard laboratory-based test for treatment decision Abbreviations: LFU, lost to follow-up; POC, point-of-care; SOC, standard of care.

Table 1. Characteristics of Study Participants and Treatment Eligibility in 2 HBV Treatment Programs, Ethiopia

	Pilot Program (N = 1303)	Scale-up Program (N = 2851)
Age (y)	31 (26–40)	30 (25–38)
Women	533 (40.9)	1310 (45.9)
ALT (U/L)	25 (19–37)	26 (17–41)
HBV VL, IU/mL	1285 (242–14,409)	654 (80–6060)
APRI	0.24 (0.17–0.37)	0.29 (0.19–0.50)
Liver stiffness (kPa)	5.9 (4.7–8.1)	N/A
Eligible for treatment the first y	328 (25.2)	871 (30.6)
Started treatment the first y	218 (16.7)	851 (29.8)
Time to treatment initiation (d)	26 (8–89)	1 (0–7)

Data are presented as number (%) or as median (interquartile range) unless otherwise stated.

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; HBV, hepatitis B virus; VL, viral load.

results (n = 10), unwillingness to start treatment (n = 4), death (n = 2), and unknown (n = 4) (Table 1).

The median time to treatment initiation was 26 days (interquartile range 8–89) in the pilot program, compared to 1 day (interquartile range 0–7) in the scale-up program ($P < .001$). The average time from blood collection to receiving an HBV VL result was 1 working day for the Xpert assay. The average cost per HBV VL test was 40 USD with the conventional assay and 15 USD with the Xpert assay.

DISCUSSION

The use of the Xpert HBV VL kit significantly reduced the time to initiation of hepatitis B treatment in a scale-up HBV program at district hospitals in Ethiopia. Notably, the prolonged turnaround time with the use of conventional HBV VL assays led to significant delays in initiating therapy and missed opportunities to prevent HBV-related complications. Indeed, of 328 treatment eligible individuals in the pilot program, 14 (4.3%) died and 21 (6.4%) were lost to follow-up while awaiting laboratory results to determine whether to start treatment or not. In the scale-up program, on the contrary, the use of the Xpert assay allowed HBV VL results to be delivered the same day. This significantly reduced attrition, waiting time, and extra costs related to travel and accommodation, and the vast majority (98%) of eligible individuals started treatment within the first year of the program.

The Xpert HBV VL assay has been validated as a reliable method for quantifying HBV DNA in resource-limited settings. In a study conducted by our own group in Ethiopia, where Genotype A and D predominates, samples from 130 HBV infected individuals with VLs ranging from <1 log10 to >7 log10 IU/mL were analyzed. The Xpert assay showed a strong correlation with the Abbott RealTi*m*e HBV VL assay ($r = 0.948$), and only 4 samples differed by more than 1 log10 IU/mL [10]. Studies from India, France, Kiribati, and the Netherlands have shown similar results [11–14].

A recent systematic review and meta-analysis compared the impact of using point-of-care HBV VL assays on uptake of testing, treatment and turnaround times. This analysis included 6 studies from 5 African countries and found that HBV point-of-care VL testing was associated with high rates of VL testing (84.1%) among HBsAg-positive individuals and high rates of treatment initiation (88.3%) in eligible individuals. The time from blood sample collection to starting treatment ranged from less than 1 day to 8 days across study sites [15]. However, only our study from Ethiopia included a comparison arm with a standard laboratory-based polymerase chain reaction approach.

In our setting, the use of the Xpert kit was cost-saving, priced at only 15 USD, compared to 40 USD for the conventional nucleic acid test. Previous studies have shown that the costs of laboratory testing by far exceed the costs for treatment in HBV programs [16, 17], which is mainly driven by the high costs of viral load testing. Therefore, price reductions of HBV VL assays and kits have a larger impact on program costs than price reductions on antiviral drugs. This is particularly relevant for countries with high HBV prevalence, where funds can be redirected toward population screening and purchasing medications, ultimately enabling the screening and treatment of larger groups of people.

Our study had certain limitations, and it should be noted that the 2 programs had other differences than only the HBV VL assay used. Thus, we cannot exclude that other factors, such as demographics, traditional beliefs, or clinic staff, might have influenced the results. Moreover, the more relaxed treatment criteria in the scale-up program led to a higher proportion eligible for treatment; however, it is unlikely that this impacted the time to treatment initiation which was the focus of the present analysis. The main strength of our study was its "real-life" design with the use of available equipment and resources.

In conclusion, using the Xpert HBV viral load kit significantly shortened the time to initiate hepatitis B treatment at regional hospitals in Ethiopia. In contrast, the longer turnaround times of traditional HBV viral load assays can cause significant delays in starting therapy, resulting in missed opportunities to prevent HBV-related complications and deaths. The Xpert platform is widely distributed in Africa and its use in CHB treatment programs should be encouraged.

Notes

Author contributions. H.D.: Conceptualization, writing—original draft, and writing—review, editing, responsible for submission. N.B.: review, editing, supervision. L.R., F.G., D.B., A.H., W.C.: data acquisition, review, editing. A.J.: conceptualization, writing—original draft, and writing—review, editing, supervision.

Financial support. This study was funded by The Norwegian Research Council, grant number 220622/H10, the South-Eastern Norway Regional Health Authority, grant number 2011068 and 2021064, and the John C

Martin Foundation, grant number 2021-G036. The sponsors had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; nor in the decision to submit the article for publication. A.J. was the recipient of the grants.

Trial registration number. NCT02344498 (ClinicalTrials.gov identifier). Registered 16 January 2015.

Potential conflicts of interest. All authors declare no conflict of interest.

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