



## OPEN Real-world experience with nucleos(t)ide analogue therapy and patient survival rates in chronic viral hepatitis B treatment centers in Eritrea

Michael Berhe Solomon<sup>1</sup>, Ghirmay Ghebrekidan Ghebremeskel<sup>2</sup>✉, Oliver Okoth Achila<sup>3</sup>, Aron Rezene Mebrahtu<sup>4</sup>, Mohammed Elfatih Hamida<sup>5</sup> & Araia Berhane Mesfin<sup>6</sup>

Real-world data on treatment outcomes or the quality of large-scale chronic hepatitis B (CHB) treatment programs in sub-Saharan Africa (SSA) is extremely difficult to obtain. In this study, we aimed to provide data on the prevalence and incidence of mortality, loss to follow-up (LFTU), and their associated factors in patients with CHB in three treatment centres in Eritrea. Additional information includes baseline clinical profiles of CHB patients initiated on nucleos(t)ide analogue (NUCs) along with a comparison of treatment with Tenofovir disoproxil fumarate (TDF) vs. TDF + Lamivudine (LAM) using specific biochemical, haematological and virologic parameters. A multicenter retrospective cohort study was conducted on CHB patients in Asmara, Eritrea (2018–2021). Demographic, clinical, and laboratory information was collected from medical records using a structured checklist. Relevant parametric and nonparametric statistics were employed to explore treatment outcomes and to evaluate differences between groups. Where appropriate, Kaplan-Meier (KM) curves and univariate and multivariate Cox regression models were implemented. A two-sided  $p$ -value  $< 0.05$  was considered significant. A total of 413 patients with HBV (median age (IQR) at diagnosis: 39 (IQR: 28–50 years; females: 118(28.6%); followed for a total of 22,921 person days) were studied. HBV/HIV co-infection was observed in 15(3.6%) and baseline ALT and AST were elevated in 99(31.2%) and 101(32.8%), respectively. The Fibrosis-4 (FIB-4) index estimates suggested that cirrhosis was highly likely in 33 (14%) patients with 49 (20.8%) patients in the indeterminate FIB-4 score category. During the follow-up period, 4.6% (95% CI: 2.5–6.6%) died, while 23.9% (95% CI: 19.8–28%) were LFTU. In the adjusted Cox proportional hazards model, LFTU were independently associated with baseline serum HBV DNA (IU/mL) (aHR = 1.3, 95% CI 1.04–1.7;  $p$ -value = 0.02); Not initiated on NUC (aHR = 3.9, 95% CI: 1.1–13.7,  $p$ -value = 0.02); and FIB-4 Score (aHR = 1.05, 95% CI: 1–1.1;  $p$ -value = 0.01). Of the 413 patients enrolled in the study, 98 cases (23.73%) were initiated on treatment. In the head-to-head comparison of the results in TDF and TDF + LAM after 12 weeks of treatment, VR was observed in 14(45.2%) vs. 17(54.8%), respectively, translating into an overall VR of 60.7% (95% CI 46.9–74.6). Furthermore, VR in TDF vs. TDF + LAM were similar, 14(45.2%) vs. 17(54.4%) respectively,  $p$ -value = 0.3). This study uncovered multiple systems- and patient-centered gaps in the three HBV treatment programs in Asmara, Eritrea. These include late presentation, high incidence of LFTU, inconsistencies in routine data, and poor data management. Interventions should target improvements in laboratory infrastructure, adherence to patient monitoring guidelines, HBV literacy, better tracking of patients, and documentation of patient's information.

**Keywords** Virologic response, TDF, Mortality, Loss to follow-up, Chronic Hepatitis B, Eritrea

<sup>1</sup>National Health Observatory Unit, Ministry of Health, Asmara, Eritrea. <sup>2</sup>General practitioner, Northern Red Sea Ministry of Health branch, Nakfa Hospital, Nakfa, Eritrea. <sup>3</sup>Unit of Clinical Laboratory Science, Orotta College of Medicine and Health Sciences, Asmara, Eritrea. <sup>4</sup>Unit of laboratory, Edaga Hamus Community Hospital, Asmara, Eritrea. <sup>5</sup>Department of Medical Microbiology, Orotta College of Medicine and Health Sciences, Asmara,

Eritrea. <sup>6</sup>Division of National Control of Communicable Diseases, Ministry of Health, Asmara, Eritrea. ✉email: GhirmayGGG@gmail.com

Infection by Hepatitis B virus (HBV) is regarded as a major global public health concern<sup>1</sup>. The According to a Global Burden of Disease (GBD) report published in 2022, prevalence of chronic HBV infection in 2019 stood at 4.1% (95% uncertainty interval [UI] 3.7–4.5%), corresponding to 316 million (UI: 284 million – 351 million) infections<sup>2,3</sup>. More recently, the World Health Organization reports suggested a slightly lower figure for HBV – 254 million. According to the WHO report, the number of patients declined from 3 million in 2019 to 2.2 million in 2022 d<sup>1</sup>. The major complications/sequelae of chronic HBV (CHB) infections - liver cirrhosis and hepatocellular carcinoma (HCC) were associated with [331 000 (UI: 279 000–392 000)] and [192 000 (UI: 162 000–224000)] global deaths respectively<sup>1</sup>. This translates into 48.8% (44.6–52.7%) of all hepatitis-related mortalities worldwide. Importantly, primary epidemiological indices such as incidence, prevalence, mortality, and years of life lost (YLL) are worse in low-middle income countries (LMICs) – particularly in the WHO Western Pacific region and sub-Saharan Africa (SSA)<sup>4</sup>.

Recognizing the problem posed by viral hepatitis, a plenary convened by the World Health Assembly (WHA) in 2016 discussed and adopted the *WHO Global Health Sector Strategy on Viral Hepatitis (WHO-GHSS)* containment and subsequent elimination plan<sup>5</sup>. Key impact goals (with 2015 a baseline) by 2020 and 2030 included a 30% vs. 10% and 95% vs. 65% reduction in incidence rates and HBV-related mortality in respective time frames<sup>5</sup>. Although partial success has been achieved with regard to reduction in CHB, HCC, mortality due to cirrhosis, and other extrahepatic sequelae<sup>6</sup>; no country is on track to meet the 2030 WHO-GHSS targets<sup>7</sup>. Inadequate access to diagnostics, poor awareness of active infection, and inadequate treatment services - a problem compounded by limited access to risk assessment tools such as non-invasive tests for fibrosis (e.g. transient elastography (TE)/Fibroscan©) remains a problem in LMIC in SSA<sup>8</sup>. In 2021, for example, WHO estimates indicated that only 6.6 million (5.3–8.3 million) of the 30.4 million (24.3–38 million) diagnosed with chronic HBV infection were placed on treatment<sup>3,9</sup>.

Even though available treatment options (interferon preparations - standard interferon alfa-2b, peginterferon alfa 2a [peg-alfa 2a]); nucleos (t)ide analogues (NUC) - Tenofovir disoproxil fumarate (TDF); Tenofovir alafenamide fumarate (TAF), Entecavir (ETV); and Lamivudine (3TC), Adefovir dipivoxil (ADF) can stop or slow progression to hard endpoints such as HCC, cirrhosis and end-stage liver disease (ESLD); they are not sterilizing cures<sup>10</sup>. Instead, patients require lifelong suppressive therapy and robust follow-up<sup>11</sup>. In SSA, these prospects are undermined by a spectrum of factors related to patients and the system that present formidable barriers to the sustainability of HBV treatment programs and the long-term health of patients. Late presentation or inadvertent delays in diagnosis are common occurrences in the WHO-AFRO region. Therefore, the probability of progression to fatal complications remains high<sup>11</sup>.

Beyond the above-stated factors, researchers agree that impact targets should be aligned with local epidemiological circumstances, health systems capacity and population structures and dynamics<sup>12</sup>. Interestingly, this requires high-quality data in a variety of HBV-related parameters: vaccination coverage, availability of treatment, patient monitoring, treatment results, mortality, and LFTU, among others. Unfortunately, real-world data on clinical profiles of patients, treatment outcomes, or the quality of care is extremely difficult to obtain in countries in the WHO-AFRO region. In the absence of data on program quality or health-related quality of life (HRQOL), gaps in large-scale government-funded test-and-treat programs are difficult to uncover. Currently, we are unaware of any study that has reported these parameters for HBV patients in Eritrea, a country with an HBV seroprevalence of 2.3%<sup>13,14</sup>. Therefore, we set out to accomplish several goals. First, to provide a comprehensive description of baseline clinical (including fibrosis/or cirrhosis status) and demographic characteristics of patients with HBV infection in three treatment centres in Zoba Maekel - the Central region of Eritrea. Secondly, an analysis of the prevalence and incidence of mortality, LFTU, and their associated factors was attempted. In a subsequent analysis of patients on NUCs; we aimed to provide comprehensive information on the clinical profile of CHB patients initiated on NUCs and compare outcomes of treatment with TDF vs. TDF + LAM using specific biochemical, haematological and virologic parameters.

## Methods

### Study design and settings

This retrospective observational cohort study was conducted on CHB patients enrolled (period: 2016–2021) in three treatment programs in Asmara, Eritrea. The country is located in the upper part of the Horn of Africa and covers a surface area of ~124,000 Km<sup>2</sup>. It is bounded to the North West by Sudan; to the East by the Red Sea; to the South by Ethiopia and the South East by Djibouti. Administratively, the country is divided into six regions (Zobas): Zoba Maekel (Central Region); Anseba; Gash-Barka, Debub; Semanawi Keih Bahri (SKB) (Northern Red Sea); and Debubawi Keih Bahri (DKB) (Southern Red Sea). Healthcare service is delivered, almost exclusively, by the Eritrea Ministry of Health (EMoH). At the time this study was undertaken, treatment for hepatitis B or C patients in the country was undertaken at specific tertiary-level facilities - Orotta National Referral Hospital, Halibet National Referral Hospital and Haz-Haz Zonal Referral Hospital. Therefore, patients are pooled both from the Central Region and other regions of Eritrea. Accordingly, data from these centres can provide vital information on the quality of care for patients with CHB virus infection in Eritrea.

Upon enrollment in the respective follow-up centres, patients are monitored [as per the EMoH Guidelines for Chronic Hepatitis B and C infection (2018)<sup>13</sup>—A document that draws heavily from the WHO<sup>15</sup> at a scheduled interval (3 months). Relevant parameters evaluated at these intervals include liver transaminases [Aspartate aminotransferase (ALT) and Alanine aminotransferase (AST)]; serum HBV-DNA; HBV serology; complete blood count (CBC); ALT/platelet (PLT) ratio (APRI); and Hepatitis B surface antigen (HBsAg). Notably, assessments/tests such as serum bilirubin (BIL); prothrombin time (PT); liver ultrasound, and international

normalized ratio (INR) are performed at the discretion of physician/or clinician and the costs of treatment are covered by the government. Importantly, specific tests such as HBV-DNA, confirmatory tests for HBV infection; and biochemical tests are undertaken at the National Health Laboratory (NHL). The HBV DNA titer is generally evaluated using HBV DNA real-time PCR assay (COBAS<sup>®</sup> AmpliPrep/COBAS<sup>®</sup> TaqMan<sup>®</sup> system (Roche Molecular Systems Inc., Branchburg, NJ, USA).

According to the Eritrea MOH guidelines, treatment should be initiated under the following circumstances: clinical evidence of HBV-related cirrhosis or advanced fibrosis (APRI > 2); age > 30 and persistently elevated ALT (ALT > 2 x ULN); HBV DNA > 20,000 IU / ml<sup>16</sup>. Of note, HBeAg status evaluation is not part of routine care. Antiviral medicines used for the management of HBV infection in adults in these facilities include Tenofovir disoproxil fumarate (TDF) (300 mg/day) and TDF + Lamivudine (LAM) (300 mg/day + 245 mg/day). After initiation of NUC therapy, HBV-DNA titer is quantified on a quarterly basis until an undetectable status is achieved and subsequently every six months.

### Participants

As previously noted, patients enrolled in the three treatment (Orotta National Referral Hospital, Halibet National Referral Hospital and Haz-Haz Zonal Referral Hospital) centres for HBV management are referred from other facilities in the country. In 2019, several patients were referred following screening campaigns among specific subgroups<sup>17</sup>. At enrollment, a file is commissioned for each patient. Variables captured at baseline, or at timed intervals, during follow-up include demographic (Age at enrollment, sex, enrollment year, and address) and clinical (treatment status, NUC regimen; HIV status, HCV antibody status, liver transaminases, HBV-DNA, and enrolment duration) information. Additional variables include outcomes such as LTFU, and death.

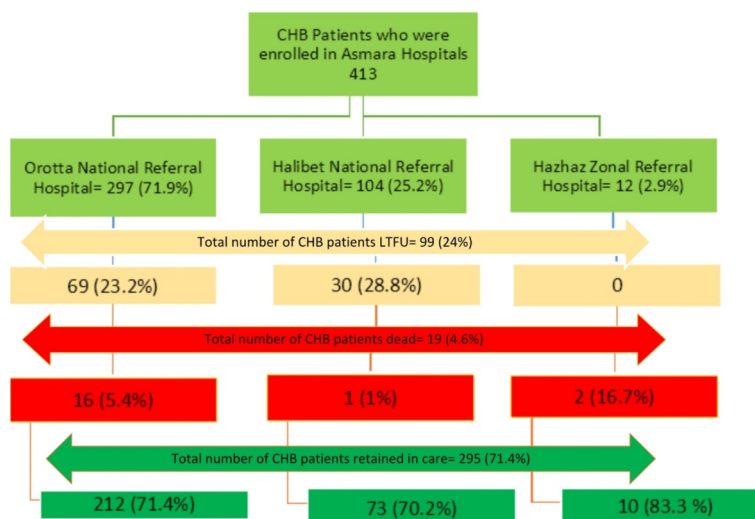
During the study period (2018–2022), a total of 413 were enrolled in these facilities: Orotta National Referral Hospital [279(71.9%)], Halibet National Referral Hospital [104 (25.2%)], and Haz-Haz Zonal Referral Hospital [12 (2.9%)]. See Fig. 1 for additional information.

### Data collection tool

Data was collected via a structured checklist from each patient's medical record. The card contains information on baseline status and information captured periodically during follow-up. Using this checklist, the following information was collected: sex, age at enrollment, address, enrollment year, marital status, treatment status, NUC regimen, HBV-DNA (baseline and follow-up), PLT, ALT, AST, BIL, HIV serostatus and HCV infection status. Follow-up outcomes (death and LTFU) were also collected. To meet specific ethical requirements, all participant data were de-identified.

### Operational definition and study outcomes

- Retention—Chronic HBV-infected patients who were alive and on follow-up in the clinics at the end of the study period.
- The death events were defined as all-cause mortality occurring during the patient's follow-up.
- Loss-to-follow-up (LTFU) was defined as nonattendance of scheduled clinic appointments after enrollment into care.
- The virologic response (VR) was defined as undetectable serum HBV DNA at least 12 weeks after initiation of treatment with NUCs<sup>18</sup>.
- Virologic nonresponse was defined as HBV DNA levels > 1000 IU/ml at least 12 weeks following treatment initiation<sup>13</sup>.



**Fig. 1.** Flow diagram of chronic viral hepatitis B patients followed in three hospitals in Asmara, Eritrea.

- Persistently elevated ALT levels (PNALT): 3 ALT evaluations > 40 U/L made at predefined intervals (12 months).
- Cirrhosis probability was defined using FIB-4 (Non-invasive Fibrosis Evaluation in Hepatitis C) formula  $[(\text{Age (years)} \times \text{AST (U/L)}) / (\text{PLT} (\times 10^9/\text{L}) \times \text{ALT}^{1/2} (\text{U/L}))]$ . Computed scores are grouped as follows: Less likely (< 1.45 points), Indeterminate (1.45–3.25 points), and highly likely (> 3.25 points) [18].
- In addition, the AST level to platelet ratio index (APRI) was also calculated:  $\text{APRI} = [(\text{AST}/\text{upper limit of the normal AST level}) \times 100] / \text{PLT} (\times 10^9/\text{L})$ . Computed scores were classified as follows: Cirrhosis unlikely (> 0.5 points), Cirrhosis possible (0.5–2 points), and Likely cirrhosis (> 2 points) [18].

### Data processing and analysis

Analysis was conducted using IBM SPSS (version 26) and STATA version 12.0 (STATA Corporation, College Station, TX). FIB-4 and APRI scores were computed using relevant formula [18]. Descriptive statistics for categorical variables were analyzed using Chi-square ( $\chi^2$ )/Fisher's exact test and summarized using proportions (percentages). For continuous variables, mean ( $\pm$  standard deviation (SD)) and median (interquartile range (IQR)) were employed. Where appropriate, parametric (t-test) and nonparametric statistics (Mann-Whitney U and Kruskal Wallis) were used to evaluate differences. HBV DNA levels were logarithmically transformed for analysis. Kaplan-Meier (KM) curves were used to estimate survival rates and failure rates at different intervals of follow-up. The Univariate and Multivariate Cox regression model was implemented to assess the variables that predict LTFU. All predictors analyzed in bivariable Cox regression model were included in multivariable analysis. Adjustments were made using conditional: Log Rank (LR) approach. Model assumptions were evaluated using visual assessment of KM curves, log (-log) plots and testing of scaled Schoenfeld residuals. The goodness of fit was assessed using Cox-Snell residual analysis. The final results are presented as an adjusted or unadjusted hazard ratio with a 95% confidence interval (CI). A two-sided p-value < 0.05 was considered significant.

### Ethical consideration

Ethical approval was obtained from the Ministry of Health (MOH) Research Ethics and protocol review committee with a letter of reference (Approval Number: Ref: 01/22). As the study also included data based on patients' clinical cards, informed consent was waived by the Eritrean ministry of health research ethics and protocol review committee. All information gathered was DE identified, and at most confidentiality was upheld. All studies procedures also followed the recommendation of the Declaration of Helsinki Convention.

### Results

A total of 413 patients were enrolled for care from 2016 to 2021 (149 (36.1%) < 2020; 104 (25.2%) = 2020; 160 (38.7%) > 2020). This translated into a total of 22,921 person-days of follow-up (PDFU) and a median duration of follow-up of 279 (IQR: 112–697) days. During this period, 19 (4.6%) died, 99 (24%) were LTFU and 295 (71.4%) were retained in care (Fig. 1).

### Clinical and demographic characteristics of study participants

The median (IQR) age at diagnosis was 39 (IQR: 28–50) years and females accounted for 118 (28.6%) of the patient's population. The majority of the participants were from the Central Zone, 246 (59.6%). HBV/HIV co-infection was observed in 15 (3.6%). At enrollment, the median titer of HBV DNA (IQR), hemoglobin, PLT, ALT and AST were 971 (IQR: 109–288832) IU/mL, 15.3 g/dL (IQR: 14–16.3 g/dL); 216 (154–290)  $\times 10^3$  U/L; 28 IU/L (19–47 IU/L) and 30 IU/L (23–48 IU/L), respectively. Baseline ALT and AST were elevated in 99 (31.2%) and 101 (32.8%), respectively. See Table 1 for additional details.

Characteristics	Population (%)	Retention n (%)	LTFU (%)	Dead (%)	P-value( $\chi^2$ )
Total	413	295 (71.4)	99 (24)	19 (4.6)	
Gender					
Male	295 (71.4)	207 (70.2)	70 (70.7)	18 (94.7)	0.07 (5.3)
Female	118 (28.6)	88 (29.8)	29 (29.3)	1 (5.3)	
Age at enrollment in years, median (IQR)	39 (28–50)	40 (29–50)	33 (24–52)	41 (35–48)	0.14 <sup>a</sup>
<21	22 (5.4)	12 (4.1)	10 (10.1)	0	0.3 (6.7)
21–50	293 (71.3)	213 (72.4)	67 (67.7)	13 (72.2)	
51–60	67 (16.3)	48 (16.3)	15 (15.2)	4 (22.2)	
> 60	29 (7.1)	21 (7.1)	7 (7.1)	1 (5.6)	
Address					
Central Zone	246 (59.6)	179 (60.7)	61 (61.6)	6 (31.6)	0.03 (6.5)
Outside central zone	167 (40.4)	116 (39.3)	38 (38.4)	13 (68.4)	
Enrollment year, median (IQR)		2020 (2019–2021)	2020 (2018–2020)	2020 (2019–2021)	< 0.001 <sup>a</sup>
< 2020	149 (36.1)	73 (24.7)	65 (65.7)	11 (57.9)	< 0.001 (94.7)
2020	104 (25.2)	66 (22.4)	33 (33.3)	5 (26.3)	
> 2020	160 (38.7)	156 (52.9)	1 (1)	3 (15.8)	
Marital status					

Characteristics	Population (%)	Retention n (%)	LTFU (%)	Dead (%)	P-value( $\chi^2$ )
Married	114 (77.6)	96 (76.2)	13 (86.7)	5 (83.3)	0.6 (0.9)
Single	33 (22.4)	30 (23.8)	2 (13.3)	1 (16.7)	
Treatment status					
On treatment	98 (23.7)	72 (24.4)	22 (22.2)	4 (21.1)	0.8 (0.2)
Not on treatment	315 (76.3)	223 (75.6)	77 (77.8)	15 (78.9)	
NAT regimen					
TDF	48 (49)	30 (41.7)	15 (68.2)	3 (75)	<b>0.007 (13.9)</b>
TDF + LAM	47 (48)	40 (55.5)	7 (31.8)	0	
HIV status					
Positive	15 (3.6)	12 (4.1)	2 (2)	1 (5.3)	0.5 (5.9)
Negative	59 (14.3)	49 (16.6)	8 (8.1)	2 (10.5)	
No data entry	339 (82.1)	234 (79.3)	89 (89.9)	16 (84.2)	
HCV antibody status					
Negative	242 (58.6)	176 (59.7)	54 (54.5)	12 (63.2)	0.6 (0.9)
No data entry	171 (41.4)	119 (40.3)	45 (45.5)	7 (36.8)	
FIB-4 score, median (IQR)	0.9 (0.6–1.9)	1 (0.6–1.8)	0.9 (0.5–2.3)	1.6 (0.6–15.7)	0.7 <sup>a</sup>
Less likely (< 1.45)	154 (65.3)	126 (65.3)	25 (67.6)	3 (50)	0.9 (0.7)
Indeterminate (1.45–3.25)	49 (20.8)	40 (20.7)	7 (18.9)	2 (33.3)	
Highly likely (> 3.25)	33 (14)	27 (14)	5 (13.5)	1 (16.7)	
APRI score, median (IQR)	0.3 (0.2–0.7)	0.3 (0.2–0.7)	0.4 (0.2–1.2)	0.3 (0.2–7.5)	0.7 <sup>a</sup>
Unlikely cirrhosis (> 0.5)	155 (63)	129 (64.5)	21 (55.3)	5 (62.5)	0.5 (3.1)
Cirrhosis possible (0.5–2)	65 (26.4)	53 (26.5)	10 (26.3)	2 (25)	
Cirrhosis likely (> 2)	26 (10.6)	18 (9)	7 (18.4)	1 (12.5)	
Initial Viral load log <sub>10</sub> HBV/DNA, median (IQR)	3.1 (2.1–4.5)	3.1 (2.1–4.6)	3.1 (2–4.6)	3.3 (2.3–4.4)	0.9 <sup>a</sup>
Baseline haematology					
Hemoglobin (g/dL), median(IQR)	15.3 (14–16.3)	15.3 (14–16.3)	15.2 (14–16)	15.8 (15–19.7)	0.3 <sup>a</sup>
Platelets ( $\times 10^9/\mu\text{L}$ ), median (IQR)	216 (154–290)	209 (151–305)	221 (141–283)	143 (61–192)	0.1 <sup>a</sup>
Baseline ALT (IU/L), median (IQR)	28 (19–47)	28 (19–44)	32.5 (19.7–65)	36 (18–57)	0.4 <sup>a</sup>
ALT < 20	94 (29.7)	70 (29)	21 (32.3)	3 (27.3)	0.4 (6)
ALT 21–40	124 (39.1)	101 (41.9)	21 (32.3)	2 (18.2)	
ALT 41–80	67 (21.1)	49 (20.3)	14 (21.5)	4 (36.4)	
ALT > 80	32 (10.1)	21 (8.7)	9 (13.8)	2 (18.2)	
Baseline AST (IU/L), median (IQR)	30 (23–48)	29 (23–48)	30.5 (22.7–63.5)	24 (17.5–73.5)	0.8 <sup>a</sup>
AST < 20	49 (15.9)	35 (15.3)	12 (18.5)	2 (14.3)	0.2 (8)
AST 21–40	158 (51.3)	121 (52.8)	29 (44.6)	8 (57.1)	
AST 41–80	64 (20.8)	49 (21.4)	15 (23.1)	0	
AST > 80	37 (12)	24 (10.5)	9 (13.8)	4 (28.6)	
Serum Bilirubin, median (IQR)	1 (0.1–2)	1 (0.1–2)	2 (1–2)	2 (0.1–2)	0.9 <sup>a</sup>
Bil < 1 mg/dL	139 (33.7)	114 (38.6)	20 (20.2)	5 (26.3)	<b>&lt; 0.001 (19.2)</b>
Bil > 1 mg/dL	77 (18.6)	60 (20.3)	14 (14.1)	3 (15.8)	
Missing data	197 (47.7)	121 (41)	65 (65.7)	11 (57.9)	
Duration of follow-up in days, median (IQR)	279 (112–697)	477 (207–859)	40.5 (4.7–384)	11 (6–75)	<b>&lt; 0.001<sup>a</sup></b>
Duration of treatment in days, median (IQR)	348 (100–868)	537(141–1086)	224(0–388)	24(7–41)	<b>&lt; 0.001<sup>a</sup></b>

**Table 1.** Characteristics of study participants stratified by survival outcome. TDF: Tenofovir; LAM: Lamivudine; FTC: Emtricitabine; EFV: Efavirenz; Anti-HCV: Anti-hepatitis C antibody; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; IQR: Interquartile range; SD: Standard deviation; NUCs: Nucleot(s)ide analogue therapy; HBV: Hepatitis B virus; DNA: Deoxyribonucleic acid; HIV: Human Immunodeficiency virus. Bil: Bilirubin. <sup>a</sup> Kruskal–Wallis test. Significant values are in bold.

### Liver fibrosis/or cirrhosis status and its association with specific host factors

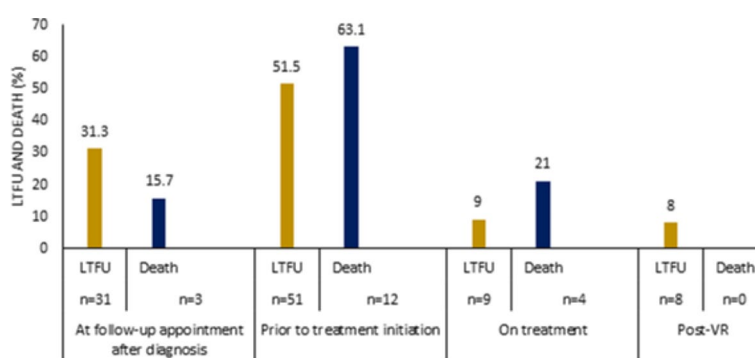
According to estimates of the FIB-4 score, cirrhosis was highly likely in 33 (14%), indeterminate in 154 (65.3%) and less likely in 49 (20.8%) of the patients. Compared to participants with FIB-4 > 3.25 points, participants with FIB-4 < 1.45 points were younger - median (IQR) age of 33 years (IQR: 25–42 years) vs. 48 (IQR: 33–55) years, p-value < 0.001. On the contrary, the median log<sub>10</sub> VL (IQR) baseline was significantly lower in participants with FIB-4 < 1.45 (FIB-4 < 1.45: 3.1 IU/mL (2.1–4.3 IU/mL) vs. FIB-4 > 3.25: 5.6 IU/mL (4.3–6.5 IU/mL),

Characteristics	Cirrhosis less likely	Indeterminate	Cirrhosis highly likely	P-value
Female n (%)	42 (72.4)	9 (15.5)	25 (12.1)	0.41
Age in years, median (IQR)	33 (25–42)	48 (33–55)	48 (42–60)	<0.001a
Baseline AST (IU/L), median (IQR)	27 (21–33)	45 (24–80)	86 (65–167)	<0.001a
Baseline ALT (IU/L), median (IQR)	24 (18–36)	35 (22–77)	67 (50–112)	<0.001a
PLT ( $\times 10^9/\mu\text{L}$ ) count, mean ( $\pm$ SD)	264 ( $\pm$ 84)	172 ( $\pm$ 57)	82 ( $\pm$ 35)	<0.0001b
Baseline Log <sub>10</sub> VL (IU/mL), median (IQR)	3.1 (2.1–4.3)	2.6 (2.1–5)	5.6 (4.3–6.5)	<0.001a
HGB (g/dL), median (IQR)	15.8 (14.9–16.7)	15 (13.1–16.2)	15 (13.1–15.4)	0.021a
NUCs, TDF (%)	9(34.6)	7(26.9)	10(38.5)	0.935
NUCs, TDF + LAM (%)	9(31)	9(31)	11(37.9)	

**Table 2.** Characteristics of the patients and stages of the Fib-4 score among the study participants.

Abbreviations: AST: aspartate aminotransferase; ALT: Alanine aminotransferase; IQR: interquartile range; PLT: platelet count; HGB: Hemoglobin; TDF: Tenofovir; LAM: Lamivudine. NUCs: Nucleotide analogue therapy.

<sup>a</sup>One-way ANOVA, <sup>b</sup> Kruskal-Wallis test. Significant values are in bold.



**Fig. 2.** LTFU and death in chronic HBV care cascade.

p-value < 0.001). No significant differences were observed across sex and treatment regimen (See Table 2 for additional details).

### Loss to follow-up and Mortality in the HBV care cascade

In this study, the reported mortality and LTFU in the clinic were 19 cases, 4.6% (95% CI 2.5–6.6) and 67 cases (23.9%, 95% CI: 19.8–28.1), respectively. Figure 2 shows the distribution of LTFU and deaths along the HBV cascade of care. LTFU and death at the follow-up appointment after diagnosis, 31 (33.3%) and 3 (15.7%); before the initiation of treatment 51 (51.5%) and 12(63.1%); on treatment with NUC, 9 (9%) and 4(21%); and post VR, 8(8%) and 0 (0%).

### Incidence rates, rate ratio, and Kaplan-Meier survival estimates for mortality

After 22, 921 (PDFU), the incidence rate of death was 0.82 (95% CI 0.52–1.3) per 1000 PDFU. In Kaplan-Meier survival analysis, male patients had a shorter mean survival duration (2,499 days (95% CI: 2452–2545) vs. 4667 days (95% CI: 4436–4897) and a higher relative risk (RR) of death, 7.3 (95% CI: 0.9–54.9) p-value log-rank 0.02) when compared to females. Further, a significantly shorter mean survival duration was observed in patient outside Central Zone (4461 days (95% CI: 4095–4826) and 4996 days (95% CI: 4885–5107), log-rank test  $p = 0.01$ ) respectively. See Table 3 for additional details.

### Incidence rates, rate ratio, and Kaplan-Meier survival estimates for LTFU

Table 4 displays Kaplan-Meier survival estimates. LTFU occurred in 99 patients, translating into a prevalence and incidence of 23.9% (95% CI 19.8–28.1) and 4.3 (95% CI: 3.5–5.2) per 1000 PDFU, respectively. In the Kaplan-Meier analysis of the relationship between the enrollment year and LTFU; the survival durations were as follows:  $\leq 2019 = 2629$  days (95% CI: 2151–3107); 2020 = 528 days (95% CI: 463–593); and 2021 = 369 days (95% CI: 365–374), log-rank test  $p < 0.001$  (Fig. 3b). Similarly, patients not initiated on NUCs had shorter mean survival duration than those on treatment with NUCs, 2740 days (95% CI: 2039–3440) vs. 3217 days (95% CI: 2502–3932), log-rank test  $p < 0.07$  (Fig. 3c).

Cohort characteristics	Person time (days)	death Events	Incidence of death per 1000 PDs (95% CI)	Relative risk rates (95% CI)	Mean duration of survival duration in days, 95% CI	P-value (log-rank)
Population	229211	19	0.8 (0.5–1.3)			-
Gender						
Female	57523	1	0.1 (0.02–1.2)	1	4667 (4436–4897)	0.02 (5.1)
Male	171688	18	1.04 (0.06–1.6)	7.3 (0.9–54.9)	2499 (2452–2545)	
Address						
Central zone	134618	6	0.4 (0.02–0.9)	1	4996 (4885–5107)	0.01
Outside central zone	94593	13	1.3 (0.7–2.3)	3 (1–9.8)	4461 (4095–4826)	
Enrollment year						
≤ 2019	161313	11	0.6 (0.03–1.2)	1	4686 (4430–4942)	0.2 (2.6)
2020	39657	5	1.2 (0.05–3.02)	0.8 (0.3–2.5)	715 (679–751)	
≥ 2021	28241	3	1.06 (0.03–3.2)	0.3 (0.09–1.3)	365 (357–372)	
Treatment status						
Under treatment	84194	4	0.4 (0.1–1.2)	1	4892 (4682–5103)	0.4 (0.4)
Not under treatment	145017	15	1.03 (0.6–1.7)	2.1 (0.6–9)	4699 (4446–4952)	
AST						
≤ 40 U/L	118503	10	0.8 (0.4–1.5)	1	4717 (4436–4997)	0.7 (0.1)
> 40 U/L	70493	4	0.5 (0.2–1.5)	0.6 (0.1–2.3)	4862 (4622–5103)	
ALT						
≤ 40 U/L	130614	5	0.3 (0.1–0.9)	1	4954 (4778–5129)	0.09 (2.8)
> 40 U/L	63119	6	0.9 (0.4–2.1)	2.4 (0.6–10.2)	4752 (4472–5032)	
Non-invasive Fibrosis Evaluation in Hepatitis B (FIB-4)						
Less likely (< 1.45)	98142	3	0.3 (0.009–0.9)	1	4697 (4507–4887)	0.7 (0.5)
Indeterminate (1.45–3.25)	41303	2	0.4 (0.01–1.9)	1.9 (0.3–11.7)	4907 (4595–5218)	
Highly likely (> 3.25)	22027	1	0.4 (0.006–3.2)	1.4 (0.1–14.1)	4938 (4605–5272)	
Aspartate aminotransferase to platelet ratio index (APRI score)						
Unlikely cirrhosis (> 0.5)	88683	5	0.5 (0.02–1.3)	1	4894 (4659–5129)	0.9 (0.08)
Cirrhosis possible (0.5–2)	56964	2	0.3 (0.008–1.4)	0.8 (0.1–4.4)	4673 (4433–4914)	
Cirrhosis likely (> 2)	18597	1	0.5 (0.007–3.8)	1.2 (0.1–10.4)	4860 (4381–5340)	

**Table 3.** Incidence rate and Kaplan-Meier survival estimates for mortality among chronic hepatitis B patients in Eritrea. AST: aspartate aminotransferase; ALT: Alanine aminotransferase; CI: confidence interval; PDs: Person days of follow-up.

### Univariate and multivariate analysis of independent predictors of LTFU in patients with CHB infections

In the adjusted Cox proportional hazards model, LTFU was independently associated with baseline serum HBV DNA (IU / ml) (aHR = 1.3, 95% CI: 1.04–1.7; p-value = 0.02); Not initiated in NUC (aHR = 3.9, 95% CI: 1.1–13.7, p-value = 0.02); and FIB-4 score (aHR = 1.05, 95% CI: 1–1.1; p-value = 0.01). See Table 5 for more details.

### Clinical profile of CHB patients initiated on NUCS therapy

Of the 413 patients enrolled in the study, 98 cases (23.73%) were initiated on treatment. The median duration of treatment was 346 (IQR: 183–526) days. Reason for initiation of treatment included the following: APRI > 2, 18 (18.3%); HIV/HBV coinfection, 13 (13.2%); age > 30 and Persistently elevated ALT and HBV DNA > 20,000, 2 (2.1%); Persistently elevated ALT, 9 (19.3%); HBV DNA > 20,000 after 6 months of monitoring, 23 (23.4%) and clinically apparent presence of cirrhosis, 12 (12.2%). Furthermore, the patients in NUC (TDF and TDF + LAM) were significantly older (41 years (IQR: 24–53) and 40 years (IQR: 31–60) years vs. 39 years (IQR 27–48 years),  $p = 0.028$ ); had a higher viral load (5.9 IU/mL (4.7–7) IU/mL and 6.4 IU/mL (4.5–7.3) IU/mL vs. 2.7 IU/mL (2–3.8) IU/mL; baseline ALT (49 IU / L (32 – 28) IU / L and 75 IU/L (47–145) vs. 23 IU/L<sup>17–35</sup> IU/L). Furthermore, 18 CHB patients who were eligible for treatment were not on treatment [6 patients had APRI > 2, 6 cases had persistently elevated viral load and 6 more patients had persistently elevated ALT]. See Table 6 for additional details.

### The Impact of NUCs on selected laboratory parameters

In this analysis, both the TDF and TDF + LAM NA regimens resulted in a statistically significant improvement in laboratory parameters. ALT, AST, FIB-4, APRI, and platelet count decreased after treatment (Fig. 4).

Cohort characteristics	Person time (days)	LTFU events	Incidence of LTFU per 1000 PDs (95% CI)	Relative risk rates (95% CI)	Mean duration of survival duration in days, 95% CI	P-value (log-rank)
Population	229211	99	4.3 (3.5–5.2)			-
Gender						
Male	171688	70	4.07 (3.2–5.1)	1	2966 (2460–3472)	0.6 (0.1)
Female	57523	29	5.04 (3.5–7.2)	1.2 (0.7–1.9)	1667 (1392–1942)	
Address						
Central zone	134618	61	4.5 (3.5–5.8)	1	3164 (2631–3697)	0.7 (0.1)
Outside central zone	94593	38	4.01 (2.9–5.5)	0.8 (0.5–1.3)	2896 (2273–3520)	
Enrollment year						
≤ 2019	161313	65	4.02 (3.1–5.1)	1	2629 (2151–3107)	< 0.001 (35.8)
2020	39657	33	8.3 (5.9–11.7)	1.5 (0.6–1.6)	528 (463–593)	
≥ 2021	28241	1	0.3 (0.04–2.5)	0.02 (0.004–0.1)	369 (365–374)	
Treatment status						
Under treatment	84194	22	2.6 (1.7–3.9)	1	3217 (2502–3932)	0.07 (3)
Not under treatment	145017	77	5.3 (4.2–6.6)	2 (1.2–3.4)	2740 (2039–3440)	
AST						
≤ 40 U/L	118503	41	3.4 (2.5–4.6)	1	2952 (2175–3729)	0.6 (0.2)
> 40 U/L	70493	24	3.4 (2.2–5.07)	0.9 (0.5–1.6)	3352 (2729–3975)	
ALT						
≤ 40 U/L	130614	42	3.2 (2.3–4.3)	1	3143 (2450–3836)	0.4 (0.5)
> 40 U/L	63119	23	3.6 (2.4–5.4)	1.1 (0.6–1.9)	3310 (2640–3980)	
Non-invasive Fibrosis Evaluation in Hepatitis C (FIB-4)						
Less likely (< 1.45)	98142	25	2.5 (1.7–3.7)	1	3592 (3027–4156)	0.8 (0.2)
Indeterminate (1.45–3.25)	41303	7	1.6 (0.8–3.5)	0.7 (0.3–1.8)	3995 (3103–4888)	
Highly likely (> 3.25)	22027	5	2.2 (0.9–5.4)	0.9 (0.3–2.4)	3879 (2890–4868)	
Aspartate aminotransferase to platelet ratio index (APRI score)						
Unlikely cirrhosis (> 0.5)	88683	21	2.3 (1.5–36.3)	1	3844 (3068–4620)	0.2 (2.7)
Cirrhosis possible (0.5–2)	56964	10	1.7(9.4–32.6)	0.9 (0.4–2)	3746 (3069–4423)	
Cirrhosis likely (> 2)	18597	7	3.7 (17.9–78.9)	1.9 (0.8–4.5)	3175 (1961–4388)	

**Table 4.** Incidence rates, rate ratio and Kaplan-Meier survival estimates for LTFU. AST: aspartate aminotransferase; ALT: Alanine aminotransferase; CI: confidence interval; PDs: Person days of follow-up.

### Survival function of virologic response (VR) in patients initiated on TDF monotherapy and TDF + LM regimen

In this analysis, 98 cases were followed for 26858 PD of treatment with NUCs. VR was observed in 31 cases, translating to an incidence rate of 11.5 (95% CI: 8.1–16.1) per 1000 PDs of treatment. Further, patients on TDF monotherapy had significantly shorter median survival duration as compared to those initiated on TDF + LM regimen, 874 (95% CI: 844–903) days vs. 330 (95% CI: 254–405) days, log-rank p-value = 0.05. See Fig. 5.

### Availability of viral load testing kits over time and its impact on treatment initiation

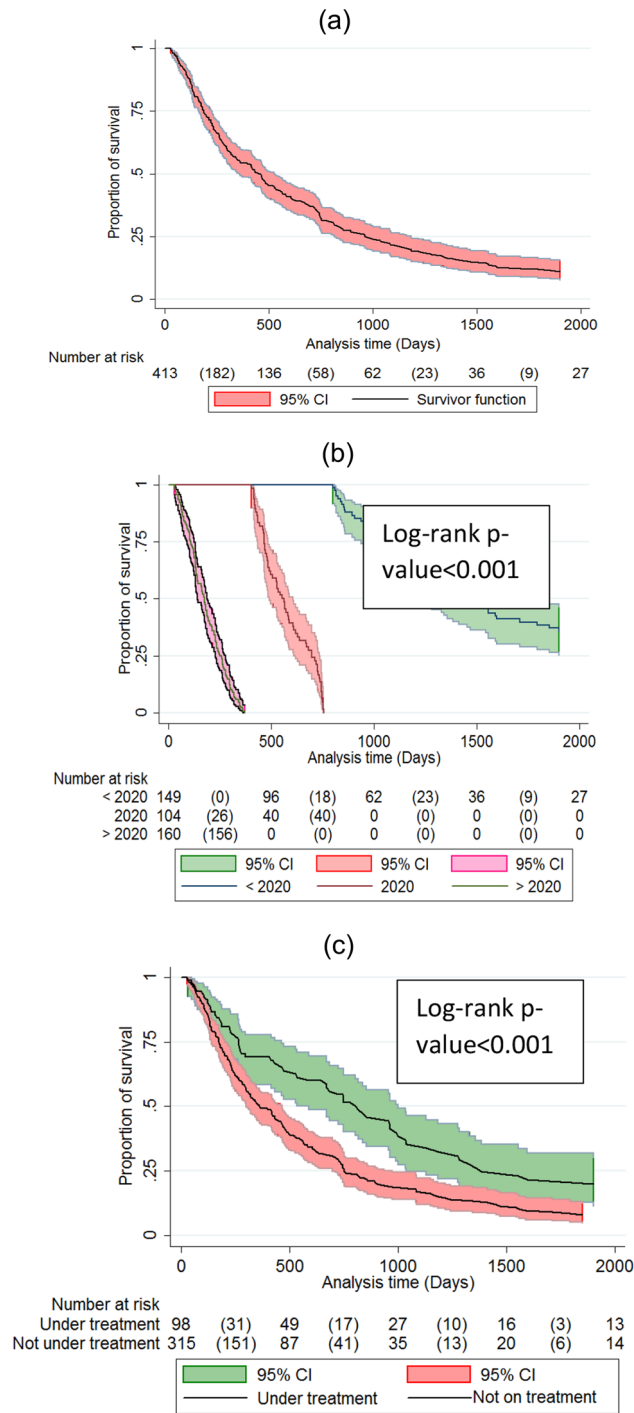
A strong time-dependent relationship was observed between the VL testing performed and VR and virologic nonresponse detection. We also found a potential connection between the availability of VL data and treatment initiation. See Figure Fig. 6 for more details.

### Discussion

In response to the WHO-GHSS position that the elimination of HBV (in the long-term) will largely be determined by progress in achieving the HBV vaccination targets, early diagnosis, appropriate linkage to care, and subsequent retention in care<sup>19</sup>; Eritrea's government established a government-funded test and treatment program for patients in 2018. Key study findings included the fact that the median (IQR) age at diagnosis in this cohort was 39 years (IQR: 28–50) years with a significantly lower proportion of females, 118(28.6%). Additional observations included a preponderance of patients from Central Zone. In contrast, LTFU was higher in patients in the central zone, while death rates were higher in patients outside the Central Zone. Other notable descriptors of the patients enrolled in the program include the high male-to-female ratio (2.5:1), the large number of patients from the central region, and the high number of patients with the APRI score [ $> 0.5 - 2$  points 2 or  $> 2$  or cirrhosis likely].

In general, a number of these observations are not unique to this setting. For example, the observed preponderance of younger individuals infected with HBV (28–50 years) has been observed in several LMICs: 43 years (IQR 34–48 years) in Gambia<sup>20</sup>; and 41.1 ( $\pm 21.05$ ) years in Iran<sup>21</sup>. Remarkably, a higher median or





**Fig. 3.** Kaplan-Meier curves for cumulative survival of chronic HBV patients followed in the three main treatment centres in Eritrea from 2018 to 2021. (a): overall cumulative proportion of survival; (b): overall cumulative proportion of survival by enrollment year; (c) cumulative proportion of survival by treatment status.

mean age has been observed in treatment centres in some high-income countries (HICs) – 56 years (45–64 years) in Calgary, Canada<sup>22</sup>; and 55 years in Hong Kong<sup>23</sup>. A number of explanations can be invoked to explain the observed age disparity: mode of exposure, age at exposure, and access to diagnostic infrastructure, among others<sup>24</sup>. However, a prominent claim is that improvements in vaccine-induced immunity in the age range of 20–49 years in HIC may be responsible for the observed shift in median age<sup>24</sup>.

Although the lopsided male-to-female ratio appears to suggest differential exposure to HBV; the disparity is not fully understood. In Eritrea, context matters. First, mass testing of HBV or HCV has not been implemented in Eritrea. The nearest thing to mass testing of HBV in the country is the testing of blood donors. For a variety

Characteristics	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Gender				
Male	1 (Ref)	0.6		
Female	1.09 (0.7–1.6)			
Age at enrollment	0.98 (0.97–1)	0.1		
Address				
Central zone	1 (Ref)	0.7		
Outside central zone	0.92 (0.6–1.3)			
Enrollment year	1.05 (0.9–1.1)	0.2		
Baseline serum HBV DNA	0.96 (0.8–1)	0.5	1.3 (1.04–1.7)	<b>0.02</b>
Treatment status				
Under NAT	1 (Ref)	0.08	1 (Ref)	<b>0.02</b>
Not initiated on NAT	1.5 (0.9–2.4)		3.9 (1.1–13.7)	
Baseline ALT		0.9		
≤ 40 U/L	1 (Ref)			
> 40 U/L	1.2 (0.7–2)	0.4		
Baseline AST				
≤ 40 U/L	1 (Ref)	0.6		
> 40 U/L	1.1 (0.6–1.8)			
FIB score	1.02 (0.9–1.07)	0.2	1.05 (1–1.1)	<b>0.01</b>

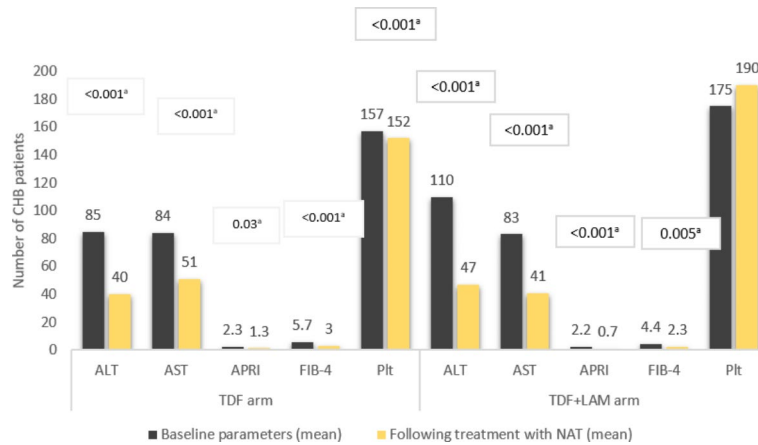
**Table 5.** Cox proportional hazards of LTFU among chronic hepatitis B patients followed in the three treatment centres in Eritrea (2016–2021). Abbreviations: ALT: alanine aminotransferase; AST: Aspartate Aminotransferase; CI: confidence interval; NAT: Nucleot(s)ide analogue therapy; HR: Hazards rate.

Variables	TDF	TDF + LAM	Not Initiated on NUCs	p-value
Age at enrollment in years, median (IQR)	41 (24–53)	40 (31–60)	39 (27–48)	0.028 <sup>a</sup>
Initial viral load (IU/mL), median (IQR)	5.9 (4.7–7)	6.4 (4.5–7.3)	2.7 (2–3.8)	< 0.001 <sup>a</sup>
Baseline AST (IU/L), median (IQR)	62 (43–135)	65 (48–158)	26 (21–34)	< 0.001 <sup>a</sup>
Baseline ALT (IU/L), median (IQR)	49 (32–78)	75 (47–145)	23 (18–36)	< 0.001 <sup>a</sup>
Baseline Platelet count ( $\times 10^9/\mu\text{L}$ ), median (IQR)	118 (76–202)	147 (76–187)	221 (161–313)	< 0.001 <sup>a</sup>
Baseline Hgb (g/dL), median (IQR)	14.8 (13–15)	15.4 (14–16.3)	15.7 (14.9–16.5)	0.46 <sup>a</sup>
Baseline Bilirubin (mg/dL), median (IQR)	1.2 (0.6–1.7)	1 (0.8–1.4)	0.7 (0.5–0.9)	< 0.001 <sup>a</sup>
FIB-4 score, median (IQR)	2.3 (1.1–10.3)	1.8 (1.2–5.5)	0.8 (0.6–1.2)	< 0.001 <sup>a</sup>
APRI score, median (IQR)	1.5 (0.7–5.3)	1.3 (0.5–2.2)	0.2 (0.2–0.4)	< 0.001 <sup>a</sup>
Duration of follow-up (years), median (IQR)	346 (71–880)	991 (421–2361)	433 (163–748)	< 0.001 <sup>a</sup>

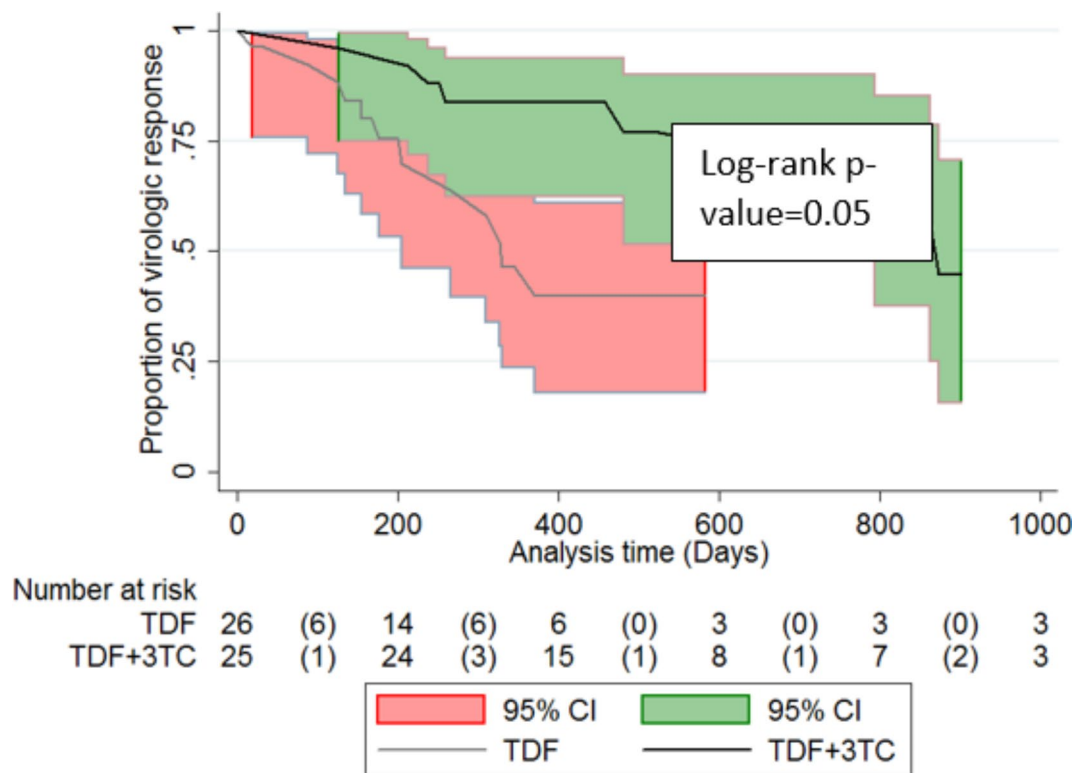
**Table 6.** Clinical profile of CHB patients on NUCs. Abbreviations: AST: aspartate aminotransferase; ALT: Alanine aminotransferase; IQR: interquartile range; PLT: platelet count; HGB: Hemoglobin; NAT: Nucleot(s)ide analogue. <sup>a</sup> Kruskal-Wallis test.

of reasons, blood donation was dominated by males (88.2%) in a study Gash-Barka<sup>25</sup>. In a subsequent within-sex analysis, the same study found a female vs. male HBV prevalence of 4.82% and 5.02%, respectively<sup>25</sup>. Aside from the higher likelihood of testing in males, the literature suggests that chronicity is likelier in males (male to female ratio 1.1:1 to 3:1) and natural progression of HBV to more severe complications (advanced fibrosis, cirrhosis, or symptomatic advanced stage HCC, and ESLD) is also faster<sup>26</sup>. Therefore, HBV-related morbidity and/or likelihood of hospitalization is higher in males. This possibility translates into higher hospitalization rates in higher-tier healthcare facilities located in the Central Region.

Another key finding was the significant number of mortality, 19 (4.6%) patients. A disproportional number of deaths occurred before treatment initiation - in the early period following program implementation (2019); and within a relatively short period of time after linkage to care, a median of 11 days (IQR: 6–75 days). Furthermore, most of the cases involved male patients and those with residences outside of the Central Region. There are many potential explanations for the observed outcome. First, the high death rate and (as we will highlight later) the high number of patients with liver cirrhosis highlights a late presentation problem. The higher death rate in the early period (< 2019) potentially reflects the cumulative effect of lack of treatment - note that the treatment program was initiated in 2018. Indeed, some reports suggest that lack of NUC treatment can increase the risk of death (weighted HR 3.05; 95% CI 2.70–3.44;  $p < 0.001$ ) in some patients<sup>27</sup>. The subsequent decline in death in our cohort potentially reflects the positive impact of treatment and monitoring in subsequent years.



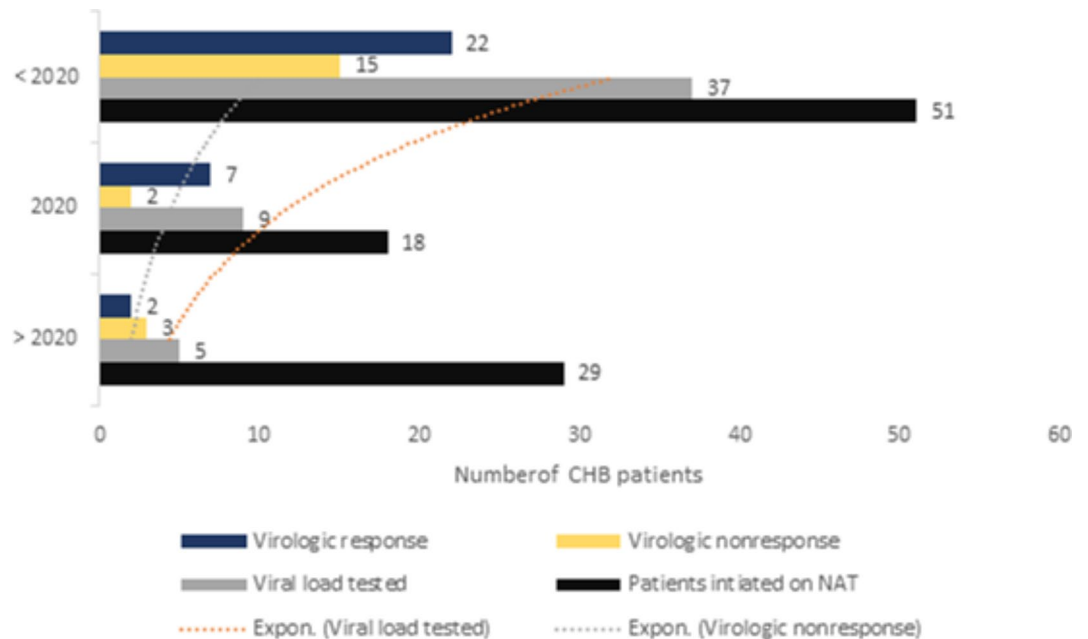
**Fig. 4.** Alterations in laboratory parameters in response to NA therapy among chronic Hepatitis B infected individuals in Eritrea. Abbreviations: AST: Aspartate aminotransferase; ALT: Alanine aminotransferase. IQR: interquartile range; VL: Viral load.<sup>a</sup> Paired samples t-test p-value



**Fig. 5.** Kaplan-Meier curves for cumulative survival stratified by NUCs regimen.

In many ways, these results are comparable to findings from the region. In a study conducted in Ethiopia, Desalegn et al. (2019) reported a slightly lower mortality rate of 2.68% over a two-year follow-up duration. The median duration (IQR) from initiation of treatment to death in this cohort was 110 days (IQR: 26–276) and most deaths were attributed to decompensated cirrhosis. The excess mortality in males is another recurring feature in HBV literature<sup>28</sup>. In a study conducted in Ethiopia, the likelihood of advanced liver disease (ALD) was higher in men<sup>28</sup>. These outcomes, experts agree; are largely driven by the asymptomatic nature of HBV - only presenting when advanced-stage sequelae emerge<sup>29</sup>. Importantly, the higher likelihood of ALD in males is potentially linked to differential exposure to hepatotoxins (hazardous alcohol consumption, aflatoxins (a toxin from *Aspergillus flavus* and *Aspergillus parasiticus* in locally brewed alcoholic drinks, and tobacco use, among others) or other high-risk behaviour<sup>24</sup>.

Data showing a higher probability of death in patients residing outside the Central Region are probably related to regional health disparities in access to advanced care. In other words, the underdiagnosis arising from



**Fig. 6.** Relationship among viral load testing and virologic nonresponse detection.

limited healthcare access, lack of screening, and inadequate links to care in other administrative zones means that most patients seeking care in higher-tier facilities located in the central region will have fairly advanced diseases. The rural-urban disparity in access to health facilities is a well-documented problem in Africa<sup>11</sup>. Indeed, attempts at decentralization of services are often undermined by multiple structural problems: lack of hepatologists, problems with logistics, imaging equipment, distance facilities, and diagnostics. Interestingly, HBV care was decentralized in Eritrea in 2020; even then, we presume that the quality of care in facilities outside the Central Zone is encumbered by similar challenges. Ultimately, the unavoidable conclusion is that access to diagnosis and prompt linkage to care should be expanded in administrative zones outside the Central Region.

According to the treatment guidelines of the Asian Pacific Association for the Study of the Liver (APASL)<sup>30</sup>, European Association for the Study of the Liver (EASL)<sup>31</sup>, and the American Association for the Study of Liver Diseases (AASLD)<sup>16</sup>; A typical workup for treatment include several serological and biochemical assays [HBsAg, HBsAb, Hepatitis core antibody (HBcAb), hepatitis Be antigen (HBeAg), hepatitis Be antibody (HBeAb)]; HBV DNA PCR; liver function tests, CBC;  $\alpha$ -fetoprotein (AFP), and imaging (transient elastography (TE) [Fibroscan [Echosens, Paris, France]]<sup>30</sup>. Although liver biopsy has been described as a useful clinical tool by major international liver societies<sup>11,31</sup>; it is rarely utilized in clinics across the WHO-AFRO region<sup>32</sup>. In our cohort, no patient underwent the procedure. Furthermore, a significant fraction of the required tests were unavailable - HBeAg, HBeAb, and TE. As such, evaluation of HBeAg positivity (+ve) or negativity (-ve) is not part of routine care in Eritrea. However, it is our presumption, based on a previous study in Eritrea; that most of the patients were HBeAg (-ve); Mohammed and colleagues reported that up to 93% of the patients in some of these clinics are HBeAg -ve<sup>33</sup>. Although HBsAg assays are widely available for use in the diagnosis of HBV in the country, their use in the assessment of treatment response was not evident in this cohort. Additional omissions included renal function test for patients on long-term TDF or TDF + LAM, AFP for assessment of HCC, poor documentation of patient history or details of physical examination - alcohol intake, family history of HCC, splenomegaly, and assessment of possible superinfection with other hepatitis viruses (HDV, HCV and/or HIV)<sup>11,30</sup>. Beyond these omissions, the lack of tests such as HBe-related assays and TE, two mainstays in treatment algorithms; meant that assessment of baseline disease activity (e.g., phase), and the risk of potentially fatal complications such as HCC or cirrhosis was inadequate. These observations, it must be emphasized; highlight the impact that the high cost of diagnostics and inadequate laboratory infrastructure is having on the treatment of CHB patients in the region.

Separately, we assessed that 98 (23.7%) of the patients in this cohort were in NUC (TDF, TDF + LAM). The preferred regimen was TDF, an oral phosphonoamidate prodrug. However, TDF + LAM, a regimen reserved for patients with HBV/HIV coinfection, was administered to a significant proportion of patients. On the whole, the proportion of patients on treatment was much lower than what has been reported in cohorts in HICs - 62% in the USA<sup>34</sup>. Predominant reasons for treatment initiation included cirrhosis (APRI > 2, 18 (18.3%) and HBV DNA > 20,000 after 6 months of monitoring, 23 (23.4%). In this regard, our data support the assertion that liver cirrhosis is the predominant reason for the initiation of treatment in SSA. At a pooled prevalence of 6.4% (95% CI 4.1-9.9,  $I^2 = 87\%$ ), a recent meta-analytical report suggested that Cirrhosis is the most important driver of HBV-related morbidity and mortality in SSA<sup>34,35</sup>.

Although HBV-associated liver cirrhosis is considered one of the most important drivers of initiation and mortality in the WHO-AFRO region; underdiagnosis remains a problem. According to some estimates,

only 10–15% of persons with liver cirrhosis in SSA are detected for linkage to appropriate treatment<sup>36,37</sup>. Recommended approaches for non-invasive diagnosis of cirrhosis such as APRI score and FIB-4 have not been validated for patients in the region. At present, experts agree that the APRI score cutoff of 2 that is used in the region underestimates advanced fibrosis<sup>38</sup>. In a study conducted in Gambia, 25% sensitivity was reported for an APRI cut-off of > 2 and an area under the receiver operating characteristic curve (AUROC) of 0.70 (CI 0.55–0.86)<sup>39</sup>. Similarly, a study in Ghana demonstrated a sensitivity of 45.4% when the cut-off was > 2. In these reports, the authors noted a significant increase in sensitivity when a cut-off of > 1 was used<sup>40</sup>. Highlighting this problem, they asserted that the current APRI threshold (> 2) is too high and should be revised to lower the cutoff with rule-in and rule-out criteria to improve the diagnosis of significant fibrosis (METAVIR score F2/F3), and possibly, METAVIR score F4<sup>40</sup>. Further corroborations of these assertions have been demonstrated by investigators who have shown that at an APRI score of > 1.0 (low cut-off); the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the diagnosis of METAVIR F4 grade cirrhosis were 71–84%, 50–69%, 52–61% and 76–84% respectively and that the corresponding values at an APRI score of 2.0 (high cut-off) were 22–49%, 81–94%, 19–34% and 91–94%<sup>41</sup>. More recently, HEPSANET joint report suggested a new rule-in and rule-out threshold of 0.65 and 0.36, respectively, for improved cirrhosis detection (liver stiffness measurement (LSM) > 12.2 kPa)<sup>29</sup>.

The overriding implication of these findings is that a significant number of patients in this cohort who were in the grey zone (0.5–2 points); may have cirrhosis or significant fibrosis. To further extrapolate, the lower number of treatment-eligible patients in cohorts in the WHO-Afro region potentially reflects the underdiagnosis of significant fibrosis or cirrhosis<sup>42</sup>. Reiterating this problem, Dusheiko and Lamoine noted in an editorial letter that the use of the WHO guideline raises several major concerns – the poor concordance between the EASL and WHO criteria (Cohen's kappa 0.518, p-value < 0.001) and its under-performance among young males and low overall sensitivity (49%). In their conclusion, they emphasized the need for SSA-specific or locally adopted treatment eligibility guidelines (more research on HBV disease) and low-cost diagnostics.

Another lingering concern pertains to appropriate cutoffs for ALT. In their latest report, the AASLD 2018 guidance update recommended male and female ALT cutoffs of 35 U/L and 25 U/L, respectively<sup>16</sup>. These recommendations are based on the observed association between ALT cutoff in the high-normal ALT range (> 40–70 IU/L) with liver necroinflammation, fibrosis, cirrhosis, HCC, and liver-related deaths<sup>43</sup>. Although the WHO guideline recommends the use of local ALT cut-offs of 30 U/L for men and 19 U/L for women<sup>44</sup>; we opted to use a cut-off of 40 U/L. This cut-off point is widely used in clinics in Eritrea<sup>33</sup> and is currently recommended, with some reservations, in the EASL guidelines<sup>31</sup>. For decades, scientists have known that some patients with persistently normal ALT (PNALT) (e.g., sustained ALT levels < 40 U/L) have cirrhosis<sup>45</sup>. In one such study in HBsAg –ve patients, researchers demonstrated the presence of cirrhosis in patients with ALT [0.5–U/L upper limit of normal (ULN)]<sup>46</sup>. Biopsy studies have uncovered similar results with some investigators concluding that ALT < 0.5 – U/L ULN levels are the most desirable<sup>47</sup>. Another extension to these disputations is the well-documented possibility that reference intervals (RIs) for ALT that are used across the WHO Afro region are locally inappropriate<sup>48,49</sup>. On this issue, it's our opinion, that the ALT cut-off (40 U/L for males and females) used in Eritrea is based on limited evidence; therefore, it can potentially undermine the evaluation of treatment eligibility in patients. To remedy this concern, studies on appropriate ALT and AST cut-offs are urgently needed in Eritrea. In particular, head-to-head comparison studies linking ALT (or APRI and FIB-4 score) levels with TE readings or biopsy findings should be considered. Overall, the lack of high-quality data on the burden of cirrhosis undermines treatment, elimination of HBV and reductions in mortality, DALY, or other quality-of-life indexes.

Similar to other real-world studies in the WHO-Afro region<sup>28</sup>, the limited range of tests performed in this cohort restricted our ability to undertake per-guideline evaluation of an ideal endpoint such as sustained off-therapy HBsAg loss (with or without seroconversion to anti-HBs), anti Be seroconversion, among others. This problem was further compounded by a lack of consistency in the use and/or reporting of available tests. For example, in our cohort, HBV DNA testing was delayed in multiple instances and 47 (48%) patients had no viral load records after treatment initiation. We also demonstrated that access to HBV DNA testing has dwindled over time. The high point was in the pre-2020-year band. Thereafter, HBV DNA testing and uptake of therapy reached a nadir (from which it is yet to recover) in 2020. The reasons behind this sustained decline remain unknown.

In a separate analysis, we demonstrated that 18 treatment eligible individuals were not on treatment. Although some lag time between treatment-eligibility and treatment initiation is expected<sup>34</sup>, lengthy delays can be harmful to patients. Moreover, treatment delay is one of the biggest problems affecting patients with CHB in SSA – as previously noted, only 6.6 million (5.3–8.3 million) of the 30.4 million (24.3–38 million) diagnosed with CHB are on treatment [18]. Multiple drivers of suboptimal treatment of CHB patients in the region are known. These include suboptimal evaluation of newly diagnosed HBV patients due to the high cost of diagnostics, problems with evaluation of treatment eligibility, delays in treatment initiation, and suboptimal monitoring of patients in care or those receiving anti-HBV therapy.

In real-world studies, these concerns have been reinforced by a study which demonstrated that only 35% of untreated patients on follow-up received HBV DNA and ALT level testing as required<sup>50</sup>. Stockouts of reagents and knowledge gaps among caregivers with the most current management recommendations<sup>43</sup> have also been implicated. On the whole, most of these barriers were identified in this setting. Priority areas in need of urgent redress include better training of personnel in HBV programs, and the need to reduce the cost of relevant laboratory assays. Importantly, data management should be optimized to support future research on the course of HBV disease, clinical decision-making; evaluation of program quality, among others.

Despite the shortcomings described above, it was possible to assess VR and biochemical response in a small subset of patients. In the head-to-head comparison of the results in TDF and TDF + LAM after 12 weeks of treatment, VR was observed in 14 (45.2%) vs. 17 (54.8%), respectively, translating into an overall VR of 60.7%

(95% CI 46.9–74.6). The observed values for TDF or TDF+LAM appear to be lower compared to data from some landmark real-world studies. Lee and colleagues recently reported a VR of 91.6% after 12 months of treatment (TDF group, 88.6% vs. 92.6% in TDF+LAM group)<sup>51</sup>. The observed disparity in VR may be due to the heterogeneous nature of patients in the environment and the limited number of controls *versus* those in a trial environment. More importantly, VR is time-dependent with higher responses correlating strongly with the duration of treatment. For example, Park and colleagues reported a time-dependent VR at 3, 6, 12, 24, and 36 months of 20%, 54%, 79%, 86%, and 91%, respectively<sup>52</sup>. These results are relatively consistent with our results. In a related analysis, we noted a significant improvement in biochemical parameters in both groups. In most studies, the biochemical response in patients treated with TDF and TDF+LAM is similar<sup>53</sup>.

Finally, we were able to demonstrate that the prevalence and incidence of LTFU in this cohort were 23.9% (95% CI 19.8–28.1) and 4.3 (95% CI: 3.5–5.2) per 1000 PDFU, respectively. Independent predictors of LTFU included baseline serum HBV DNA, treatment status (not on treatment), and FIB-4 score. Much of this is supported by bivariate data demonstrating that a significant number of patients with LTFU were having ALT > 40 U/L (23[35.4%]) or were in the likely cirrhosis or unlikely cirrhosis category, 17(44.7%). The connection between the increasing levels of HBV DNA, the FIB score, and LTFU is hard to understand, in part because it runs counter to specific models of patient behaviour - the health belief model (HBM) posits that patients with more severe forms of disease tend to seek and stay in care. Furthermore, we believe that the high rate of LTFU before treatment initiation may, at least partially, be explained by unmet patient monitoring requirements. In other words, patients are rational actors. Therefore, when they fail to receive any testing, treatment or information on their status during scheduled visits; high attrition rates can be expected. In this regard, poor adherence to monitoring guidelines may act as a driver of attrition.

Apart from these concerns, we have to emphasize the fact that the outcome in patients who were LTFU remains unknown. This notwithstanding, we assume that the likelihood of death, flare-ups of necroinflammation and progression to more advanced HBV-sequelae is high. In addition to these detrimental effects, the financial costs associated with retreatment or re-entry into care represent unnecessary/or avoidable costs for programs. Another concerning finding was the fact that a large proportion of patients who were LTFU had viremia. Because viral suppression reduces a patient's ability to transmit HBV; this outcome undermines the ultimate goal of eliminating HBV as a public health threat in Eritrea. Therefore, interventions designed to reduce LTFUs represent a powerful tool for HBV elimination. At a minimum, our finding reinforces the need for efforts directed at improvements in patient literacy and patient tracking (e.g., HBV registry, linked with outreach to patients).

### Limitations of the study

Although our study adds important real-world evidence regarding the feasibility of large-scale government-sponsored treatment of HBV in emerging treatment programs in SSA; it has several limitations. Like many retrospective studies, this study had a missing data problem. As such, specific evaluations were only undertaken in a fraction of patients in multiple analyses. The consequent loss of power undermined our ability to undertake multivariable analysis. The missing data problem also contributed to the relatively short period of tracking of outcomes in VR. Furthermore, the descriptive nature of the study means that the direction of causality cannot be inferred. Therefore, none of the associations uncovered can be assumed to be causative.

### Conclusions of the study

This study demonstrated that significant number of patients presented with active disease at baseline – APRI > 2, 18 (18.3%); persistently elevated ALT, 19 (19.3%); HBV DNA > 20,000 after 6 months of monitoring, 23 (23.4%) and clinically apparent presence of cirrhosis, 12 (12.2%). In spite of the significant number of cirrhosis (a marker of late presentation) in newly enrolled patients, potential underdiagnosis remains a concern. In many ways, our study provides a powerful illustration of the impact of inadequate diagnostic infrastructure (laboratory or imaging) on emerging HBV treatment programs in SSA. Note that in this program, it was associated with suboptimal evaluation of treatment eligibility; inability and /or delays in monitoring treatment response (serological, virological, and biochemical), poor adherence to the monitoring guideline; and inability to diagnose HBV-related sequelae such as HCC or specific health quality indexes. It may also contribute to high attrition rates. Despite a significant missing data problem, we demonstrated that the VR observed in this cohort are comparable to previous data from other real-world studies. Furthermore, VR after 12 weeks of follow-up was nearly similar in patients in the TDF and TDF+LAM treatment arms. Lastly, our study demonstrated that high LTFU occurred across the HBV care continuum, including prior to treatment initiation and the post treatment initiation period. On the whole, there are opportunities to achieve significant improvements in HBV management in Eritrea. Interventions include educational initiatives for caregivers/and or patients, improvements in laboratory infrastructure - to a level that can sustain mass HBV testing and per-guideline monitoring of patients; prompt linkage to care; treatment scale-ups, better tracking and documentation of patient's data.

### Data availability

The data set supporting the conclusions of this article is available from the corresponding author on reasonable request.

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## Author contributions

GGG and MBS conceived the study and formulated the study design. G.G.G, MBS and ARM performed data collection. G.G.G, MBS, and O.O.A did the statistical analysis and data presentation. G.G.G, MBS, O.O.A, M.E.H, and A.B.M wrote/edited the manuscript. All authors read and approved the final manuscript.

## Declarations

### Competing interests

The authors declare no competing interests.

### Conflict of interest

The authors declare that they have no competing interests.

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## Additional information

**Correspondence** and requests for materials should be addressed to G.G.G.

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