Clinical outcomes of untreated adults living with chronic hepatitis B in The Gambia: an analysis of data from the prospective PROLIFICA cohort study

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Summary

Background Expanding antiviral therapy to people with chronic hepatitis B virus (HBV) infection who are ineligible to receive treatment under current international criteria has been increasingly debated. Evidence to support this approach is scarce, especially in Africa. We aimed to address this knowledge gap by analysing the clinical outcomes of people with chronic hepatitis B in The Gambia who were untreated and ineligible for antiviral therapy at diagnosis.

Methods Between Dec 7, 2011, and Jan 24, 2014, we implemented the prospective PROLIFICA cohort study in The Gambia. Participants with chronic hepatitis B aged 16 years or older were recruited after large-scale, community-based HBV screening; blood bank-based HBV screening in Edward Francis Small Teaching Hospital, Banjul; and prospective follow-up of HBsAg-positive individuals via historical, population-based HBsAg serosurveys in two rural villages (Keneba and Manduar). Participants underwent HBV serology and other laboratory tests, fasting FibroScan, and abdominal ultrasound. Survival data were collected between Dec 7, 2011, and Aug 17, 2021. Between Oct 9, 2018, and Aug 17, 2021, all HBsAg-positive participants enrolled in the 2011–14 cohort were invited for a reassessment. For this analysis, we included HBsAg-positive people and excluded all participants who were eligible for treatment according to the 2012 European Association for the Study of the Liver (EASL) criteria at baseline and those who were treated irrespective of treatment eligibility. The primary outcome was all-cause mortality, assessed in all treatment-ineligible and treatment-naive participants with follow-up data. The secondary outcome, analysed in those who were reassessed, was disease progression, defined as becoming eligible for antivirals per 2017 EASL criteria; having an increase in liver fibrosis of at least one stage; or having a clinical diagnosis of hepatic decompensation or hepatocellular carcinoma.

Findings 943 HBsAg-positive people with chronic hepatitis B were recruited to the PROLIFICA study. Of these 943, 58 (6%) fulfilled 2012 EASL treatment eligibility criteria at baseline, 35 (4%) were ineligible for treatment but received antiviral therapy, and 44 (5%) were immediately lost to follow-up. Thus, 806 (85%) participants were analysed for the primary outcome (486 [60%] were male and 320 [40%] were female). After a median follow-up of 6·11 years (IQR 5·34–6·80), 708 (88%) participants were confirmed to be alive at last surveillance, 71 (9%) were lost to follow-up and were censored, and 27 (3%) died, giving an all-cause mortality rate of 582 per 100 000 person-years (95% CI 399–849). Of the 27 people who died, five (19%) had liver-related deaths. Of 708 participants confirmed to be alive, 544 (77%) attended follow-up and were assessed for the secondary outcome. Disease progression occurred in 36 (7%) participants: five (1%) became newly eligible for antiviral therapy per EASL 2017 criteria without liver fibrosis progression; 18 (3%) had liver fibrosis progression alone; 13 (2%) had liver fibrosis progression and newly fulfilled the treatment criteria; and none had hepatic decompensation or developed hepatocellular carcinoma. In multivariable analysis adjusted for sex and age, only a baseline HBV DNA of 20 000 IU/mL or more, compared with the baseline HBV DNA of 2000 IU/mL or lower as the reference, was significantly associated with liver disease progression (odds ratio 5·39, 95% CI 1·37–21·23).

Interpretation Among people with chronic hepatitis B who were ineligible for antiviral therapy in The Gambia, all-cause mortality and liver disease progression were low. The clinical benefit of expanding antiviral therapy in this subgroup of patients remains uncertain.

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Research in context

Evidence before this study

Indications for antiviral therapy among people living with chronic hepatitis B virus (HBV) infection are restrictive and based on complex criteria using tests that are largely inaccessible in low-income and middle-income countries. WHO and liver societies have revised or are revising their guidelines for the management of chronic hepatitis B, with a key focus on expansion and simplification of treatment criteria. Longitudinal data from untreated people with chronic hepatitis B who were deemed not eligible for treatment are crucial to best address whether and how treatment indications should be broadened. However, such data have been mainly obtained from Asian, European, and North American cohort studies and no data have been obtained from Africa. Therefore, whether and how treatment criteria should be expanded in people living with chronic hepatitis B in Africa is unknown. Debates have emerged around treating all individuals living with chronic hepatitis B in Africa, irrespective of other key variables currently recommended by liver societies (HBV viral load, liver inflammation, or fibrosis). We searched PubMed and Scopus for articles published in English from database inception to Jan 31, 2024, using the terms ("hepatitis B" OR "HBV") AND "natural history" AND "Africa" AND ("cohort" OR "longitudinal studies") AND ("HCC" OR "mortality" OR "outcomes"). We found one study published by our group in 2016 reporting data on hepatocellular carcinoma incidence and liver disease progression among people with chronic hepatitis B in The Gambia, but without differentiating participants who were eligible and ineligible for treatment. We found a 2023 study from Ethiopia that focused on treated people with chronic hepatitis B and did not specifically report the rate of liver disease progression among untreated individuals. This search highlights a major knowledge gap regarding the natural history of chronic hepatitis B in Africa, especially in untreated individuals with chronic hepatitis B who were deemed ineligible for treatment.

Added value of this study

We assessed medium-term mortality and disease progression among a unique cohort of well characterised, untreated people with chronic hepatitis B in The Gambia who had been deemed ineligible for antiviral therapy at diagnosis. We found that, among these individuals, all-cause mortality was similar to that observed in the general population and risk of hepatocellular carcinoma was negligible.

Implications of all the available evidence

To our knowledge, PROLIFICA was the first cohort study of people with chronic hepatitis B who were ineligible for antiviral therapy at the time of diagnosis and untreated during the follow-up in the WHO African region. This analysis provides evidence-based data for the management of chronic hepatitis B in Africa. Our findings, which will need to be substantiated with a longer duration of follow-up, do not provide strong evidence for expanding treatment eligibility criteria, including a treat-all approach.

Introduction

Chronic infection with hepatitis B virus (HBV) affects approximately 300 million people worldwide and is a leading cause of cirrhosis, hepatocellular carcinoma, and death.[1] Low-income and middle-income countries (LMICs), especially countries in the WHO African region, have the highest burden of chronic hepatitis B.[2] The seroprevalence of HBsAg among children younger than 5 years (2·7%) and among adults (7·5%) is highest in Africa,[1,3] and chronic hepatitis B remains the main cause of hepatocellular carcinoma, one of the most frequent cancers and a major cause of death across the region.[4,5] As a result, WHO has recognised Africa as the priority region for the development and implementation of HBV elimination strategies.[2] Among these strategies, two approaches have been increasingly discussed: expanding antiviral therapy indication to people with chronic hepatitis B who are ineligible for treatment under current liver society treatment criteria and treating all people with chronic hepatitis B, irrespective of current criteria, following the model of HIV elimination.

Increasing antiviral therapy coverage to 80% by 2030 among people with chronic hepatitis B who are eligible for treatment under current international liver society criteria was one of the key elimination targets set up by WHO in 2016.[6] However, according to 2022 WHO estimates, only 4·2% of people with chronic hepatitis B have been diagnosed and, among those diagnosed, only 5·5% have received antiviral therapy in Africa,[2] partly due to low capacity to assess treatment eligibility and manage chronic liver disease in routine clinical care in most African countries.[7] In the absence of an HBV cure, international liver societies[8–10] and 2015 WHO guidelines[11] recommend treating only people with chronic hepatitis B who are at risk of liver complications evidenced by established cirrhosis or substantial liver fibrosis (measured with liver biopsy or non-invasive tests, including transient elastography) or people with liver inflammation (based on liver biopsy or alanine aminotransferase [ALT]) in the presence of increased HBV viral load. However, these criteria were developed with data from Asian,[12–15] European, and North American cohort studies[16–18] without any African data. Data from non-African studies indicate that people with chronic hepatitis B and low HBV replication (HBV DNA <2000 IU/mL), normal ALT concentrations, and an absence of or mild liver fibrosis (usually negative for HBe antigen [HBeAg], formerly defined as inactive carriers) who represent the vast majority of people with chronic hepatitis B worldwide, have a low risk of liver disease progression and therefore do not require antiviral therapy.[14,16–18] For people with chronic hepatitis B

who are not strictly classified as being in any phase and do not fulfil current treatment criteria, and are thus in a grey zone, antiviral therapy indication is debated.

There is scarce evidence for these treatment criteria in Africa, where HBV genotypes and environmental characteristics differ from other regions and where the natural history of chronic hepatitis B has barely been documented.[19] In Africa, whether treatment criteria should be expanded among people with chronic hepatitis B who are not eligible for current criteria is unknown, and there is no evidence to recommend treating all HBsAg-positive individuals irrespective of viral load, liver enzymes, or stage of liver fibrosis. We aimed to address this knowledge gap by analysing the clinical outcomes of a unique cohort of people with chronic hepatitis B in The Gambia who were untreated and deemed ineligible for antiviral therapy at diagnosis.[20]

Methods

Study design and participants

Between Dec 7, 2011, and Jan 24, 2014, we conducted a multicentre, prospective cohort study of individuals living with chronic hepatitis B via the Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) programme in The Gambia, the first screen-and-treat programme for people with HBV monoinfection in sub-Saharan Africa.[19,20] As described elsewhere, participants were recruited after large-scale, community-based screening for HBV among individuals in The Gambia born before the implementation of the hepatitis B vaccine (ie, aged 30 years or older) residing in randomly selected rural and urban areas;[20] after blood bank-based HBV screening among people aged 16 years or older who presented for blood donation in the main Gambian teaching hospital (ie, Edward Francis Small Teaching Hospital, Banjul, The Gambia);[20] and after prospective follow-up of individuals known to be HBsAg-positive through historical, population-based HBsAg serosurveys in two Gambian rural villages (ie, Keneba and Manduar) of the Kiang West district.[19] For the 2011–14 PROLIFICA cohort study,[19,20] inclusion criteria were being older than 16 years, having tested positive for HBsAg after community-based or blood bank-based screening or known to be HBsAg-positive via the historical serosurveys, and being able to provide written, informed consent in English (information forms were explained to participants in local languages (ie, Mandinka, Wolof, Pulaar, and Jola).

Between Oct 9, 2018, and Aug 17, 2021, we conducted a prospective study among HBsAg-positive participants enrolled in the 2011–14 PROLIFICA cohort study, who were invited to a liver reassessment. Participants provided additional written informed consent for this reassessment. For this current analysis, we excluded all participants who were eligible for treatment according to the 2012 European Association for the Study of the Liver (EASL) criteria at baseline and those who were treated irrespective of treatment eligibility. The 2011–14 prospective cohort study and this analysis were approved by the Gambian Government and the Medical Research Council (MRC) The Gambia Unit Joint Ethics Committee (SCC1579).

Procedures

For baseline assessment, data on sociodemographic, anthropometrics, and medical history were collected at the MRC clinic in Fajara or the MRC Keneba field station. All patients had a physical examination and a comprehensive liver assessment, including a fasting FibroScan (Echosens, Paris, France), abdominal ultrasound (portable MyLab25Gold, Esaote, Cambridge, UK), and liver biopsy (if indicated).[21] On the basis of liver stiffness measurement, clinically significant fibrosis (Meta-analysis of Histological Data in Viral Hepatitis [METAVIR] F2) was defined as ≥7·9 kPa, advanced fibrosis (F3) was defined as 8·2–9·4 kPa, and cirrhosis (F4) was defined as 9·5 kPa or more. Liver stiffness measurement of 7·8 kPa or lower was defined as no or mild fibrosis (F0–1). These cutoffs had been previously established against liver histology as a reference in this Gambian cohort; the cutoff for liver stiffness measurement of 9·5 kPa had a 100% sensitivity and 89% specificity to diagnose cirrhosis.[21] Sex was self-reported by the participant in agreement with their identity card, which was checked for each participant to confirm name, sex, and date of birth. Participants could report male or female sex. All participants had laboratory tests for liver enzymes and creatinine; full blood count; α-fetoprotein (ARCHITECT i1000SR, Abbott, Green Oaks, IL, USA); HBsAg (ARCHITECT, Abbott, Green Oaks, IL, USA); HBeAg (ETI-EBK PLUS, Diasorin, Saluggia, Italy); antibodies to anti-hepatitis D virus (HDV; ETI-AB-DELTAK-2, Diasorin, Saluggia, Italy); antibodies to hepatitis C virus (HCV; AxSYM anti-HCV, Abbott, Chicago, IL, USA); and HBV DNA (RealTime HBV, Abbott, Green Oaks, IL, USA). Antibodies to HIV-1 and HIV-2 were detected with an enzyme immunoassay (Genscreen ULTRA HIV Ag-Ab, Bio-Rad, Hercules, CA, USA). HBV genotype was established in HBsAg-positive samples with detectable viraemia at the Cancer Research Center of Lyon (Lyon, France; Platinum Taq DNA polymerase, Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA). Participants who attended the clinics and who were eligible for antiviral therapy according to 2012 EASL criteria[22] were offered free-of-charge oral tenofovir disoproxil fumarate (300 mg daily). People eligible for treatment (and people with cirrhosis but without HBV viraemia, who were not eligible under EASL criteria) were monitored (by clinical examination, liver ultrasound, and FibroScan, and assessment of liver enzymes, serum creatinine, and HBV viral load) every 6 months for treatment adherence and hepatocellular carcinoma surveillance.

Between Dec 7, 2011, and Aug 17, 2021, survival data were prospectively collected by trained members of the research team (GN, SB, GLa, ML, DL, and YH) in

all treated and untreated participants via two systems. The first was a passive surveillance from the start of the study; each participant was given a study card and, when admitted at MRC or any other clinical services, the research team was informed as admission costs were covered by the project. Mortality data and any liver-related event (ie, liver decompensation or hepatocellular carcinoma) were collected after a review of clinical records, in which a copy of the death certificate is usually kept. The second was an active surveillance beginning Feb 1, 2013; participants or their trusted relatives were contacted at least once per year for survival or liver-related events, either by telephone call or home visits, and up to five attempts were made per year in case of failure to establish contact (GN, SB, GLa, DL, YH, and ML). We used the contact details (ie, telephone numbers and home addresses) of each study participant and two of their trusted relatives, which were recorded at enrolment. Whenever a death was confirmed, we documented the date, place, and potential cause or causes of death. For participants who died outside the MRC hospital setting, we obtained details from verbal autopsy with the trusted relatives or linkage with the The Gambian National Cancer Registry, with whom the MRC The Gambia Unit and the PROLIFICA programme had research agreements,[23] to ascertain a potential death due to hepatocellular carcinoma.

Between Oct 9, 2018, and Aug 17, 2021, all HBsAg-positive participants enrolled in the 2011–14 PROLIFICA cohort were invited to a comprehensive liver reassessment, including a fasting FibroScan, abdominal ultrasound, and all laboratory investigations as done at baseline (except HBV genotyping, which was not repeated). To measure HBsAg and HBeAg loss, we repeated HBsAg and HBeAg serologies in all participants. Sociodemographics, anthropometrics, medical history, and physical exams were also repeated and patients were reassessed for treatment eligibility per 2017 EASL guidelines. Reasons for not being seen in a clinic for follow-up were documented. All data were prospectively collected and recorded by trained members of the research team (GN, SB, GLa, RB, ML, PI, DL, and YH).

Outcomes

The primary outcome was all-cause mortality, assessed in all treatment-ineligible and treatment-naive participants with follow-up data.

Secondary outcomes were assessed in all participants who attended the 2018–21 clinical reassessment. As a secondary outcome of disease progression, we used the composite of becoming eligible for antiviral therapy according to the 2017 EASL treatment criteria;[8] having an increase in liver fibrosis of at least one stage based on liver stiffness measurement; having clinically diagnosed hepatic decompensation with jaundice, ascites, hepatic encephalopathy, or variceal bleeding; or having a diagnosis of hepatocellular carcinoma.[4] Additional endpoints were rates of HBsAg and HBeAg loss.

Statistical analysis

Categorical variables are presented as n (%) and comparisons were made with χ^2 test. Continuous variables are presented as mean (SD) or median (IQR) and comparisons were made with Mann–Whitney *U* or *t* tests. Person-years of follow-up for mortality were calculated from the date of cohort enrolment to the date of death or the last date when we confirmed survival status. For participants who died with an unknown date of death, it was defined as the midpoint between the last confirmed date of their survival status and the first confirmed date when we verified their deaths.

Risk factors associated with all-cause mortality were assessed via Cox proportional-hazards regression; risk factors associated with disease progression were assessed via logistic regression. In univariable analysis, we evaluated these predefined potential risk factors for all-cause mortality and disease progression: baseline age, sex, recruitment origin, phase of natural history, HBeAg-negative chronic infection stratified by viral load and liver stiffness measurement, HIV co-infection, HCV co-infection, HDV co-infection, fibrosis stage (METAVIR score), aspartate aminotransferase-to-platelet ratio index (APRI), Fibrosis-4 Index for Liver Fibrosis (FIB-4), HBV DNA viral load, HBeAg (positive vs negative), quantitative HBsAg (qHBsAg), ALT, BMI, and high blood pressure (systolic ≥130 mm Hg or diastolic ≥80 mm Hg).[24] Due to the small number of participants with the primary or secondary endpoint, variables with significant associations with each of these outcomes in the univariable analysis ($p<0·05$) were subsequently adjusted in a multivariable analysis, in which only age and sex were considered as covariates. To prevent table 2 fallacy, multivariable analysis was not used to evaluate the individual effects of age or sex.

To compare the mortality rate in this cohort of untreated individuals with chronic hepatitis B and the mortality rate in the general population in The Gambia, we obtained age-standardised mortality rates (ASMR), specific to each sex, by applying age-specific and sex-specific mortality rates in this cohort to the age structure of the standard Gambian population.[25] Because most people included in this analysis were aged 30 years or older at enrolment, we restricted the analysis to those who were either aged 30 years or older at enrolment or who reached the age of at least 30 years during the follow-up period. The age-specific and sex-specific mortality rates in the general population, also restricted by age were obtained from the WHO 2019 life table for The Gambia.[26] Standard error of ASMR was obtained via the formula[27]

$$\frac{1}{\sum w_i}\sqrt{\sum \frac{w_i^2 d_i}{(pyar_i)^2}}$$

in which $_i$ represents the different age bands, w_i represents the number of individuals in the standard population, d_i represents the number of deaths in the study population,

and $pyar_i$ represents the number of person-years in the study population within the $_i$ age band.

HBsAg loss was compared between male and female participants. To evaluate potential bias related to censoring, we conducted a post-hoc sensitivity analysis to estimate all-cause mortality and hazard ratios (HRs) under two scenarios: assuming all people censored due to loss to follow-up were alive at the last survival follow-up in 2021 and assuming all censored people died immediately after the last observation time. Missing data were excluded from analyses.

All analyses were done in Stata, version 17.0.

Role of the funding source

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

Results

943 HBsAg-positive people with chronic hepatitis B were recruited to the 2011–14 PROLIFICA study. 402 (43%) of 943 were recruited from community-based screening;[20] 300 (32%) were recruited from blood bank-based screening at the main Gambian hospital;[20] and 241 (26%) were recruited from historical, population-based serosurveys.[19] Of 943 HBsAg-positive participants, 58 (6%) fulfilled the 2012 EASL treatment eligibility criteria at baseline, 35 (4%) were ineligible for treatment but received antiviral therapy outside the treatment criteria, and 44 (5%) were lost to follow-up for their survival status immediately after recruitment. 2012 EASL guidelines were also applied to participants recruited in 2011 due to time taken to acquire blood results. As a result, 806 (85%) participants were analysed for the primary outcome (figure; appendix pp 1–2). Participants in the primary outcome population had mainly HBV genotype E,[20] and 486 (60%) were male and 320 (40%) were female. At baseline, among the 850 treatment-ineligible and treatment-naive participants (and the 806 in whom the primary outcome was assessed), there was no history of hepatocellular carcinoma or liver decompensation and no participant acknowledged excessive alcohol intake (ie, more than 30 g per day for male individuals and 20 g per day for female individuals; table 1; appendix p 1).

After a median follow-up duration of 6·11 years (IQR 5·34–6·80), overall mortality could be assessed among 806 individuals with chronic hepatitis B, 529 (66%) of whom were younger than 40 years at enrolment. 665 (85%) of 787 who could be classified were in a HBeAg-negative chronic infection phase (table 2; appendix pp 1–2). Of 806 participants, 708 (88%) were confirmed to be alive at last survival surveillance, 71 (9%) were lost to follow-up before the primary endpoint assessment, and 27 (3%) were confirmed to have died, giving an all-cause mortality rate of 582 per 100 000 person-years (95% CI 399–849). Of the 27 people who died, five (19%) had liver-related deaths, but none were documented to have had hepatocellular carcinoma.

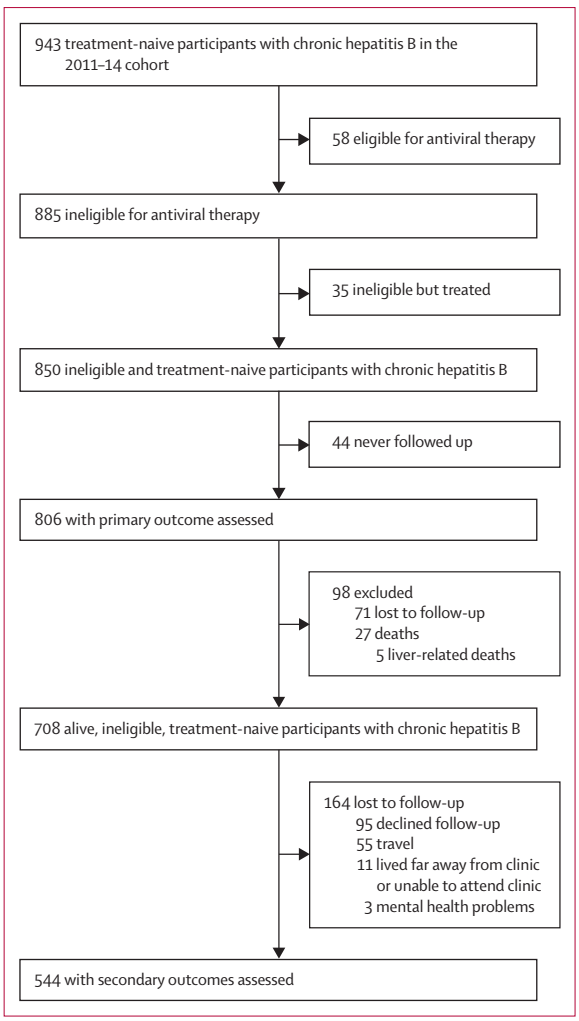

Figure: **Analysis profile**

See **Online** for appendix

Risk factors associated with all-cause mortality in univariable analyses included age, HBeAg-negative chronic hepatitis, positive HIV serology, positive HCV serology, APRI, FIB-4, and high blood pressure (table 2). In multivariable analysis adjusted for sex and age, baseline APRI, positive HCV serology, and high blood pressure remained associated with all-cause mortality (table 2). BMI of 25 kg/m² or more was associated with a reduced hazard of all-cause mortality. Phases of chronic hepatitis B at baseline and HBV DNA viral load were not predictive for all-cause mortality on multivariable analysis.

The post-hoc sensitivity analyses assumed that all participants censored due to loss to follow-up were either alive at the last survival follow-up or died immediately after the last observation time (appendix pp 3–8). The first sensitivity analysis did not affect the risk factors identified in the main analysis. The second sensitivity analysis consistently identified age, an APRI

of more than or equal to 2·0, and blood pressure as being associated with all-cause mortality. Sex and recruitment origin were newly identified as being associated and HCV coinfection, BMI, and APRI at the 0·65 and 0·5 cutoffs were no longer associated with all-cause mortality.

In the 754 individuals aged 30 years or older at enrolment or who reached at least 30 years of age during the follow-up period, ASMRs (male participants 9·57 per 1000 person-years [95% CI 3·63–15·51]; female participants 7·69 per 1000 person-years [3·32–12·06]) were not significantly different to the general Gambian population

	Participants ineligible for treatment at baseline who remained untreated (n=850)	Participants who died (n=27)	Participants with unknown survival (n=115)*	Participants who survived but were not retained in care (n=164)	Participants who survived and were retained in care (n=544)	p value†
Age, years	35 (31–43)	55 (38–69)	32 (27–36)	36 (31–45)	36 (31–43)	0·0001
Sex	..	..	..	..	..	0·0055
Male	518/850 (61%)	14/27 (52%)	87/115 (76%)	96/164 (59%)	321/544 (59%)	..
Female	332/850 (39%)	13/27 (48%)	28/115 (24%)	68/164 (41%)	223/544 (41%)	..
Attended primary school	389/728 (53%)	7/24 (29%)	60/93 (65%)	79/154 (51%)	243/457 (53%)	0·014
Median BMI, kg/m²	22·4 (20·1–25·7)	20·3 (18·5–22·2)	22·1 (20·5–25·0)	21·8 (19·9–26·0)	22·8 (20·2–26·1)	0·0055
BMI	..	..	..	..	..	0·20
<25·0 kg/m²	584/835 (70%)	24/27 (89%)	84/112 (75%)	114/158 (72%)	362/538 (67%)	..
25·0–29·9 kg/m²	178/835 (21%)	2/27 (7%)	21/112 (19%)	30/158 (19%)	125/538 (23%)	..
≥30·0 kg/m²	73/835 (9%)	1/27 (4%)	7/112 (6%)	14/158 (9%)	51/538 (10%)	..
Blood pressure	..	..	..	..	..	0·0015
Normal	473/737 (64%)	6/24 (25%)	59/93 (63%)	101/156 (65%)	307/464 (66%)	..
SBP 130–139 mm Hg or DBP 80–89 mm Hg	149/737 (20%)	8/24 (33%)	21/93 (23%)	23/156 (15%)	97/464 (21%)	..
SBP ≥140 mm Hg or DBP ≥90 mm Hg	115/737 (16%)	10/24 (42%)	13/93 (14%)	32/156 (21%)	60/464 (13%)	..
Liver steatosis on ultrasound or liver biopsy	68/850 (8%)	2/27 (7%)	6/115 (5%)	14/164 (9%)	46/544 (8%)	0·70
Ever drank alcohol	54/850 (6%)	2/27 (7%)	7/115 (6%)	12/164 (7%)	33/544 (6%)	0·92
Family history of hepatocellular carcinoma	27/850 (3%)	0/27	4/115 (3%)	2/164 (1%)	21/544 (4%)	0·28
Liver stiffness, kPa‡	4·9 (4·1–5·9)	4·7 (4·3–5·4)	5·3 (4·5–6·2)	4·8 (4·0–6·0)	4·8 (4·0–5·8)	0·045
METAVIR score	..	..	..	..	..	0·67
F0–1	773/813 (95%)	25/25 (100%)	106/112 (95%)	145/154 (94%)	497/522 (95%)	..
F2–3	33/813 (4%)	0/25	5/112 (4%)	6/154 (4%)	22/522 (4%)	..
F4	7/813 (1%)	0/25	1/112 (1%)	3/154 (2%)	3/522 (1%)	..
ALT, IU/L	24 (19–30)	20 (17–26)	24 (20–33)	24 (18–29)	24 (19–30)	0·093
ALT ≥40 IU/L	81/835 (10%)	2/26 (8%)	14/112 (13%)	19/158 (12%)	46/539 (9%)	0·43
AST, IU/L	29 (24–34)	31 (26–35)	30 (25–35)	30 (24–35)	29 (24–34)	0·44
γ-Glutamyl transferase, IU/L	25 (20–34)	26 (21–33)	25 (19–31)	25 (19–34)	26 (20–34)	0·70
Platelets, 10^9 cells per L	195 (156–243)	183 (134–204)	191 (151–226)	207 (160–260)	196 (156–245)	0·048
HBeAg-positive	18/850 (2%)	0/27	2/115 (2%)	4/164 (2%)	12/544 (2%)	0·86
HBV DNA	..	..	..	..	..	0·75
Undetectable	382/790 (48%)	16/24 (67%)	54/107 (51%)	73/159 (46%)	239/500 (48%)	..
50–1999 IU/mL	360/790 (46%)	6/24 (25%)	48/107 (45%)	73/159 (46%)	233/500 (47%)	..
2000–19 999 IU/mL	23/790 (3%)	1/24 (4%)	3/107 (3%)	7/159 (4%)	12/500 (2%)	..
20 000–199 999 IU/mL	8/790 (1%)	0/24	0/107	2/159 (1%)	6/500 (1%)	..
≥200 000 IU/mL	17/790 (2%)	1/24 (4%)	2/107 (2%)	4/159 (3%)	10/500 (2%)	..
HBV genotype	..	..	..	..	..	0·71
A	35/265 (13%)	0/7	6/38 (16%)	7/48 (15%)	22/172 (13%)	..
E	230/265 (87%)	7/7 (100%)	32/38 (84%)	41/48 (85%)	150/172 (87%)	..
Median $\log_{10}$ qHBsAg, IU/mL	3·9 (3·3–4·2; 420)	3·2 (1·6–4·2; 12)	4·1 (3·7–4·3; 53)	3·9 (3·3–4·2; 78)	3·8 (3·2–4·1; 277)	0·0095
HIV-positive	24/850 (3%)	3/27 (11%)	4/115 (3%)	7/164 (4%)	10/544 (2%)	0·014

(Table 1 continues on next page)

	Participants ineligible for treatment at baseline who remained untreated (n=850)	Participants who died (n=27)	Participants with unknown survival (n=115) *	Participants who survived but were not retained in care (n=164)	Participants who survived and were retained in care (n=544)	p value†
(Continued from previous page)						
HCV-positive	9/850 (1%)	2/27 (7%)	3/115 (3%)	1/164 (1%)	3/544 (1%)	0·0025
HDV-positive	9/850 (1%)	0/27	0/115	6/164 (4%)	3/544 (1%)	0·0035
Phase of natural history§	..	..	..	..	..	0·54
HBeAg-positive chronic infection	12/830 (1%)	0/26	1/114 (1%)	3/159 (2%)	8/531 (2%)	..
HBeAg-positive chronic hepatitis	6/830 (1%)	0/26	1/114 (1%)	1/159 (1%)	4/531 (1%)	..
HBeAg-negative chronic infection	701/830 (85%)	23/26 (89%)	95/114 (83%)	126/159 (79%)	457/531 (86%)	..
HBeAg-negative chronic hepatitis	4/830 (1%)	1/26 (4%)	0/114	1/159 (1%)	2/531 (<1%)	..
HBeAg-negative grey zone (ie, increased ALT)	69/830 (8%)	1/26 (4%)	13/114 (11%)	16/159 (10%)	39/531 (7%)	..
HBeAg-negative grey zone (ie, increased viral load)	31/830 (4%)	1/26 (4%)	3/114 (3%)	9/159 (6%)	18/531 (3%)	..
Compensated cirrhosis	7/830 (1%)	0/26	1/114 (1%)	3/159 (2%)	3/531 (1%)	..
Decompensated cirrhosis	0/850	0/27	0/115	0/164	0/544	..
Hepatocellular carcinoma	0/850	0/27	0/115	0/164	0/544	..

Data are n/N (%), median (IQR), or median (IQR; n), unless otherwise specified. ALT=alanine aminotransferase. AST=aspartate aminotransferase. DBP=diastolic blood pressure. HBV=hepatitis B virus. HCV=hepatitis C virus. HDV=hepatitis D virus. METAVIR=Meta-analysis of Histological Data in Viral Hepatitis. qHBsAg=quantitative HBsAg. SBP=systolic blood pressure. *Including the 44 participants who were never followed up. †Obtained by comparing the four groups of outcomes (ie, participants who died, participants whose survival status was unknown, participants confirmed to have survived but not retained in care, and participants confirmed to have survived and retained in care). Comparisons were made with χ^2 or Fisher's exact tests for categorical variables and with Mann–Whitney *U* or *t* tests for continuous variables. ‡Excluding 31 participants without measurement and six with unreliable measurements. §Excluding 20 participants without cirrhosis and with missing HBeAg at baseline.

Table 1: **Baseline characteristics of participants who were ineligible for treatment at baseline and remained untreated during follow-up, by study outcome**

(male 14·43 per 1000 person-years; female 11·38 per 1000 person-years).

Of 708 participants confirmed to be alive at the most recent survival surveillance, 544 (77%) attended their follow-up assessment (figure), whereas 164 (23%) were not retained in care. 95 (58%) of 164 were not retained due to refusal of clinical reassessment, 55 (34%) because they were travelling, 11 (7%) due to living far away from or being unable to come to the clinic, and three (2%) due to mental health problems.

544 participants were reassessed, 164 were alive at last survival surveillance but not reassessed, 115 had unknown survival status (including 44 who were lost to follow-up for their survival status immediately after recruitment and 71 who were confirmed to be alive after recruitment but were subsequently lost to follow-up), and 27 died (table 1). At baseline, participants retained in care were similar to those not retained in care, except for HIV and HDV co-infections, which were more frequently observed in those not retained in care (table 1). Participants with unknown survival status were younger and mainly male, but had similar liver stiffness and median viral load at baseline compared with participants who were alive but not reassessed (table 1).

Among the 544 participants who attended the clinical follow-up assessment, the median interval between the first assessment in 2011–14 and the follow-up assessment in 2018–21 was 6·07 years (IQR 5·56–6·75). Fully reassessed participants were mainly male, had a median age of 41 years (IQR 37–48), and had a median BMI of 24·2 kg/m² (20·8–28·0; table 3) at re-assessment. None reported excessive alcohol intake and no participants had received previous antiviral or antiretroviral therapy. At reassessment, most participants were in an HBeAg-negative chronic HBV infection phase (table 3), but 136 (25%) of 537 with data had HBV DNA 2000 IU/mL or more and 49 (9%) of 541 with data had an ALT concentration of 40 IU/L or more.

Of 544 participants who were fully reassessed, three had invalid liver stiffness measurements and one had a missing liver stiffness measurement, leaving 540 participants with valid liver stiffness measurements. Of these 540, 36 (7%) had elevated liver stiffness measurements (ie, ≥7·9 kPa), suggesting clinically significant liver fibrosis, including 13 (2%) with compensated cirrhosis. There were two participants with elevated α-fetoprotein (395 ng/mL and 375 ng/mL, respectively); both were pregnant at the time of blood sampling and there was no space-occupying lesion by ultrasound.

Compared with baseline evaluation, the composite secondary outcome of disease progression occurred in 36 (7%) of 544 participants: five (1%) became newly eligible for antiviral therapy per EASL 2017 criteria without liver fibrosis progression; 18 (3%) had liver fibrosis progression alone; 13 (2%) had liver fibrosis progression and newly fulfilled the treatment criteria; and none had hepatic decompensation or developed hepatocellular carcinoma. Overall, 18 (3%) of 544

	Number of deaths (n/N)	Person-years of follow-up	Incidence rate per 100 000 person-years (95% CI)	Crude hazard ratio (95% CI)	Crude hazard ratio p value	Adjusted hazard ratio (95% CI)*	Adjusted hazard ratio p value
Overall	27/806 (34%)	4639	582 (399–849)	..	..	..	..
Age at baseline	..	..	..	..	<0·0001	..	..
<40 years	7/529 (13%)	2946	238 (113–498)	1 (ref)	..	..	..
40–49 years	1/154 (1%)	968	103 (15–733)	0·43 (0·05–3·49)	..	..	..
≥50 years	19/123 (15%)	726	2618 (1670–4105)	11·01 (4·63–26·20)	..	..	..
Sex	..	..	..	..	0·65	..	..
Female	13/320 (4%)	1999	650 (378–1120)	1 (ref)	..	..	..
Male	14/486 (3%)	2640	530 (314–895)	0·84 (0·39–1·79)	..	..	..
Recruitment origin	..	..	..	..	0·0055	..	0·099
Community-based screening	21/359 (6%)	2279	921 (601–1413)	1 (ref)	..	1 (ref)	..
Blood bank screening	1/229 (<1%)	1026	97 (14–692)	0·11 (0·01–0·84)	..	0·22 (0·02–1·76)	..
Historical cohort	5/218 (2%)	1334	375 (156–900)	0·41 (0·15–1·09)	..	0·42 (0·15–1·12)	..
Phase of natural history†	..	..	..	..	0·47	..	..
HBeAg-negative chronic infection	23/665 (4%)	3818	602 (400–906)	1 (ref)	..	..	..
HBeAg-positive chronic infection	0/11	72	0 (NA)	<0·01 (NA)	..	..	..
HBeAg-positive chronic hepatitis	0/6	31	0 (NA)	<0·01 (NA)	..	..	..
HBeAg-negative chronic hepatitis	1/4 (25%)	23	4421 (623–3100)	7·85 (1·05–58·35)	..	..	..
HBeAg-negative grey zone	2/94 (2%)	546	366 (92–1465)	0·60 (0·14–2·54)	..	..	..
Cirrhosis	0/7	36	0 (NA)	<0·01 (NA)	..	..	..
HBeAg-negative chronic infection†	..	..	..	..	0·22	..	..
Viral load undetectable and LSM <7·9	13/296 (4%)	1685	772 (448–1329)	1 (ref)	..	..	..
Viral load detectable or LSM ≥7·9	10/369 (3%)	2133	469 (252–871)	0·59 (0·26–1·36)	..	..	..
HIV-positive†	..	..	..	..	0·015	..	0·30
No	23/771 (3%)	4431	519 (345–781)	1 (ref)	..	1 (ref)	..
Yes	3/23 (13%)	129	2318 (748–7189)	4·48 (1·34–14·96)	..	1·91 (0·55–6·55)	..
HCV-positive†	..	..	..	..	0·0015	..	0·0095
No	24/782 (3%)	4486	535 (359–798)	1 (ref)	..	1 (ref)	..
Yes	2/6 (33%)	344	5815 (1454–23250)	10·68 (2·52–45·31)	..	6·96 (1·62–29·88)	..
HDV-positive†	..	..	..	..	0·42	..	..
No	26/787 (3%)	4515	576 (392–846)	1 (ref)	..	..	..
Yes	0/9	58	0 (NA)	<0·01 (NA)	..	..	..
METAVIR score (per biopsy or LSM)†	..	..	..	..	0·32	..	..
F0–1	25/732 (3%)	4240	590 (398–873)	1 (ref)	..	..	..
F2–3	0/30	161	0 (NA)	<0·01 (NA)	..	..	..
F4	0/7	36	0 (NA)	<0·01 (NA)	..	..	..
APRI†	..	..	..	..	..	..	..
<2·0	24/764 (3%)	4394	546 (366–815)	1 (ref)	<0·0001	1 (ref)	0·0035
≥2·0	2/5 (40%)	24	8510 (2128–34027)	16·14 (3·80–68·59)	..	9·74 (2·19–43·28)	..
<0·65‡	16/653 (3%)	3764	425 (260–693)	1 (ref)	0·0015	1 (ref)	0·0015
≥0·65	10/116 (9%)	653	1530 (823–2844)	3·68 (1·67–8·13)	..	4·27 (1·87–9·73)	..
<0·5	12/529 (2%)	3061	391 (222–690)	1 (ref)	0·013	1 (ref)	0·011
≥0·5	14/240 (6%)	1356	1032 (611–1742)	2·66 (1·23–5·75)	..	2·80 (1·26–6·24)	..
FIB-4†	..	..	..	..	0·0015	..	0·061
<3·25	22/747 (3%)	4291	513 (338–779)	1 (ref)	..	1 (ref)	..
≥3·25	4/21 (19%)	123	3250 (1220–8659)	6·33 (2·18–18·38)	..	2·85 (0·95–8·54)	..
HBV DNA†	..	..	..	..	0·93	..	..
<2000 IU/mL	22/703 (3%)	4087	538 (354–817)	1 (ref)	..	..	..
2000–19 999 IU/mL	1/22 (5%)	132	756 (107–5370)	1·39 (0·18–10·38)	..	..	..
≥20 000 IU/mL	1/24 (4%)	152	656 (92–4658)	1·22 (0·16–9·12)	..	..	..

(Table 2 continues on next page)

	Number of deaths (n/N)	Person-years of follow-up	Incidence rate per 100 000 person-years (95% CI)	Crude hazard ratio (95% CI)	Crude hazard ratio p value	Adjusted hazard ratio (95% CI)*	Adjusted hazard ratio p value
(Continued from previous page)							
HBeAg†	..	..	..	..	0·27	..	..
Negative	26/769 (3%)	4422	588 (400–864)	1 (ref)	..	..	..
Positive	0/17	103	0 (NA)	<0·01 (NA)	..	..	..
qHBsAg†	..	..	..	..	0·033	..	0·34
<3 log_{10}	5/66 (8%)	409	1224 (509–2940)	1 (ref)	..	1 (ref)	..
≥3 log_{10}	7/337 (2%)	2027	345 (165–724)	0·28 (0·09–0·90)	..	0·55 (0·16–1·85)	..
ALT†	..	..	..	..	0·78	..	..
<40 IU/L	24/714 (3%)	4118	583 (391–870)	1 (ref)	..	..	..
≥40 IU/L	2/76 (3%)	421	475 (119–1900)	0·81 (0·19–3·45)	..	..	..
BMI†	..	..	..	..	0·035	..	0·012
<25 kg/m²	24/551 (4%)	3138	765 (513–1141)	1 (ref)	..	1 (ref)	..
≥25 kg/m²	3/241 (1%)	1420	211 (68–655)	0·27 (0·08–0·91)	..	0·21 (0·06–0·70)	..
High blood pressure (SBP ≥130 mm Hg or DBP ≥80 mm Hg†	..	..	..	..	<0·0001	..	0·0085
No	6/453 (1%)	2732	220 (99–489)	1 (ref)	..	1 (ref)	..
Yes	18/249 (7%)	1443	1248 (786–1980)	5·80 (2·30–14·66)	..	3·60 (1·39–9·30)	..

ALT=alanine aminotransferase. APRI=aspartate aminotransferase-to-platelet ratio index. DBP=diastolic blood pressure. FIB-4=Fibrosis-4 Index for Liver Fibrosis. HBV=hepatitis B virus. HCV=hepatitis C virus. HDV=hepatitis D virus. LSM=liver stiffness measurement. METAVIR=Meta-analysis of Histological Data in Viral Hepatitis. NA=not applicable. qHBsAg=quantitative HBsAg. SBP=systolic blood pressure. *Adjusted by age and sex. †Data do not add up to total due to missing data. ‡Cutoff derived from Johannessen and colleagues.[28]

Table 2: **Overall mortality rates and associated risk factors**

participants became newly eligible for antiviral therapy per EASL 2017 criteria and 31 (6%) of 518 had liver fibrosis progression (excluding 19 patients who had missing liver stiffness measurements at baseline, three who had invalid liver stiffness measurements at baseline, three who had invalid liver stiffness measurements at follow-up, and one who had missing liver stiffness measurement at follow-up). 13 (3%) of 518 were classified as newly having cirrhosis (appendix p 8). Of 488 participants with no or mild liver fibrosis (F0–1) at baseline, 29 (6%) had fibrosis progression, including 11 (2%) people with new cirrhosis (appendix p 8).

The only risk factors that were significantly associated with liver-disease progression in univariable analyses were baseline HBV DNA and METAVIR score (table 4). The proportions of patients who had disease progression and available data were 6% (27 of 472), 17% (two of 12), and 19% (three of 16) in those with baseline viral loads of less than 2000 IU/mL, 2000–19 999 IU/mL, and 20 000 IU/mL or more, respectively. After adjusting for sex and age in the multivariable analysis, baseline HBV DNA was significantly associated with an increased risk of composite endpoint. Compared with HBV DNA of less than 2000 IU/mL, the adjusted odds ratios were 3·63 (95% CI 0·73–17·99) for HBV DNA of 2000–19 999 IU/mL and 5·39 (1·37–21·23) for HBV DNA of 20 000 IU/mL or more (p_{trend}=0·0061). For the METAVIR score, the adjusted odds ratio for liver disease progression in the F2–F3 group compared with the F0–F1 group was 3·29 (0·99–10·88, p=0·050).

During follow-up, 23 (4%) of 544 participants lost HBsAg, with an incidence rate of 0·69 per 100 person-years (95% CI 0·46–1·04). The rate of HBsAg loss was higher among female participants (1·10 per 100 person-years, 0·67–1·79) than among male participants (0·37 per 100 person-years, 0·17–0·78), with a rate ratio adjusted for age and sex of 2·56 (95% CI 1·03–6·34; p=0·042). Among 12 HBeAg-positive individuals, eight (67%) spontaneously lost HBeAg.

Discussion

Via data from a unique cohort of people with chronic hepatitis B in The Gambia, we found that untreated individuals who were ineligible for antiviral therapy at diagnosis had a low rate of all-cause mortality, similar to the general population in The Gambia. Moreover, these individuals had a low risk of disease progression at a median follow-up of around 6 years.

Although there is an accumulation of data on the natural history of chronic hepatitis B among untreated people from Asian, European, and North American studies,[29] data from Africa are scarce. We previously reported the incidence of cirrhosis and hepatocellular carcinoma in a cohort of individuals with chronic hepatitis B in The Gambia;[19] however, the analysis of this cohort did not differentiate between participants who were eligible and ineligible for treatment at baseline. To the best of our knowledge, the current analysis is the first to report medium-term mortality rate and clinical outcomes among people with chronic hepatitis B who were

	Participants reassessed for secondary outcome
Age, years	41 (37–48)
Sex	
Female	223/544 (41%)
Male	321/544 (59%)
Ever drank alcohol	33/544 (6%)
Median BMI, kg/m²	24·2 (20·8–28·0)
BMI	
<25·0 kg/m²	296/531 (56%)
25·0–29·9 kg/m²	151/531 (28%)
≥30·0kg/m²	84/531 (16%)
Waist circumference, cm	87 (78–94)
Waist circumference >94 cm for male participants and >80 cm for female participants	226/537 (42%)
Blood pressure	
Normal	164/542 (30%)
SBP 130–139 mm Hg or DBP 80–89 mm Hg	141/542 (26%)
SBP ≥140 mm Hg or DBP ≥90 mm Hg	237/542 (44%)
Liver steatosis on ultrasound	37/544 (7%)
Median liver stiffness, kPa*	5·1 (4·2–6·1)
Liver stiffness, kPa*	
<7·9 kPa (F0–1)	504/540 (93%)
7·9–9·4 kPa (F2–3)	23/540 (4%)
≥9·5 kPa (F4)	13/540 (2%)
ALT, IU/L	20 (14–28)
ALT ≥40 IU/L	49/541 (9%)
AST, IU/L	26 (21–33)
γ-Glutamyl transferase, IU/L	27 (19–36)
Platelets, 10⁹ cells per L	182 (152–219)
HBeAg-positive	4/542 (1%)
HBV DNA	
Undetectable	224/537 (42%)
50–1999 IU/mL	177/537 (33%)
2000–19 999 IU/mL	106/537 (20%)
20 000–199 999 IU/mL	25/537 (5%)
≥200 000 IU/mL	5/537 (1%)
(Table 3 continues in next column)	
(Continued from previous column)	
Median log_{10} qHBsAg, IU/mL	3·8 (3·2–4·1)
HIV-positive	10/544 (2%)
HCV-positive	3/544 (1%)
HDV-positive	3/544 (1%)
Phase of natural history	
Lost HBsAg	23/542 (4%)
HBeAg-positive chronic infection	2/542 (<1%)
HBeAg-positive chronic hepatitis	2/542 (<1%)
HBeAg-negative chronic infection	348/542 (64%)
HBeAg-negative chronic hepatitis	17/542 (3%)
HBeAg-negative grey zone (ie, increased ALT)	28/542 (5%)
HBeAg-negative grey zone (ie, increased viral load)	109/542 (20%)
Compensated cirrhosis	13/542 (2%)
Decompensated cirrhosis	0/542
Hepatocellular carcinoma	0/542
Eligible for EASL 2012 criteria	16/544 (3%)
Eligible for EASL 2017 criteria	18/544 (3%)

Data are n/N (%) or median (IQR). ALT=alanine aminotransferase. AST=aspartate aminotransferase. DBP=diastolic blood pressure. EASL=European Association for the Study of the Liver. HBV=hepatitis B virus. HCV=hepatitis C virus. HDV=hepatitis D virus. qHBsAg=quantitative HBsAg. SBP=systolic blood pressure. *Excludes one participant without a measurement and three participants with unreliable measurements.

***Table 3*: Characteristics of participants who had a full liver reassessment in 2018–23**

ineligible for treatment at baseline in Africa. Such data are valuable to assess whether Africans with chronic hepatitis B who do not meet treatment eligibility criteria should receive treatment or not. One study from Ethiopia analysed the 5-year clinical outcomes of a hospital-based cohort of people with chronic hepatitis B on treatment.[30] The study was, however, focused on the effects that tenofovir disoproxil fumarate had on survival and liver fibrosis regression and did not specifically report the rate of liver disease progression among untreated people with chronic hepatitis B.

We estimated that, in The Gambia, the ASMRs among people (aged ≥30 years) living with chronic hepatitis B who were ineligible for treatment at diagnosis were similar to those observed in the Gambian general population for both sexes. Moreover, most deaths in our cohort were not liver-related, suggesting a low liver-related mortality risk in individuals with chronic hepatitis B in Africa who are ineligible for treatment. However, the duration of our follow-up was modest and we could have therefore underestimated liver-related mortality in this population. Further long-term follow-up data will be informative.

No hepatocellular carcinoma-related deaths were identified in this analysis. In Taiwan, after a 13-year follow-up, the REVEAL-HBV study similarly found a low risk of hepatocellular carcinoma (<0·1%) among inactive carriers of chronic hepatitis B,[31] and a systematic review that analysed inactive carriers with untreated chronic hepatitis B exclusively from east Asia, Europe, or North America also found a low hepatocellular carcinoma incidence.[32]

We chose all-cause mortality and not liver-related mortality as our primary outcome because establishing cause of death in Africa is difficult due to few diagnostic tools, a high number of deaths occurring at the home, the absence of routine autopsy, and not having any fully reliable nationwide cancer registries.[23] Nevertheless, we made the best efforts to collect data on causes of death by conducting verbal autopsy with two trusted relatives and by systematically reviewing clinical records and National Cancer Registry data for participants.

	Participants (n/N [%])	Crude odds ratio (95% CI)	p value
Overall	36/544 (7%)	..	..
Age at baseline	..	..	0·53
<30 years	5/86 (6%)	1 (ref)	..
30–39 years	18/274 (7%)	1·35 (0·49–3·69)	..
40–49 years	10/107 (9%)	1·68 (0·55–5·13)	..
≥50 years	3/77 (4%)	0·67 (0·15–2·92)	..
Sex	..	..	0·19
Female	11/223 (5%)	1 (ref)	..
Male	25/321 (8%)	1·63 (0·78–3·38)	..
Recruitment origin	..	..	0·80
Community-based screening	14/222 (6%)	1 (ref)	..
Blood bank screening	13/170 (8%)	1·23 (0·56–2·69)	..
Historical cohort	9/152 (6%)	0·93 (0·39–2·21)	..
Phase of natural history	..	..	0·23
HBeAg-negative chronic infection	26/457 (6%)	1 (ref)	..
HBeAg-positive chronic infection	1/8 (13%)	2·36 (0·28–19·97)	..
HBeAg-positive chronic hepatitis	1/4 (25%)	5·52 (0·55–54·97)	..
HBeAg-negative chronic hepatitis	0/2	<0·01 (NA)	..
HBeAg-negative grey zone (ie, increased ALT)	3/39 (8%)	1·38 (0·39–4·78)	..
HBeAg-negative grey zone (ie, increased viral load)	3/18 (17%)	3·31 (0·90–12·18)	..
Cirrhosis	0/3	<0·01 (NA)	..
HBeAg-negative chronic infection	..	..	0·27
Viral load undetectable and LSM <7·9	14/198 (7%)	1 (ref)	..
Viral load detectable or LSM ≥7·9	12/259 (5%)	0·63 (0·28–1·41)	..
HIV-positive	..	..	0·67
No	35/529 (7%)	1 (ref)	..
Yes	1/10 (10%)	1·56 (0·19–12·73)	..
HCV-positive	..	..	NA
No	36/532 (7%)	1 (ref)	..
Yes	0/3	<0·01 (NA)	..
HDV-positive	..	..	NA
No	36/540 (7%)	1 (ref)	..
Yes	0/3	<0·01 (NA)	..
METAVIR score (per biopsy or LSM)	..	..	0·046
F0–1	31/498 (6%)	1 (ref)	..
F2–3	4/23 (17%)	3·17 (1·01–9·89)	..
F4	0/4	<0·01 (NA)	..
(Table 4 continues in next column)			
(Continued from previous column)			
APRI	..	..	..
<2·0	35/518 (7%)	1 (ref)	NA
≥2·0	0/1	<0·01 (NA)	..
<0·65*	29/444 (7%)	1 (ref)	0·64
≥0·65	6/75 (8%)	1·24 (0·49–3·10)	..
<0·5	22/361 (6%)	1 (ref)	0·37
≥0·5	13/158 (8%)	1·38 (0·67–2·81)	..
FIB-4	..	..	NA
<3·25	35/511 (7%)	1 (ref)	..
≥3·25	0/8	<0·01 (NA)	..
HBV DNA	..	..	0·020*
<2000 IU/mL	27/472 (6%)	1 (ref)	..
2000–19 999 IU/mL	2/12 (17%)	3·29 (0·68–15·79)	..
≥20 000 IU/mL	3/16 (19%)	3·80 (1·02–14·15)	..
HBeAg	..	..	0·16
Negative	32/519 (6%)	1 (ref)	..
Positive	2/12 (17%)	3·04 (0·63–14·48)	..
qHBsAg	..	..	..
<3 $\log_{10}$	1/49 (2%)	1 (ref)	..
≥3 $\log_{10}$	15/228 (7%)	3·38 (0·43–26·21)	..
ALT	..	..	0·58
<40 IU/L	32/489 (7%)	1 (ref)	..
≥40 IU/L	4/46 (9%)	1·36 (0·45–4·03)	..
BMI	..	..	0·77
<25 kg/m²	25/362 (7%)	1 (ref)	..
≥25 kg/m²	11/176 (6%)	0·89 (0·43–1·87)	..
High blood pressure (SBP ≥130 or DBP ≥80)	..	..	0·23
No	15/307 (5%)	1 (ref)	..
Yes	12/157 (8%)	1·61 (0·73–3·53)	..

Composite outcome was becoming newly eligible for antiviral therapy, having an increase in liver fibrosis of at least one stage, developing hepatic decompensation, or developing hepatocellular carcinoma. For a categorical variable with three or more categories that showed a dose–response relationship with the outcome, we used a test for trend. ALT=alanine aminotransferase. APRI=aspartate aminotransferase-to-platelet ratio index. FIB-4=Fibrosis-4 Index for Liver Fibrosis. DBP=diastolic blood pressure. HBV=hepatitis B virus. HCV=hepatitis C virus. HDV=hepatitis D virus. LSM=liver stiffness measurement. METAVIR=Meta-analysis of Histological Data in Viral Hepatitis. qHBsAg=quantitative HBsAg. SBP=systolic blood pressure. *Cutoff derived from Johannessen and colleagues.[28]

Table 4: **Risk factors for liver-disease progression**

In our analysis, an APRI of 2·0 or more, a biomarker of cirrhosis based on liver enzyme and platelet count, was an independent predictor of all-cause mortality, suggesting possible missed diagnosis of cirrhosis at enrolment. However, we previously reported a low performance of APRI for the diagnosis of cirrhosis in people with chronic hepatitis B in Africa, where clinical conditions (eg, malaria) can cause a decrease in platelets, which increases APRI.[28] Therefore, we used a lower cutoff of 0·65 or more, which was identified after conducting an individual participant data meta-analysis of 3548 people with chronic hepatitis B living in eight sub-Saharan African countries.[28] We found that this lower APRI cutoff, as well as the newly WHO-recommended cutoff of 0·5 or more for treatment eligibility,[33] were both associated with all-cause mortality,

even in the sensitivity analysis assuming participants lost to follow-up were alive at the last survival follow-up.

Hypertension was also an independent risk factor of all-cause mortality after adjusting for sex and age, highlighting the neglected burden of hypertension in Africa.[34] By contrast, a BMI of 25 kg/m² or more was associated with a reduced risk of death. Increased BMI in LMICs is more likely to mean increased socioeconomic status and access to health care.[35] The association between mortality and positive HCV serology in our cohort was in line with the well established, multiplicative effect of HBV and HCV co-infection on liver complications and emphasises the need for HCV screening and treatment interventions in Africa, where access to direct-acting antivirals is unfortunately low.

In our analysis, a small proportion of people had disease progression, with some progressing to cirrhosis according to liver stiffness measurement and some becoming newly eligible for antiviral therapy. We found that HBV DNA of 20 000 IU/mL or more was associated with an increased risk of disease progression, in line with a 2023 systematic review that reported a dose–response relationship between HBV DNA at baseline and the incidence of liver-related complications and deaths in people with chronic HBV infection.[29,33]

We cannot exclude the notion that the EASL treatment criteria applied in this analysis, which have been exclusively developed from Asian, European, and North American studies, are not fully applicable to the African population. At baseline and reassessment, only a small proportion of participants with chronic hepatitis B enrolled in this cohort was eligible for treatment according to either the 2012 or 2017 EASL criteria. This small proportion could be due to the fact that participants were recruited mainly in communities, outside of health facilities, and so were more likely to have less severe disease. As previously shown, the proportion of HBsAg-positive individuals who are eligible for treatment in the community is lower than that among patients seen in hospitals, who present with more advanced disease.[36] Yet, liver-related morbidity and mortality in The Gambia is high, which might be attributable to poor diagnosis of HBV infection, little access to treatment for those who are eligible, inadequate management of cirrhosis, and the absence of a hepatocellular carcinoma surveillance programme.[4]

Our findings suggest that regular monitoring of untreated African individuals with chronic hepatitis B is required, that HBV DNA measurement at low cost should be made widely accessible to provide optimal care to individuals with chronic hepatitis B in Africa, and that antiviral therapy could be expanded to people with chronic hepatitis B and a viral load of 20 000 IU/mL or more, irrespective of ALT measurement, as also suggested by a modelling study in South Korea.[37] By contrast, our findings do not provide strong evidence to support a treat-all approach in people living with chronic hepatitis B in Africa. Such an approach has been increasingly debated to simplify the HBV care pathway and to improve retention in care of people living with chronic hepatitis B. However, our analysis showed that after around 6 years of follow-up, a large proportion of untreated participants could be retained in care. Furthermore, we previously found that the treat-all strategy could be effective, but not cost-effective in LMICs.[38] Our analysis indicates that HBV DNA is a key predictor of disease progression so efforts should be made in Africa to implement access to HBV DNA measurement via low-cost reflex HBV viral load testing or alternative accurate biomarkers of HBV DNA.[39]

We acknowledge that our analysis has some limitations. First, the PROLIFICA study mainly analysed inactive HBV carriers during a medium-term follow-up period, and so cannot exclude any long-term beneficial effects of antiviral therapy for the prevention of liver fibrosis and hepatocarcinogenesis in this population. Our results will need to be substantiated after a longer follow-up duration. Second, despite active tracing, some participants were lost to follow-up. However, we found that fewer people were lost to follow-up than was reported among people living with HIV in Africa after 4 years.[40] Loss to follow-up is a common issue in studies conducted in Africa due to the long distance to clinics, structural poverty, and lack of awareness. As a result, we might have underestimated clinical outcomes and all-cause mortality in our cohort. However, we conducted post-hoc sensitivity analyses assuming that all participants who were lost to follow-up were either alive at the last survival follow-up or died after the last observation. We acknowledge that the assumption that participants died after the last observation is likely to be inaccurate, particularly considering the young mean age of those lost to follow-up. Third, although The Gambia has a national cancer registry, a previous study found that its completeness was suboptimal.[23] Therefore, we might have underestimated incidence of hepatocellular carcinoma. Fourth, we conducted a single liver reassessment due to resource constraints, which suggests that participants classified in a chronic HBV infection phase could have been in a quiescent period of chronic hepatitis phase. Finally, we acknowledge that our population might not be representative of other African populations, such as those who are hospital-based, those with more severe disease, and those who have increased risk of progression of liver disease due to excessive alcohol consumption or metabolic disorders.

Our findings suggest that, in The Gambia, the 6-year risks of death and hepatocellular carcinoma in people with chronic hepatitis B who are ineligible for treatment are low. This finding will need to be substantiated in research with a longer follow-up period. However, there is a small risk of disease progression, including cirrhosis. Further data are needed to support our results and improve knowledge of this neglected disease in Africa.

Contributors

GN, YS, MM, RN, UD'A, MT, and ML conceptualised the analysis. ML and YS designed the analysis. ML acquired funding. GN, DL, GL, PI, ML, SB, RB, and EV-Q assessed participants. GN, DL, SB, RB, IM, LB, AC, SD, QB-L, GL, PH, PI, YH, EV-Q, SC, GC, OB, GL, CT-K, MM, RN, IC, and ML collected data. GN, YS, LB, and ML curated data. YS conducted the formal analysis, with input from ML. AC, IC, GL, CT-K, SD, and SC contributed to the virological analysis. GN, YS, and ML accessed and verified the underlying data and wrote the original draft of the manuscript. All authors reviewed and edited the final draft of the manuscript, had full access to all the data in the analysis, and had final responsibility for the decision to submit for publication.

Declaration of interests

ML, YS, MT, and GN received research funding and consultancy fees from Gilead Sciences and Abbott. ML received consultancy fees from Cepheid and Abbott and is the recipient of the funding. YS received research materials from Fujirebio and Abbott. GC is an employee of Abbott. PI received consultancy fees from Gilead, AbbVie, and ViiV Healthcare. All other authors declare no competing interests.

Data sharing

Deidentified anonymous participant supporting our findings and additional, related documents (ie, informed consent forms, information sheet, and protocol) are available from the corresponding author upon request from the date of publication.

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