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Clinical characteristics and outcomes of patients with cirrhosis and hepatocellular carcinoma in The Gambia, west Africa: a prospective cohort study

Gibril Ndow*, Erwan Vo-Quang*, Yusuke Shimakawa*, Amie Ceesay, Saydiba Tamba, Harr F Njai, Lamin Bojang, Charlotte Hateley, Yuki Takao, Emmanuel Opoku, Zakary Warsop, Patrick Ingiliz, Umberto D'Alessandro, Isabelle Chemin, Maimuna Mendy, Mark Thursz, Ramou Njie, Maud Lemoine



Summary

Background Chronic liver disease is a major cause of premature death in sub-Saharan Africa. Efficacy of antiviral therapy among patients with hepatitis B virus (HBV)-related cirrhosis is not well established in Africa. We described the clinical characteristics and outcomes of patients with cirrhosis and hepatocellular carcinoma in The Gambia and assessed the impact of tenofovir disoproxil fumarate (TDF) on survival of HBV-infected patients with cirrhosis.

Methods In this prospective cohort study, we followed up adults who were consecutively diagnosed with cirrhosis or hepatocellular carcinoma between 2012 and 2015 in The Gambia, west Africa. Patients with chronic HBV infection and cirrhosis, without hepatocellular carcinoma, were offered TDF. Primary outcome was overall survival. To determine the effect of TDF on survival, we performed a Cox proportional hazard regression model with inverse probability of treatment weighting (IPTW) based on propensity score.

Findings Of 529 patients enrolled in this study, 336 patients (252 with hepatocellular carcinoma and 84 with cirrhosis) were analysed. Patients were predominantly male (253 [75%] men and 83 [25%] women), with a median age of 42 years (IQR 33–55). 276 (84%) of 327 of patients with data were positive for HBV biomarkers, 31 (10%) of 311 were positive for hepatitis C virus antibodies, and 22 (10%) of 223 were positive for hepatitis D virus antibodies. 64% of patients with hepatocellular carcinoma had multifocal tumour, with a median size of 7.5 cm (IQR 5.4–10.8). 173 patients with hepatocellular carcinoma and 70 patients with cirrhosis were included in the survival analysis. Median survival was 1.5 months (95% CI 1.1–2.0) in patients with hepatocellular carcinoma and 17.1 months (11.2–24.0) in patients with cirrhosis (log-rank $p < 0.0001$). In patients with hepatocellular carcinoma, ascites (hazard ratio [HR] 1.78, 95% CI 1.21–2.60), partial or complete portal thrombosis (HR 2.61, 1.58–4.30), and platelet count (HR 1.80, 1.19–2.70) were independent predictive factors of mortality at baseline. In HBV-infected patients with cirrhosis, median turnaround time between cirrhosis diagnosis and TDF initiation was 4.9 months (IQR 3.2–7.3). In IPTW analysis, TDF treatment was associated with improved survival in patients with HBV-related cirrhosis (adjusted HR 0.14, 0.06–0.34; $p < 0.0001$).

Interpretation These results highlight poor survival of patients with cirrhosis or hepatocellular carcinoma as well as the effectiveness of TDF in reducing the premature mortality of patients with cirrhosis and HBV infection. Interventions for early diagnosis and treatment of cirrhosis as well as screening programmes for hepatocellular carcinoma are urgently required in Africa.

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Introduction

Cirrhosis and liver cancer are leading causes of death globally, accounting for 1.3 million and 830 000 annual deaths, respectively.^{1,2} Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are major causes of cirrhosis and hepatocellular carcinoma, especially in sub-Saharan Africa where the prevalence of these infections is high, and access to curative treatments of advanced liver disease is scarce.³

West Africa has the highest burden of hepatocellular carcinoma in the WHO Africa region, and hepatocellular

carcinoma is one of the most common cancers in west African countries.⁴

HBV is well established as a major cause of cirrhosis and hepatocellular carcinoma in The Gambia^{5,6} and other African countries.³ However, survival of patients with cirrhosis or hepatocellular carcinoma has not been well documented in sub-Saharan Africa, and the efficacy of antiviral therapy on survival in HBV-infected patients with cirrhosis is unknown in the region.

In sub-Saharan Africa, a region with limited access to curative therapy for cirrhosis and hepatocellular

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For the French translation of the abstract see [Online](#) for appendix 1

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Research in context

Evidence before this study

In sub-Saharan Africa, cirrhosis and hepatocellular carcinoma are a major cause of premature death and are mainly attributable to viral hepatitis B and C. Yet, prevention, surveillance, and treatment programmes for cirrhosis and hepatocellular carcinoma are almost non-existent in sub-Saharan Africa and clinical characteristics and outcomes of patients with these disorders have not been well documented.

We searched MEDLINE and Embase for articles written in English or French and published before July, 2022, with terms incorporating "cirrhosis", "HCC", and "Africa". Published studies, including key studies from The Gambia, were mainly focused on aetiology of hepatocellular carcinoma and cirrhosis. Only two studies reported survival of patients with hepatocellular carcinoma in The Gambia (Bah et al, 2011) and across eight countries in Africa (Yang et al, 2017). We did not find papers reporting the efficacy of hepatitis B virus (HBV) antiviral therapy in patients with cirrhosis in sub-Saharan Africa, except one pilot study from Ethiopia reporting antiviral effect of tenofovir disoproxil fumarate (TDF) at 1 year in patients with chronic hepatitis B (Desalegn et al, 2018). Only one study reported the benefits of TDF, sorafenib, and trans-arterial chemoembolisation in 46 patients with hepatocellular carcinoma in Ethiopia (Sultan et al, 2020). The need for urgent action to improve the prevention and management of hepatocellular carcinoma in sub-Saharan Africa has recently been emphasised.

Added value of this study

There are two novel elements of this study: first, we collected longitudinal data and estimated the survival rate in patients with hepatocellular carcinoma and in patients with cirrhosis

without hepatocellular carcinoma, and second, we assessed the effectiveness of TDF on survival in HBV-positive patients with cirrhosis in a real-life African setting.

We analysed the clinical characteristics of patients with hepatocellular carcinoma and cirrhosis in a prospective cohort using high-quality diagnostic tests (including liver histology in a subgroup of patients) in The Gambia, west Africa. As previously shown in African countries, our study found that viral hepatitis, especially HBV infection, remains the main cause of these two disorders, and that patients present at very advanced disease stages in The Gambia.

We reported poor survival in both patients with hepatocellular carcinoma (median 1.5 months) and those with cirrhosis (median 17.1 months) and demonstrated that antiviral treatment with TDF is associated with improved survival in HBV-infected patients with cirrhosis (adjusted hazard ratio 0.14, 95% CI 0.06–0.34; $p < 0.0001$). Importantly, our study highlighted a long median turnaround time between diagnosis of cirrhosis and TDF initiation of 4.9 months, with a high rate of patients who did not come back to the clinic before treatment initiation.

Implications of all the available evidence

Early diagnosis and antiviral treatment initiation are urgently required in HBV-infected patients with cirrhosis in sub-Saharan Africa to reduce HBV-related mortality. Scaling up early diagnosis and treatment programmes for HBV-infected patients with cirrhosis and hepatocellular carcinoma in Africa are urgently needed. This should be underlined in the forthcoming updated WHO guidelines for the prevention and management of chronic hepatitis B.

carcinoma, including surgical resection or liver transplantation,⁷ the clinical relevance of implementing early diagnosis and treatment programmes for cirrhosis or hepatocellular carcinoma in people known to have viral hepatitis remains unclear.

The Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) programme,⁸ the first screen-and-treat programme for people with HBV mono-infection in sub-Saharan Africa, was established in 2011 in west Africa. As part of this programme, we identified risk factors for liver disease severity, evaluated the performance of inexpensive and simple diagnostic tools, and developed simple algorithms for the management of chronic HBV infection in Africa.^{9,10}

In this study, we prospectively followed up patients with advanced liver disease to assess: (1) the characteristics, causes, and clinical outcomes of patients with cirrhosis or hepatocellular carcinoma, and (2) the effectiveness of antiviral therapy using tenofovir disoproxil fumarate (TDF) on survival of HBV-infected patients with cirrhosis in The Gambia.

Methods

Study population

In June, 2012, the PROLIFICA programme recruited consecutive patients with advanced liver disease to study biomarkers of cirrhosis and hepatocellular carcinoma and to assess the association between birth order and risk of hepatocellular carcinoma.^{11,12} The study was hosted at the PROLIFICA liver clinic in the Medical Research Council Unit The Gambia (MRCG), which was the only health-care facility providing diagnosis of cirrhosis and hepatocellular carcinoma in The Gambia. Using the referral system established by the Gambia National Cancer Registry, individuals with suspected cirrhosis or hepatocellular carcinoma were systematically referred to the liver clinic, allowing the study to have representative samples of patients with advanced liver disease in the country. The study was approved by the Gambia Government/MRCG Joint Ethics Committee. All patients provided written informed consent.

According to the inclusion criteria, eligible patients were aged 15 years or older and had cirrhosis hepatocellular carcinoma, or both.

Cirrhosis was defined either histologically (F4 Metavir score) or in patients without biopsy, using transient elastography (liver stiffness measurement ≥ 9.5 kPa; Fibroscan402, Echosens, France). A cutoff for LSM of 9.5 kPa had a 100% sensitivity and 89% specificity to indicate cirrhosis diagnosed by histopathology in this Gambian cohort.¹⁰ Liver decompensation (jaundice, ascites, encephalopathy, or variceal bleeding) was clinically ascertained. Patients with cirrhosis had an ultrasound every 6 months to screen for hepatocellular carcinoma.

Hepatocellular carcinoma was confirmed either histologically in patients with biopsy, or clinically using one of the following criteria: (1) confirmed focal liver lesion of 2 cm or larger consistent with hepatocellular carcinoma on ultrasound and alfa-fetoprotein (AFP) of 200 ng/mL or higher, irrespective of cirrhosis; (2) liver cirrhosis with suspected liver lesion of 2 cm or larger suggestive of hepatocellular carcinoma, irrespective of AFP level; or (3) focal liver lesion suggestive of hepatocellular carcinoma without documented size and AFP of 200 ng/mL or higher.¹³ For the quality of this analysis, we excluded patients with AFP higher than 200 ng/mL but no visible mass on ultrasound. Contrast CT scan was not accessible during the study period.

Clinical assessment

Following the provision of written informed consent, patients completed demographic, environmental, and clinical questionnaires and had a physical examination, fasting LSM using transient elastography (Fibroscan402), a non-contrast abdominal ultrasound, and blood and urine sample collection. Unless contraindicated, a liver biopsy of both non-tumoural and tumoural tissue was performed in patients with suspected mass on ultrasound.

Laboratory analysis

All patients had standard blood tests (biochemistry and full blood count) and AFP measurement (ARCHITECT i1000 SR; Abbott Park, IL, USA), hepatitis B surface antigen (HBsAg; Alere Determine; Abbott), HCV antibody (ARCHITECT; Abbott), and human immunodeficiency virus type 1 and 2 (HIV-1 and 2) antibodies (Genscreen ULTRA HIV Ag-Ab; BioRad; Marnes-la-Coquette, France). Aflatoxin B1 exposure was assessed by examining mutation of the p53 tumour suppressor gene (p53249S) in cell-free DNA.

HBsAg-positive patients were also tested for hepatitis B e antigen (HBeAg; ETI-EBK-PLUS; Diasorin, Saluggia, Italy) and anti-hepatitis D virus (HDV; ETI-AB-DELTAK-2; Diasorin). HBV DNA level was quantified using an in-house real-time PCR assay (detection limit 50 IU/mL) that was validated against a commercial quantitative PCR (qPCR; Abbott).¹⁴ HBV genotype was determined in HBsAg-positive samples with detectable viraemia. Prothrombin time was not

routinely available. As a result, we were unable to estimate the severity of cirrhosis based on Child-Pugh or MELD scores. To estimate the severity of hepatocellular carcinoma, we measured albumin-bilirubin (ALBI) and platelet-ALBI (P-ALBI) scores.^{15,16}

Clinical management

Radiological or surgical treatment for hepatocellular carcinoma was unavailable in The Gambia during the study period; only palliative care was offered to patients with this disorder.¹⁷ In the absence of contraindications, patients with ascites were given oral furosemide 40–80 mg/day or paracentesis without albumin infusion, or both. Spontaneous bacterial peritonitis was treated with antibiotics as per international guidelines.¹⁸ At that time, there was no endoscopy in The Gambia, thus endoscopic intervention was not routinely available for patients at risk of variceal bleeding. Vasopressin or its analogues were unavailable in The Gambia during the study period.

Patients with HBV infection and cirrhosis were offered free oral TDF 300 mg, one pill per day, adjusted to the estimated glomerular filtration rate. TDF was initiated at a subsequent visit to the clinic, once the results of HBsAg, anti-HIV antibodies, HBV DNA, and creatinine levels were available using the blood samples collected at the first visit. Patients lost to follow-up in our study were unlikely to receive antiviral treatment since the PROLIFICA liver clinic was the only facility within The Gambia where nucleos(t)ide analogues were prescribed and dispensed for patients with HBV mono-infection. Patients who received TDF were seen every 3 months for TDF supply, and adherence was assessed using the Morisky scale.¹⁹ HCV antiviral treatment was not available in The Gambia at the time of the study. Appendix 2 (p 1) summarises the clinical practice available in The Gambia for managing decompensated cirrhosis and hepatocellular carcinoma during the study period.

Follow-up and survival analysis

The total follow-up duration for the study was 24 months. Overall survival was ascertained by clinic attendance among patients retained to care or by scheduled telephone calls in January, 2015, and July, 2019, for patients who did not come back to the clinic. Those who were confirmed to be alive at the follow-up telephone call in 2019, irrespective of whether they visited the liver clinic, were assumed to have survived until the day of the telephone call. Date, place, and potential causes of death were confirmed by reviewing case notes for patients who died in hospital or by verbal autopsy with close relatives for patients who died elsewhere.

Statistical analysis

Categorical variables were described as frequency and percentage and compared using χ^2 test or Fisher's exact

See Online for appendix 2

test. Continuous variables were examined as mean or median and compared using the *t* test or, in cases of non-normality, Mann-Whitney test. The survival curves were computed using the Kaplan-Meier method and compared with the log-rank test. Among patients with hepatocellular carcinoma, we assessed factors associated with mortality using univariate and multivariable Cox proportional hazards regression models.

In patients with HBV infection and cirrhosis, we performed weighted propensity score analysis to control for differences in baseline characteristics. A propensity score for each patient was calculated as the predicted probability of TDF from multivariable logistic regression that included confounding factors associated with survival: age, gender, decompensated cirrhosis, HBeAg status, total bilirubin, albumin, HBV DNA, creatinine, and platelet counts. We generated the propensity model using the inverse probability of treatment weighting (IPTW) approach. A Cox proportional hazards model was used for weighted analyses to calculate weighted hazard ratios (HRs) and *p* values. To check the potential bias related to censoring, we did a post-hoc sensitivity analysis to estimate HRs according to three scenarios: assuming all censored patients (due to lost to follow-up) were alive at 24 months (scenario 1); assuming all censored patients died immediately after the last observation time (scenario 2); and assuming half of the censored patients died immediately after the last observation

time and the remaining half were alive at 24 months (scenario 3). We also estimated the HR at 3 months.

All analyses were performed using RStudio statistical software (version 1.4.869) and statistical significance was based on a two-sided test at 5% significance level.

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

Between June, 2012, and July, 2015, 529 consecutive patients aged 15 years or older with suspected cirrhosis or hepatocellular carcinoma were enrolled in the study. Of these, 193 were excluded from this analysis because of incomplete baseline data (*n*=119; including 69 of 119 patients with elevated AFP but no focal lesion on ultrasound and no evidence of cirrhosis) or diagnosis other than cirrhosis or hepatocellular carcinoma (*n*=74). Among the 336 patients included in this analysis, 252 had hepatocellular carcinoma and 84 had cirrhosis without hepatocellular carcinoma (figure 1).

The study population was predominantly male (*n*=253/336, 75%), with a median age of 42 years (IQR 33–55) and median BMI of 19.6 kg/m² (IQR 17.6–22.0; table 1). About half of the patients (172/312, 55%) had a WHO performance status of 2 or higher at diagnosis. Only 34 (10%) of 330 reported occasional alcohol intake but none acknowledged excessive intake. Markers for viral hepatitis were positive in 317 (97%) of 327 patients: HBsAg (223/327, 62%), anti-HCV antibodies (31/311, 10%), and anti-HDV antibodies (22/223, 10%). Occult HBV infection was found in 53 (51%) of 104 HBsAg-negative patients. 58 (57%) of 102 patients had aflatoxin exposure, with no significant differences between patients with cirrhosis and hepatocellular carcinoma.

Patients with hepatocellular carcinoma presented at late stage, with 129 (64%) of 202 patients having multifocal tumour. The median tumour size was 7.5 cm (5.4–10.8) and median AFP was 1986 ng/mL (315–8000). Two-thirds (66%) of patients with hepatocellular carcinoma were positive for HBsAg. Among the 84 patients with cirrhosis and without hepatocellular carcinoma, 57 (68%) had decompensated cirrhosis at presentation, mainly with ascites (48%). Similar to patients with hepatocellular carcinoma, 63 (75%) were HBsAg-positive, of whom nine (14%) were positive for anti-HDV antibodies.

Among the 252 patients with hepatocellular carcinoma at baseline, 79 (31%) were excluded from the survival analysis (they did not come back to the clinic and could not be contacted by telephone calls), and 173 (69%) were included in the analysis. Characteristics were similar between patients with survival data and those without survival data, except for AFP level, which was higher in

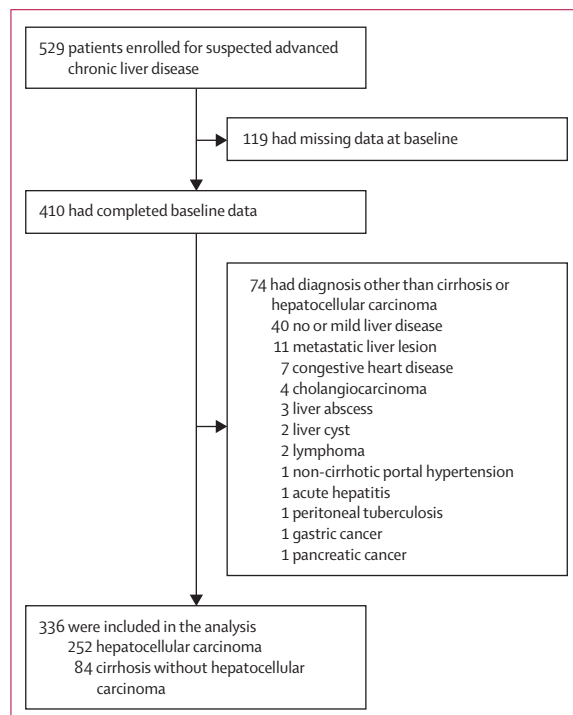


Figure 1: Trial profile

	Overall (n=336)	Hepatocellular carcinoma (n=252)	Cirrhosis without hepatocellular carcinoma (n=84)	p value*
Age, years	42 (33–55)	43 (35–56)	36 (28–47)	<0.0001
Gender	0.47
Male	253/336 (75%)	192/252 (76%)	61/84 (73%)	..
Female	83/336 (25%)	60/252 (24%)	23/84 (27%)	..
Local ethnic group	NA
Aku	1/326 (<1%)	1/244 (<1%)	0	..
Balanta	2/326 (1%)	1/244 (<1%)	1/82 (1%)	..
Bambara	3/326 (1%)	3/244 (1%)	0	..
Fula	59/326 (18%)	42/244 (17%)	17/82 (21%)	..
Jola	41/326 (13%)	25/244 (10%)	16/82 (20%)	..
Karoninka	1/326 (<1%)	0	1/82 (1%)	..
Mandinka	96/326 (29%)	73/244 (30%)	23/82 (28%)	..
Manjago	11/326 (3%)	8/244 (3%)	3/82 (4%)	..
Serahule	22/326 (7%)	19/244 (8%)	3/82 (4%)	..
Serere	12/326 (4%)	9/244 (4%)	3/82 (4%)	..
Wolof	67/326 (21%)	56/244 (23%)	11/82 (13%)	..
Others	11/326 (3%)	7/244 (3%)	4/82 (5%)	..
Performance status 0/1/2/3/4	15.7%/29.2%/25.3%/17.9%/11.9%	8.6%/30.6%/28.0%/18.5%/14.3%	36.3%/25.0%/17.5%/16.2%/5.0%	<0.0001
0	49/312 (15.7%)	20/232 (8.6%)	29/80 (36.3%)	..
1	91/312 (29.2%)	71/232 (30.6%)	20/80 (25.0%)	..
2	79/312 (25.3%)	65/232 (28.0%)	14/80 (17.5%)	..
3	56/312 (17.9%)	43/232 (18.5%)	13/80 (16.2%)	..
4	37/312 (11.9%)	33/232 (14.3%)	4/80 (5.0%)	..
Current or past smoking history	162/330 (49%)	126/248 (51%)	36/82 (44%)	0.28
Alcohol intake (any)	34/330 (10%)	23/248 (9%)	11/82 (13%)	0.28
BMI (kg/m ²)	19.6 (17.6–22.0)	19.2 (17.4–21.3)	21.2 (18.2–24.3)	0.0025
Decompensated cirrhosis	57/336 (17%)	NA	57/84 (68%)	..
Ascites	130/318 (41%)	91/237 (38%)	39/81 (48%)	0.12
Variceal bleeding	22/329 (7%)	17/246 (7%)	5/83 (6%)	0.78
Hepatic encephalopathy	20/325 (6%)	18/243 (7%)	2/82 (2%)	0.10
Jaundice	161/324 (50%)	130/242 (54%)	31/82 (38%)	0.013
Haemoglobin (g/dL)	12.0 (10.0–13.9)	11.8 (9.8–13.7)	12.9 (10.4–14.4)	0.028
Platelets (×10 ⁹ /L)	211 (143–316)	238 (168–342)	140 (100–218)	<0.0001
AST (U/L)	166 (68–312)	209 (104–370)	58 (34–92)	<0.0001
ALT (U/L)	49 (31–89)	58 (36–104)	32 (25–61)	<0.0001
GGT (U/L)	296 (113–495)	339 (182–563)	76 (46–198)	<0.0001
Total bilirubin (μmol/L)	24 (14–54)	25 (15–76)	20 (11–41)	0.051
Creatinine (μmol/L)	68 (55–88)	68 (53–92)	69 (57–84)	0.87
Sodium (mmol/L)	139 (135–142)	138 (135–141)	141 (137–143)	<0.0001
Albumin (g/L)	34 (29–39)	33 (29–38)	35 (28–41)	0.43
ALBI score	−1.90 (−2.46 to −1.33)	−1.87 (−2.33 to −1.38)	−2.00 (−2.88 to −1.24)	0.21
ALBI grade	<0.0001
Grade 1 (≤−2.60)	65/304 (21%)	39/230 (17%)	26/74 (35%)	..
Grade 2 (−2.60 to −1.39)	154/304 (51%)	131/230 (57%)	23/74 (31%)	..
Grade 3 (>−1.39)	85/304 (28%)	60/230 (26%)	25/74 (34%)	..
P-ALBI score	−1.86 (−2.31 to −1.42)	−1.77 (−2.22 to −1.30)	−2.12 (−2.55 to −1.62)	..
P-ALBI grade	<0.0001
Grade 1 (≤−2.53)	43/294 (15%)	22/220 (10%)	21/74 (28%)	..
Grade 2 (−2.53 to −2.09)	63/294 (21%)	44/220 (20%)	19/74 (26%)	..
Grade 3 (>−2.09)	188/294 (64%)	154/220 (70%)	34/74 (46%)	..

(Table 1 continues on next page)

	Overall (n=336)	Hepatocellular carcinoma (n=252)	Cirrhosis without hepatocellular carcinoma (n=84)	p value*
(Continued from previous page)				
Any positive viral hepatitis biomarkers†	317/327 (97%)	235/243 (97%)	82/84 (98%)	>0.99
Any positive HBV biomarkers‡	276/327 (84%)	204/243 (84%)	72/84 (86%)	0.69
Positive HBsAg	223/327 (68%)	160/243 (66%)	63/84 (75%)	0.12
Positive HBsAg and detectable HBV DNA§	186/212 (88%)	140/149 (94%)	46/63 (73%)	<0.0001
Positive HBsAg and undetectable HBV DNA§	26/212 (12%)	9/149 (6%)	17/63 (27%)	<0.0001
HBsAg negative and detectable HBV DNA¶	53/104 (51%)	44/83 (53%)	9/21 (43%)	0.11
Positive HCV Ab	31/311 (10%)	23/227 (10%)	8/84 (10%)	0.87
Positive HDV Ab	22/223 (10%)	13/160 (8%)	9/63 (14%)	0.081
Positive HIV Ab	19/319 (6%)	15/235 (6%)	4/84 (5%)	0.79
Exposure to aflatoxin B1	58/102 (57%)	50/86 (58%)	8/16 (50%)	0.55
HBV parameters
Positive HBeAg	57/212 (27%)	44/149 (30%)	13/63 (21%)	0.48
HBV DNA	1231 (79–158 045)	1650 (112–157 660)	421 (22–122 149)	0.031
HBsAg levels	4642 (1267–9263)	3356 (633–7753)	5551 (2301–9811)	0.15
HBV genotype	0.0075
A	32/128 (25%)	27/81 (33%)	5/47 (11%)	..
A + E	4/128 (3%)	3/81 (4%)	1/47 (2%)	..
E	92/128 (72%)	51/81 (63%)	41/47 (87%)	..
Hepatocellular carcinoma characteristics				
Single mass	..	73/202 (36%)	NA	..
Multiple masses	..	129/202 (64%)	NA	..
Median tumour size (cm)	..	7.5 (5.4–10.8)	NA	..
AFP (ng/mL)	369 (15–5169)	1986 (315–8000)	10 (4–28)	<0.0001
Partial or complete portal thrombosis	<0.0001
No thrombosis	306/336 (91%)	222/252 (88%)	84/84 (100%)	..
Complete thrombosis	7/336 (2%)	7/252 (3%)	0	..
Partial thrombosis	23/336 (7%)	23/252 (9%)	0	..
Histologically confirmed	69/336 (21%)	41/252 (16%)	28/84 (33%)	<0.0001
Data are n/N (%) or median (IQR). AFP=alfa-fetoprotein. ALBI=albumin-bilirubin. ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=gamma-glutamyl transferase. HBeAg=hepatitis B e antigen. HBsAg=Hepatitis B surface antigen. HBV=hepatitis B virus. HCV=hepatitis C virus. HDV=hepatitis D virus. NA=not applicable. P-ALBI=platelet-albumin-bilirubin. *Calculated by Student's t test (or the Mann-Whitney test, if appropriate) and χ^2 test (or Fisher's exact test, if appropriate). †Any positive viral hepatitis biomarkers: HBsAg, HCV antibodies, HDV antibodies, detectable HBV DNA at any level. ‡Any positive HBV biomarkers: HBsAg, detectable HBV DNA at any level. §Detectable HBV DNA among positive HBsAg patients: ≥ 50 IU/mL. ¶Occult HBV infection was defined as negative HBsAg and detectable HBV DNA of 50 IU/mL or higher.				
Table 1: Characteristics of the study population				

patients without survival data (appendix 2 p 3). In patients with hepatocellular carcinoma included in survival analysis (n=173), median follow-up was 1.5 months. At 24 months, four (2%) of 173 patients were lost to follow-up and 164 (95%) of 173 had died. The median survival among patients with hepatocellular carcinoma was 1.5 months (95% CI 1.1–2.0), with survival rates at 3, 6, 12, and 24 months of 30.0%, 14.0%, 6.9%, and 3.4%, respectively.

When analysing the survival according to ALBI and P-ALBI grade scores at baseline, patients with a grade 3 ALBI score had a median survival dramatically lower (0.4 months, 95% CI 0.3–0.8) than those with a grade 1 score (3.0 months [2.1–7.4]) or grade 2 score (2.0 months [1.5–2.5]; p<0.0001; appendix 2 p 10). Similar results were observed when using the P-ALBI score (appendix 2 p 11).

Among 142 (82%) of 173 patients with hepatocellular carcinoma and a known cause of death, 134 (94%) died of liver-related cause, mainly because of variceal bleeding. At baseline, ascites (HR 1.78, 95% CI 1.21–2.60), partial or complete portal thrombosis (HR 2.61, 1.58–4.30), and platelet count (HR 1.80, 1.19–2.70) were independent factors of mortality in patients with hepatocellular carcinoma (table 2).

Among the 84 patients with cirrhosis and no hepatocellular carcinoma at baseline, 14 (17%) were excluded (they did not come back to the clinic and could not be contacted by telephone calls) and 70 were included in survival analysis. Characteristics of patients without survival data and patients with survival data were similar, except for BMI and HBsAg seropositivity, which were lower in patients without survival data than in those with survival data (appendix 2 p 5).

	Number of participants	Person-months at risk	Number of events	Incidence rate (1000 person-months)	Crude analysis		Adjusted analysis	
					HR (95% CI)	p value	HR (95% CI)*	p value
Total	173	537	164	305
Age								
≤35 years	44	98	42	429	1.00 (ref)	0.36	1.00 (ref)	0.89
>35 and ≤50 years	67	213	63	296	0.79 (0.53–1.20)	..	0.97 (0.62–1.50)	..
>50 years	55	204	52	255	0.75 (0.49–1.10)	..	1.03 (0.65–1.60)	..
Gender								
Female	39	102	38	372	1.00 (ref)	0.29	1.00 (ref)	0.57
Male	133	432	125	289	0.82 (0.57–1.20)	..	0.88 (0.56–1.40)	..
Ascites								
No	95	382	89	233	1.00 (ref)	0.0012	1.00 (ref)	..
Yes	68	136	65	478	1.70 (1.20–2.40)	..	1.78 (1.21–2.60)	0.0031
Portal thrombosis								
No	147	500	138	276	1.00 (ref)	0.0036	1.00 (ref)	..
Partial or complete	26	37	26	703	2.00 (1.30–3.00)	..	2.61 (1.58–4.30)	0.0002
Multifocal tumour hepatocellular carcinoma (≥2 nodules)								
No	57	157	55	350	1.00 (ref)	0.83
Yes	85	230	81	352	1.00 (0.74–1.50)
AFP level, ng/mL								
≤200	46	147	43	292	1.00 (ref)	0.73
>200	121	380	115	303	1.10 (0.75–1.50)
Platelets (×10 ⁹ cells per L)								
>150	125	420	118	281	1.00 (ref)	0.032	1.00 (ref)	..
≤150	33	70	32	457	1.60 (1.10–2.30)	..	1.80 (1.19–2.70)	0.0054

AFP=alpha-fetoprotein. HR=hazard ratio. *Multivariable analyses were adjusted for age, gender, ascites, portal thrombosis, and platelets.

Table 2: Univariable and multivariable analyses to identify factors associated with mortality among patients with hepatocellular carcinoma

In patients with cirrhosis included in the survival analysis (n=70), median follow-up was 9.5 months. At 24 months, 13 (23%) of 57 patients were lost to follow-up and 32 (84%) of 70 had died. Survival rate was significantly higher among patients with cirrhosis than in patients with hepatocellular carcinoma ($p<0.0001$; appendix 2 p 12). Among patients with cirrhosis, median survival was 17.1 months (95% CI 11.2–24.0), with survival rates at 3, 6, 12, and 24 months being 79%, 68%, 55%, and 47%, respectively.

We further stratified patients with cirrhosis according to hepatic decompensation. In 21 patients with compensated cirrhosis, median survival was not reached, and the actuarial survival rates at 3, 6, 12, and 24 months were 95%, 95%, 72%, and 72%, respectively (figure 2). In patients with decompensated cirrhosis (n=49), the median survival was 11.3 months (95% CI 4.7–24.0), and survival rates at 3, 6, 12, and 24 months were 72%, 57%, 48%, and 38%, respectively. Survival rates significantly differed between patients with compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma ($p<0.0001$; figure 2).

Among 84 patients with cirrhosis and without hepatocellular carcinoma, 63 (75%) were positive for HBsAg and naive for antiviral therapy. Of these

63 patients with HBV-related cirrhosis, seven (11%) were excluded (did not come back to the clinic and could not be contacted by telephone calls) and 56 were included in survival analysis. Characteristics of patients without survival data and patients with survival data were similar except a higher proportion of patients who did not attend school suggesting a lower education level in patients without survival data than in patients with survival data (data not shown). Of the remaining 56 patients, 31 (55%) attended their second visit and started TDF (treated group) while 25 (45%) were not retained to care and therefore did not initiate TDF but could be reached by telephone to obtain survival data (untreated group).

The main baseline characteristics of the treated and untreated patients are presented in appendix 2 (p 4). The median turnaround time between the first diagnosis of cirrhosis and initiation of TDF in the treated group was 4.9 months (IQR 3.2–7.3). Among the 31 treated patients, no patient was lost to follow-up before 24 months. A total of nine (29%) of 31 had died, mainly (89%) with decompensated cirrhosis that was present at baseline. The vast majority of treated patients reported a high adherence at month 3 (88%), month 12 (90%), and month 24 (83%). At 12 and 24 months

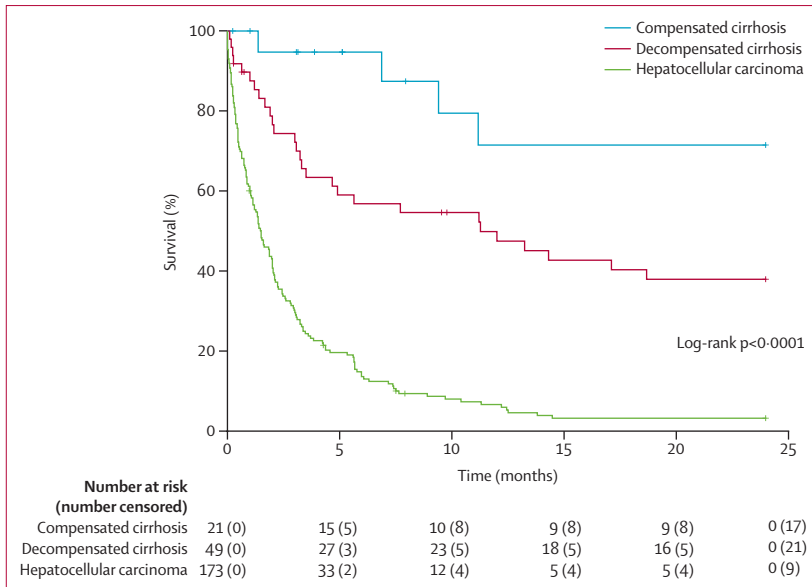


Figure 2: Overall survival in 21 compensated cirrhosis, 49 decompensated cirrhosis, and 173 hepatocellular carcinoma cases

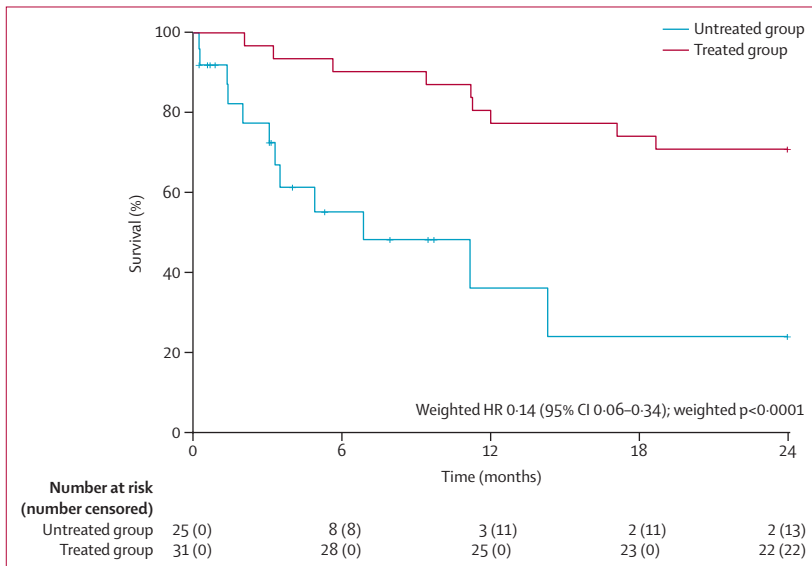


Figure 3: Overall survival in untreated and treated HBsAg-positive patients with cirrhosis without hepatocellular carcinoma (n=56)
HBsAg=Hepatitis B surface antigen.

after treatment initiation, most patients (94%) had viral suppression (appendix 2 p 4).

Among the untreated patients, 11 (44%) of 25 were lost to follow-up before 24 months (including four [16%] before 3 months) and 12 (48%) had died. Untreated patients had a median survival of 6.9 months (95% CI 3.3–6.9) and survival rates at 3, 6, 12, and 24 months of 77.0%, 55.0%, 36.0%, and 24.0%, respectively, compared with a median survival that was not reached and survival rates at 3, 6, 12, and 24 months of 97%, 90%, 77%, and 71%, respectively, among the

treated group (unweighted HR 0.21; 95% CI 0.08–0.52, unweighted $p=0.00084$).

Treated HBV-infected patients with cirrhosis and positive HDV antibodies (n=4) had lower survival than those without HDV antibodies (n=27; $p < 0.0001$; appendix 2 p 13). Among 31 patients treated with TDF, two (6%) developed hepatocellular carcinoma despite good adherence to treatment, viral suppression, and no HDV antibodies.

Baseline characteristics between treated and untreated HBV-positive patients with cirrhosis before and after IPTW analysis are described in appendix 2 (p 8). After IPTW adjustment, TDF was still associated with improved survival (weighted HR 0.14, 95% CI 0.06–0.34, weighted $p < 0.0001$; figure 3).

Results from our sensitivity analyses using both unweighted and weighted approaches showed that the effect of TDF was more or less consistent across all the three scenarios including the most conservative and unlikely scenario (assuming all lost to follow-up survived throughout the study period of 24 months), indicating the robustness of our results despite the substantial difference in rates of loss to follow-up between the two groups. Similar results between survival of treated and untreated patients using both unweighted and weighted approaches were observed at 3 months (appendix 2 p 9).

Discussion

Although causes of cirrhosis and hepatocellular carcinoma have been well established in sub-Saharan Africa,^{3,7} the clinical outcomes of patients with advanced liver disease have been poorly documented and the effectiveness of TDF in improving survival of HBV-infected patients living with cirrhosis in Africa remains unknown.

The Gambia was the first African country to integrate HBV vaccination in its national infant immunisation programme in 1986 and to adopt the hepatitis B birth-dose vaccination in 1997.²⁰ Our study shows that HBV infection still occupies a large proportion of cases of cirrhosis and hepatocellular carcinoma in The Gambia. Most participants with HBV infection (85%) were born before the vaccination programme. As previously reported, we also found that hepatitis D^{6,21} and hepatitis C^{3,22} account for significant proportions of cases of hepatocellular carcinoma and cirrhosis in The Gambia. Yet, they remain neglected diseases; routine HDV and HCV screening is not performed in most African countries, where HDV RNA quantification is not available and access to direct acting antivirals is very limited.

Our study reports late presentation and poor survival of patients with hepatocellular carcinoma in The Gambia. One African retrospective study,⁷ which analysed 1315 patients with hepatocellular carcinoma, reported a very low survival of 2.5 months. However, that study⁷ did

not analyse patients with cirrhosis and without hepatocellular carcinoma. In the absence of cirrhosis registries and surveillance programmes, survival data in cirrhosis are scarce in sub-Saharan Africa. Furthermore, to the best of our knowledge, the effectiveness of antiviral therapy to reduce the premature mortality in HBV-infected patients with cirrhosis has not been reported in Africa, especially in settings where standard of care for decompensated cirrhosis is not available.²³

Our study demonstrates a high effectiveness of TDF to improve survival of HBV-infected patients with cirrhosis. This finding was even confirmed after sensitivity analysis of censored patients. Although TDF successfully suppressed viral replication and improved survival, its 71% survival rate at 2 years is well below those reported in European and Asian studies (>95%).^{24,25} This difference could be explained by late patient presentation, HDV co-infection, prolonged time interval between diagnosis of cirrhosis and antiviral therapy initiation, and limited access to facilities for adequate management of decompensated cirrhosis as observed in other African countries.²⁶ While we applaud the increasing access to low-cost TDF across Africa, we must emphasise that decompensated cirrhosis is a complex systemic disease with multi-organ dysfunction that requires transdisciplinary care (endoscopy, radiology, and surgery), which is hardly accessible in sub-Saharan Africa.

As observed in patients with hepatocellular carcinoma, patients with cirrhosis presented late, with more than two-thirds having clinical decompensation at diagnosis. Patients with decompensated cirrhosis had a median survival of 11·3 months and a survival rate at 12 months of only 48%. These results are similar to non-African data before the era of highly effective antiviral treatments.²⁷

Structural poverty, or distance from suitable hospitals could explain the delay in seeking care for advanced chronic liver disease.²⁸ A prolonged time (4·9 months) between the first clinical assessment and TDF initiation in patients with cirrhosis, partly due to significant delay in obtaining viral load result, may have contributed to the high proportion of patients who never came back to initiate treatment. According to the current international guidelines,²⁹ patients with cirrhosis and HBV infection are eligible for antiviral therapy if they have detectable viral load and therefore require HBV DNA measurement before TDF initiation.

Together with the reported effectiveness of TDF in cirrhosis and HBV infection, our results strengthen the urgent need for early diagnosis and treatment programmes of cirrhosis using simplified and decentralised algorithms adapted to people living in remote areas.

Our study has limitations. First, we excluded patients lost to follow-up without survival data from the survival analysis. However, baseline characteristics of patients without survival data and patients with survival data were

similar. Second, TDF was not assigned randomly in patients with cirrhosis and HBV infection, and baseline variables could affect the chance of survival. Nevertheless, we performed weighted propensity score analysis to control for differences in baseline characteristics. Third, as frequently observed in studies conducted in resource-limited countries, the rate of loss to follow-up was high. To check potential bias related to censored patients with cirrhosis and HBV infection, we conducted sensitivity analysis using both unweighted and weighted approaches, which did not find any major impact on our survival rates. Fourth, in case of death outside the hospital, we estimated the mortality based on verbal autopsy, a method commonly used in Africa despite its known limitations for collection of causes of deaths. Fifth, the number of patients with cirrhosis and HBV infection was small and survival in this subgroup should be interpreted with caution. Sixth, because of an important turnaround time between the diagnosis of cirrhosis and result of HBV viral load, which is a prerequisite for TDF initiation, those who started TDF must have survived at least for this interval; this selection bias might have contributed to the overestimation of survival in treated patients with cirrhosis and HBV infection. Finally, although our study was not a multi-country study, our findings are likely to be translatable to most sub-Saharan African countries where similar sub-optimal care for cirrhosis and hepatocellular carcinoma is provided.³⁰

Despite its limitations, our study provides novel, important data on survival of patients with cirrhosis or hepatocellular carcinoma in Africa and on effectiveness of TDF to reduce the premature mortality of patients with cirrhosis and HBV infection. Strategies for early diagnosis and treatment of cirrhosis and hepatocellular carcinoma surveillance programmes are urgently needed.

Contributors

GN, YS, MT, RN, MM, and ML contributed to the conception of the study. GN, YS, AC, ST, HFN, LB, CH, YT, EO, MM, UD'A, IC, PI, RN, and ML contributed to the collection of data. GN, EVQ, YS, ZW, IC, and ML contributed to the analysis and interpretation of the data, drafting of the manuscript, and editing of the manuscript. All authors had access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have seen and approved the final version of the manuscript. ML, YS, GN, EVQ, and LB accessed and verified the data.

Declaration of interests

ML, YS, PI, and GN received research funding and consultancy fees from Gilead Sciences. PI reports speaker's honoraria not related to the published work from Gilead France, AbbVie Germany, ViiV Germany, and Eiger France. ML reports consulting fees from Abbott; consulting fees and payments from Gilead for participation on a scientific advisory board and for lectures; and receiving tenofovir from Gilead Sciences for PROLIFICA. All other authors declare no competing interests.

Data sharing

The dataset generated during the study, including anonymised individual data that were analysed for this study, is available from the corresponding author (ML) and the data management team (YS, GN, and LB) upon reasonable request and a written protocol.

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References

- GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020; **5**: 245–66.
- Rumgay H, Arnold M, Ferlay J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. *J Hepatol* 2022; **77**: 1598–606.
- Alberts CJ, Clifford GM, Georges D, et al. Worldwide prevalence of hepatitis B virus and hepatitis C virus among patients with cirrhosis at country, region, and global levels: a systematic review. *Lancet Gastroenterol Hepatol* 2022; **7**: 724–35.
- Akinjemiju T, Abera S, Ahmed M, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level. *JAMA Oncol* 2017; **3**: 1683–91.
- Umoh NJ, Lesi OA, Mendy M, et al. Aetiological differences in demographical, clinical and pathological characteristics of hepatocellular carcinoma in The Gambia. *Liver Int* 2011; **31**: 215–21.
- Mahale P, Aka P, Chen X, et al. Hepatitis D virus infection, cirrhosis and hepatocellular carcinoma in The Gambia. *J Viral Hepat* 2019; **26**: 738–49.
- Yang JD, Mohamed EA, Aziz AOA, et al. Characteristics, management, and outcomes of patients with hepatocellular carcinoma in Africa: a multicountry observational study from the Africa Liver Cancer Consortium. *Lancet Gastroenterol Hepatol* 2017; **2**: 103–11.
- Lemoine M, Shimakawa Y, Njie R, et al. Acceptability and feasibility of a screen-and-treat programme for hepatitis B virus infection in The Gambia: the Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) study. *Lancet Glob Health* 2016; **4**: e559–67.
- Shimakawa Y, Lemoine M, Njai HF, et al. Natural history of chronic HBV infection in West Africa: a longitudinal population-based study from The Gambia. *Gut* 2016; **65**: 2007–16.
- Lemoine M, Shimakawa Y, Nayagam S, et al. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. *Gut* 2016; **65**: 1369–76.
- Ladep NG, Dona AC, Lewis MR, et al. Discovery and validation of urinary metabolites for the diagnosis of hepatocellular carcinoma in West Africans. *Hepatology* 2014; **60**: 1291–301.
- Shimakawa Y, Lemoine M, Bottomley C, et al. Birth order and risk of hepatocellular carcinoma in chronic carriers of hepatitis B virus: a case-control study in The Gambia. *Liver Int* 2015; **35**: 2318–26.
- Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020–22.
- Ghosh S, Sow A, Guillot C, et al. Implementation of an in-house quantitative real-time polymerase chain reaction method for hepatitis B virus quantification in West African countries. *J Viral Hepat* 2016; **23**: 897–904.
- Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. *J Clin Oncol* 2015; **33**: 550–58.
- Roayaie S, Jibara G, Berhane S, et al. PALBI—an objective score based on platelets, albumin & bilirubin stratifies HCC patients undergoing resection & ablation better than Child's classification. The Liver Meeting, San Francisco, CA, USA: American Association for the Study of Liver Diseases, 2015.
- Shimakawa Y, Takao Y, Anderson ST, et al. The prevalence and burden of symptoms in patients with chronic liver diseases in The Gambia, West Africa. *Palliat Med* 2015; **29**: 184–85.
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018; **69**: 406–60.
- Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986; **24**: 67–74.
- The Gambia Hepatitis Intervention Study. The Gambia Hepatitis Study Group. *Cancer Res* 1987; **47**: 5782–87.
- Stockdale AJ, Kreuels B, Henrion MYR, et al. The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. *J Hepatol* 2020; **73**: 523–32.
- Maucort-Boulch D, de Martel C, Franceschi S, Plummer M. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. *Int J Cancer* 2018; **142**: 2471–77.
- Mokdad AA, Lopez AD, Shahraz S, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. *BMC Med* 2014; **12**: 145.
- Papatheodoridis GV, Sypsa V, Dalekos G, et al. Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population. *J Hepatol* 2018; **68**: 1129–36.
- Su TH, Hu TH, Chen CY, et al. Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. *Liver Int* 2016; **36**: 1755–64.
- Myer L, Smith E, Mayosi BM. Medical inpatient mortality at Groote Schuur Hospital, Cape Town, 2002–2009. *S Afr Med J* 2012; **103**: 28–31.
- D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006; **44**: 217–31.
- Boye S, Shimakawa Y, Vray M, Giles-Vernick T. Limited awareness of hepatitis B but widespread recognition of its sequelae in rural Senegal: a qualitative study. *Am J Trop Med Hyg* 2020; **102**: 637–43.
- European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370–98.
- Spearman CW, Dusheiko G, Jonas E, et al. Hepatocellular carcinoma: measures to improve the outlook in sub-Saharan Africa. *Lancet Gastroenterol Hepatol* 2022; **7**: 1036–48.