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Field battle against hepatitis B infection and HCC in Africa

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1 **Field battle against hepatitis B infection and HCC in Africa**

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Abstract

Despite effective and safe HBV vaccine and antiviral therapies, HBV-related hepatocellular carcinoma remains a major cause of deaths in young adults in Africa. Barriers to control the burden of HBV infection and HCC are multiple. In comparison to other major infectious diseases, hepatitis B virus infection and liver diseases have received remarkably little attention from the global health community. Improving birth dose vaccine coverage and implementing screening and treatment interventions are urgently needed. This requires a dramatic simplification of the management of chronic hepatitis B in Africa with access to reliable, robust and inexpensive diagnostic tools but also strong support from the local governments and the international health community. This review analyses 1) the characteristics of HBV viral hepatitis and HCC epidemics in Africa and 2) the barriers and requested solutions to control it.

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ML and MRT have equally contributed to the manuscript.

56 Introduction

57
58 Hepatocellular carcinoma (HCC) is a leading cause of deaths in Africa and is mainly due to
59 chronic infection with hepatitis B virus (HBV). However little attention has been paid to this
60 burden of disease over the last decades and many barriers still contribute to the epidemic in
61 the continent. This review analyses 1) the epidemiological characteristics of HCC and its main
62 cause -chronic hepatitis B- in Africa and 2) the barriers and requested solutions for the control
63 of this burden of diseases.

64

65 Viral hepatitis B and HCC epidemics in Africa

66 Epidemiology

67 According to the estimates of the Global Burden of Disease study, deaths due to viral hepatitis
68 increased by 63% from 0·89 million to 1·45 million between 1990 and 2013 and Africa is one of
69 the regions with highest mortality rate ¹. Worldwide, HCC is the second most common cause of
70 death from cancer, estimated to be responsible for about 750,000 deaths in 2012 ². HCC is a
71 cancer of poor countries, which account 80% of the global cases. Africa, especially West
72 Africa, represents one of the most endemic regions in the world. HCC is the most common fatal
73 malignancy in adult males on the continent and the third most common fatal malignancy in
74 women ^{3,4}. The prognosis of HCC is very poor, especially in resource-limited countries (Figure
75 1). The incidence of HCC matches precisely the fatality rate as the majority of patients present
76 at a late stage of the disease where no therapeutic options exist. Very few data on survival in
77 HCC patients living in Africa are available. These are derived from sparse cancer registry data
78 collated by the International Agency for Research on Cancer (IARC). Although the data can be
79 criticised for accuracy and completeness ⁵ it probably gives a reasonable perspective on HCC-
80 related deaths. In contrast there is virtually no system for collecting data on deaths attributable
81 to decompensated cirrhosis. Although it is likely that the number of people dying from cirrhosis

82 is the same order of magnitude as the number dying from HCC this is not reflected in the global
 83 burden of disease study. In The Gambia, the Prevention of Liver Fibrosis and Cancer in Africa
 84 (PROLIFICA) programme ⁶ reported a very poor median survival of HCC patients, estimated at
 85 91 days (4-789) (unpublished data). In patients with acute-on-chronic liver failure, a case-
 86 controlled study nested in the PROLIFICA programme found a poor cumulative mortality rate at
 87 28-and 90 day, 70.0% 92.9% respectively. Moreover, the vast majority of the patients were
 88 young men (median age 45 years (35–56)) ⁷. In Europe the median age at presentation with
 89 HCC is 65 years ⁸; in contrast the median age in sub-Saharan Africa is 45 years ⁹. A
 90 consortium of collaborating centers on HCC in Africa has recently reported that 43% of HBV-
 91 related HCC developed in adults younger than 40 years with a most frequent age range at
 92 HCC diagnosis at 32.5–37.5 years ¹⁰ (Figure 2). By contrast HCV-related HCC occurred later
 93 mainly after 50 years with a peak between 57.5–62.5 years (Figure 2) ^{9,10}. In Africa, HCC is
 94 therefore a disease, which kills large numbers of young and middle aged men and women and
 95 therefore deserves a robust public health response.
 96 The aetiology of HCC in Africa has been partly documented ^{3,4,9,11}. Chronic hepatitis B is the
 97 main cause of HCC in the continent, but the proportion of cases attributable to HIV and/or
 98 hepatitis delta co-infections remain poorly analysed although these viruses are highly endemic
 99 in the continent. Over 50-60% of the HCC cases in sub-Saharan Africa arise in patients who
 100 are HBs antigen (HBsAg) positive ^{9 3,10} and it is likely that another 20 to 50 % have previously
 101 had chronic HBV infection or occult HBV infection (HBsAg negative but detectable viraemia)
 102 ^{12,13}. The number of HCC attributable to occult hepatitis B is probably underestimated and
 103 deserves to be better documented. Chronic HCV infection has also been identified as an
 104 important cause of HCC in North Africa (particularly Egypt) ¹⁴ and in central Africa (Cameroon)
 105 ¹⁵. Occult hepatitis B has also been identified as a cofactor of HCC in patients with chronic
 106 hepatitis C ¹⁶.

107 Although the global distribution of the viral hepatitis epidemic is heterogeneous in Africa, the
 108 continent represents one of the most endemic parts of the world for HBV infection ¹⁷. Of the
 109 240 million people estimated to be chronically infected with HBV, 80 million reside in sub-
 110 Saharan Africa. Prior to immunisation programmes the prevalence of chronic infection in West
 111 Africa was around 15% in the adult population and more than two third of children aged 12-19
 112 years old had evidence of spontaneous clearance of the infection ¹⁸.

113 Good quality viral hepatitis sero-prevalence data are still lacking in Africa as the sero-surveys
 114 have been often conducted in selected populations (mainly blood donors, pregnant women or
 115 HIV-infected subjects). Within the PROLIFICA programme, a recent population-based study
 116 conducted in The Gambia and Senegal confirmed a high prevalence of HBsAg in both
 117 countries (over 8%) ¹⁹. A relatively lower prevalence of HBsAg has been reported in East Africa
 118 and in South Africa (6-8%) ¹⁷.

119 In Africa, HBV is mainly transmitted early in life. Although horizontal transmission represents
 120 the main mode of HBV transmission, perinatal transmission, is thought to account for around
 121 10% of chronic HBV infection ²⁰. Horizontal transmission occurs between the ages of 2 and 10
 122 through mechanisms that remain poorly understood. It is likely that children with high levels of
 123 viraemia pass the virus on through cuts and grazes to susceptible siblings ²¹.

124 **Natural history of chronic hepatitis B and incidence of HCC in Africa**

125 The incidence of HCC in HBV-infected adults shows considerable differences globally from
 126 34/100,000 in European men ²² to 530/100,000 in East Asian men ²³. In Sub-Saharan Africa,
 127 very few data are available and the natural history of chronic hepatitis B in Africa remains
 128 poorly documented. A study conducted in the Senegalese army in the 1990's reported an
 129 incidence rate at 68/100,000 ²⁴. Our more recent analysis obtained from a Gambian population-
 130 based cohort reported an incidence at 183.5/100,000 in males ²⁵. Therefore, the incidence of
 131 HCC seems to be lower in West Africa as compared to East Asia. This is partly due to

132 differences in terms of routes of transmission, natural history, HBV genotypes and levels of
 133 exposure to environmental toxins such as aflatoxin. Indeed, HBeAg seropositivity and high HBV
 134 DNA levels have been shown to be strongly associated with the risk of HCC ^{23,26,27}. At the age
 135 of 20 years, about half of Asian people still carry HBe antigen and have high viral load. In
 136 Gambia, we found that half of chronic carriers lost HBeAg by the age of puberty, and among
 137 those who cleared, the vast majority became inactive carriers with low or undetectable HBV
 138 DNA and few developed HCC or HBeAg-negative chronic hepatitis ²⁵. We found that HBsAg
 139 and HBeAg sero-clearance rate were 1.0%/year (95% CI: 0.8 to 1.2) and 7.4%/year (95% CI:
 140 6.3 to 8.8), respectively. Of note the clearance rates were slower in subjects born to HBsAg
 141 positive mothers underlying the importance of interrupting HBV mother-to-child transmission
 142 (MTCT). The PROLIFICA project may provide additional data on the natural history of chronic
 143 hepatitis B in West Africa.

144 **Risk factors of HCC in Africa**

145 **Viral factors**

146 Good quality studies on HCC in sub-Saharan Africa are scarce. As previously discussed, the
 147 main risk factor of HCC in Africa is chronic hepatitis B. HBeAg positivity and HBV DNA levels
 148 are strongly associated with HBV-related HCC ^{9,28} as described in Asian population ^{23,26}.
 149 In our population-based study in The Gambia HBV genotype A was more frequently associated
 150 with fibrosis and eligibility for treatment ²⁵; preliminary unpublished data from the PROLIFICA
 151 programme also suggest an association between HCC and genotype A. This association has
 152 been suggested in only one study conducted in South African patients with HBV-induced HCC.
 153 In this study the relative risk of developing HCC when being infected with a genotype A virus
 154 was 5.5 (95% CI 1.86-10.9) ²⁹. These data need to be confirmed in other African cohorts. In
 155 Africa genotype E prevails in West and Central Africa and genotype A is mainly observed in
 156 Southern, Central and Eastern Africa. In our PROLIFICA Gambian cohort 83% and 17% of the

157 patients were infected with a HBV genotype E and A, respectively ¹⁹. Genotype D, which has
 158 been suggested to be associated with more severe liver diseases in Asia, has been mainly
 159 identified in Northern and some Eastern African countries ³⁰.

160 In West Africa, HBV perinatal transmission has been found to be associated with higher liver
 161 complications including HCC ^{25,31}. In a case-control study conducted in The Gambia within the
 162 PROLIFICA project, we found that HCC cases, compared to controls, had earlier birth order, a
 163 proxy for young maternal age and maternal HBV viraemia at birth ³¹.

164 **Host and environmental factors**

165 Aflatoxin (AFB1), is a major cofactor of HCC in Africa. Aflatoxin is a mycotoxin produced by the
 166 aspergillus fungus and has been classified by IARC and WHO as a class 1 human carcinogen.
 167 This fungus grows in warm environment on stored grains such as peanuts and corn which are
 168 the basis of many traditional African meals.

169 A systematic review and meta-analysis reported a population attributable risk of aflatoxin-
 170 related HCC at 17% (14-19%) overall, 21% in HBsAg positive individuals and 8.8% in HBsAg
 171 negative populations ³².

172 Globally, males are more frequently affected by HCC (three to five times more likely) and this
 173 has been confirmed in Africa as well ⁹. This difference may be the consequence of different
 174 impact on inflammatory cytokines release and HBV DNA levels by sex hormones ³³.

175 In Western countries, obesity has been demonstrated to be associated with a higher risk of
 176 cancer including HCC with a hazard ratio at 1.19 (1.12–1.27) ³⁴. Over the last decade, obesity
 177 and diabetes have emerged as serious public health concerns in Africa and may represent
 178 emerging serious cofactors of liver carcinogenesis, especially in HBV-infected subjects already
 179 at high risk of HCC. Indeed, in a large cohort of Taiwanese HBV-infected individuals
 180 (n=23,820), diabetes was associated with a higher risk of HCC (relative risk (RR): 2.27 (1.10-
 181 4.66). The association of obesity and diabetes increased even more the risk of HCC in the

182 same cohort (RR: 264.7) ³⁵. Thus, a similar synergistic effect in African chronic HBsAg carriers
 183 can be expected.

184 Excessive alcohol consumption in African countries is a neglected public health issue. Yet, a
 185 recent WHO report on global alcohol consumption undelined a steadily increase in alcohol
 186 consumption in Africa ³⁶. For example, Mali ranks third country in the world in terms of alcohol
 187 consumption. Therefore the role of alcohol in the development of HCC is probably
 188 underestimated in the African continent and has not been well documented so far. Yang et al.
 189 recently reported that out of 1,552 HCC patients in Africa, 695 (45%) had a tumor not
 190 attributable to HBV or HCV suggesting underlying occult hepatitis B but also alcoholic liver
 191 diseases ¹⁰.

192 The association between smoking and HCC remains controversial. In a case-control study of
 193 HCC in The Gambia no association between tobacco and HCC was observed ³¹ whilst it has
 194 been reported in a large Taiwanese cohort of patients ²³.

195

196 **Barriers and solutions to control the epidemic of chronic hepatitis B and** 197 **HCC in Africa**

198 **Hepatitis B vaccination programmes**

199 HBV vaccine, available since the early 1980s, is the first effective and safe vaccine against a
 200 major human cancer and universal HBV immunization seems cost-effective to prevent hepatic
 201 complications in low and middle-income countries ^{37,38}. Since 1997 the WHO has
 202 recommended the vaccine to be incorporated into the expanded program of immunisation (EPI)
 203 for all countries. Currently licensed HBV vaccines are given in three doses and are associated
 204 with a response rate over 90% in non immunocompromised subjects. Over the past decade
 205 three-dose coverage of infants has increased greatly across low-and middle income countries.

206 It now exceeds 80% worldwide (82% in 2014 *versus* 1% in 1990) but still needs to be improved
 207 in Africa ³⁹.

208 HBV immunisation programmes have been highly successful all over the world and a recent
 209 systematic review suggested a significant decrease in global HBV prevalence ¹⁷. The
 210 Taiwanese universal HBV immunization programme represents a model of successful HBV
 211 immunization programme. In 1984, Taiwan, one of the most endemic countries for HBV in the
 212 world, launched a mass immunisation programme ⁴⁰ which led to a dramatic decrease in
 213 HBsAg prevalence as well as incidence of HCC in children and young adults. The programme
 214 includes birth dose vaccine and HBV-hyperimmune immunoglobulin (HBIG) that has been
 215 shown to significantly reduce the perinatal transmission rate from 86-96% to 12-14% of babies
 216 born to highly infectious mothers and from 10-12% to 3-4% of babies born to less infectious
 217 HBV mothers ⁴¹ ; In infants over 6 years old, sero-surveys confirmed a profound fall of the
 218 HBsAg prevalence from 10.5% to 1.7% between 1989 and 1993 ⁴². In other endemic countries
 219 where universal programmes have been successfully implemented, similar results have been
 220 observed ^{43,44}. In sub-Saharan africa, the vast majority of data regarding the effectiveness of
 221 HBV immunization on HBsAg prevalence and chronic carriage have been generated by the
 222 The Gambia Hepatitis Intervention Study (GHIS) ⁴⁵. This study was launched in 1986 with the
 223 support of the WHO/ IARC and the Medical Research Council (MRC) Laboratories. The study,
 224 has not been completed yet and aims to assess the efficacy of the vaccine given in early
 225 childhood, in preventing HBV infection and its complications including cirrhosis and HCC. The
 226 study started with a randomised vaccine trial. Over a four year period a total of 124,577
 227 children were recruited, one half received the usual EPI vaccines (BCG, Diphteria Tetanus and
 228 Pertussis (DTP), oral polio vaccine (OPV), measles, yellow fever) and the other half received
 229 the HBV vaccine in addition to the EPI ones. Between 2007 and 2008, 753 adults born during
 230 the first phase of GHIS were randomly selected to be tested for HBsAg. In subjects fully

231 vaccinated with 3 or 4 doses during childhood, the HBsAg prevalence was 1.6 % (0.4-8.5)
 232 compared to 12.4 % (9.6-15.6) in subjects who were not vaccinated. These results suggest a
 233 vaccine efficacy of 94% (95% CI 77-99) ⁴⁶.

234 A sero-survey conducted in 2009 and 2010 in children aged between 3 months and 6 years
 235 old, admitted in hospitals in Cameroon and Senegal also reported low prevalence of HBsAg
 236 (0.7% in Cameroon and 0.2% in Senegal) a few years after the introduction of the vaccine in
 237 these countries. However, in Central African Republic the same study reported a high HBsAg
 238 prevalence (5.1%) ⁴⁷, since the HBV vaccine was introduced only in 2007 in Central African
 239 Republic where the coverage remains below 50%.

240 HBV immunisation programmes have also shown a significant reduction of HCC incidence in
 241 Asia. The Taiwanese programme has led to a dramatic decrease in incidence of HCC in
 242 children as well as young adults who benefited the vaccine as compared to unvaccinated
 243 adults born before 1984 ^{48,49}. Of note, incomplete vaccination was strongly associated to the
 244 risk of HCC (HR: 2.52) ⁵⁰. The impact of HBV vaccine on the incidence of HCC has been
 245 reported in other countries ⁵¹. In China, the HBV/Global Alliance for Vaccines and
 246 Immunizations (GAVI) programme has probably prevented 24 million of chronic HBV infections
 247 and 4.3 million deaths attributable to acute hepatitis, cirrhosis, HCC or acute hepatitis ⁵². In
 248 contrast, the impact of HBV vaccine on the incidence of HCC in Africa has not been assessed
 249 yet. The GHIS will assess the impact of HBV child vaccination on HCC incidence and liver-
 250 related mortality in The Gambia in the near future.

251 **Prevention of HBV mother-to-child transmission**

252 **Birth dose vaccine**

253 Because HBV transmission occurs perinatally in highly endemic countries and since HBV
 254 infection during early childhood is associated to higher risk chronic hepatitis ⁵³ the WHO has
 255 recommended the administration of HBV vaccine to all newborns in endemic countries within

256 the first 24 hours of birth since 2009. However, the global coverage of infants with birth dose
 257 remains very low estimated at only 38% in 2014 (Figure 3) ³⁹.

258 As vertical transmission has been considered to be a minor source of infection in Africa there
 259 have been limited efforts in prevention of HBV perinatal transmission with resources
 260 concentrated on childhood vaccination as part of the EPI. Although all African countries have
 261 now integrated the HBV vaccine into their EPI, the HBV birth dose has rarely been
 262 implemented in the continent (Figure 3). Only a few sub-Saharan African countries have
 263 adopted the hepatitis B birth dose vaccine schedule (e.g Botswana, Cape Verde, Djibouti, The
 264 Gambia, Nigeria and Sao Tome and Principe islands and more recently Senegal and
 265 Mauritania). However these countries have been facing considerable difficulties in
 266 implementing this measure ⁵⁴. For example, in The Gambia, one of the first countries in the
 267 world to have implemented national HBV immunization, less than 3% of infants receive the
 268 HBV vaccine within 24 hours of birth ²⁰. This is probably due to multiple social, financial,
 269 logistical and cultural barriers. The vast majority of sub-Saharan African countries provide the
 270 first dose of HBV vaccine as a fixed combination vaccine starting at 6-8 weeks after birth,
 271 because: i) the pentavalent vaccine (DTP-HepB-Hib) provided by the GAVI cannot be
 272 administered at birth; ii) GAVI does not provide the monovalent vaccine to the governments
 273 and this is not purchased by health ministries in Africa despite its low cost (20c per dose), iii) a
 274 birth dose vaccine poses logistical challenges where a large proportion of births take place at
 275 home ⁵⁵. The majority of women in Africa give birth outside of medical facilities and often with
 276 the help of a non-medical birth assistant. Finally, HBIG, which increase the protection against
 277 transmission, is not a practical solution in Africa due to the high cost of the medication and the
 278 requirement for a cold chain. In addition, birth dose alone is not sufficient to control HBV MTCT
 279 in HBeAg positive women. One non-randomized trial, conducted in Côte d'Ivoire, reported a
 280 high rate of HBV MTCT in HBeAg Positive mothers: the risk of contaminating infants born to

281 HBeAg positive mothers who received the birth was high (37.5%) ⁵⁶. This result suggests that
282 the birth dose alone is not enough to prevent MTCT in HBeAg positive mothers. Unfortunately,
283 pregnant women in Africa are neither screened for HBV nor given any antiviral therapy during
284 pregnancy. Due to the lack of evidence-based data from Africa, the WHO is currently not able
285 to provide strong recommendations on the prevention of HBV MTCT in Africa besides the birth
286 dose vaccine ⁵⁷.

287 **Screening and treatment of high vireamic mothers in Africa**

288 A recent systematic review and meta-analysis confirmed that antiviral treatment during
289 pregnancy is effective and safe to reduce HBV replication and the risk of HBV MTCT ⁵⁸.
290 However, in Africa, prevention of HBV MTCT is a neglected public health issue and to date no
291 recommendations on the use of antiviral therapy during pregnancy in Africa have been made
292 by the WHO ⁵⁷ or the African ministries of health,. This is due to 1) the low estimated rate of
293 perinatal transmission in Africa and 2) the absence of clinical trials in pregnant women in the
294 continent. Yet, despite the relatively low frequency of perinatal transmission in Africa,
295 prevention of HBV MTCT is critical in the continent. Indeed, this mode of transmission has
296 been suggested to be associated with higher risk of developing chronic liver disease, and its
297 complications including cirrhosis and HCC, than horizontal transmission later in life ²⁰. In The
298 Gambia, 54% of chronic HBV carriers with significant liver fibrosis have been estimated to be
299 attributable to mother-to-infant transmission ²⁵.

300 **Screening and treatment programmes**

301 In Africa, millions of people are still infected with HBV and remain at risk of developing cirrhosis
302 and liver cancer. But HBV screening and treatment programmes are almost inexistent in the
303 continent. Indeed costs of screening and treatment are still the responsibility of the patients and
304 even the African blood banks still provide imperfect screening for viral hepatitis ¹⁹. By
305 suppressing viral replication, it has been clearly demonstrated that HBV treatments using oral

nucleos(t)ide analogues 1) can reverse liver fibrosis and cirrhosis⁵⁹, 2) significantly reduce the incidence of HCC^{26,60,61} and 3) are cost-effective⁶². HBV treatment is available in some countries but availability is limited to the private healthcare sector. Several governments, including Senegal, Uganda and Ethiopia are now evaluating the feasibility of HBV programmes. There are two main reasons for the absence of treatment programmes to date: 1) tenofovir is bought at generic prices as low as \$50 per patient per year by the Global Fund (GF) and some health ministries but tenofovir is not licensed for the treatment of HBV in many countries and the GF does not allow the tenofovir that it supplies to be used in the treatment of HBV mono-infection; 2) the management of the disease is complex and requires sophisticated and expensive technologies/assays that are often not available in Africa⁶³. In the Gambia, we demonstrated that screening and treatment intervention in the community is feasible¹⁹ and cost-effective⁶⁴. However, the current international criteria for treatment eligibility rely on parameters, which are often difficult to assess in routine in Africa (e.g HBV viral load and liver fibrosis). As a result, the management of HBV infection in Africa should be simplified, adapted to the local environment, and treatment criteria based on simple parameters including male sex, age, first birth order³¹, HBV positive maternal status, family history of HCC, liver function tests, deserve to be assessed in Africa.

HBV DNA measurement

Most countries in sub-Saharan Africa have relatively few laboratories with the capability to provide viral load assays and the cost of these assays is about 100-150 euros per test. The real-time quantitative Polymerase Chain Reaction (qPCR) requires time, skilled lab technicians, sophisticated laboratories and machines. In sub-Saharan Africa, only central laboratories in capital cities have capacity to perform qPCR for HBV DNA. As a result, most infected subjects

are left without care and treatment even when antiviral therapy (tenofovir) is available at generic price. The logistical barriers of collecting and transporting blood samples to the laboratories exacerbate this problem. There is an urgent need for alternative assays to measure HBV viral replication that is simple, inexpensive, and feasible even in a peripheral laboratory in Africa. As this has been done for liver fibrosis, alternatives such as dry blood spots, GeneExpert, Loop-mediated isothermal amplification assay (LAMP)⁶⁵, HBV semi-quantitative PCR, HBsAg quantification to HBV DNA qPCR and decentralization of molecular biology are urgently needed.

Fibrosis assessment

In most resource-limited settings liver biopsy is impractical. Beyond its invasive aspect, this procedure is expensive and requires well-trained liver histopathologists. In The Gambia, for example, there is only one histopathologist and about one third of the patients refuse the procedure⁶⁶. Within the PROLIFICA programme, we confirmed the difficulty of performing liver histology and sample preparation⁶⁶. Although transient elastography (Fibroscan®) represents an excellent non-invasive diagnostic tool of fibrosis there are still very few machines in Africa due to the capital costs. Unfortunately the diagnostic performance of cheap, non-invasive tools such as AST-to-platelet ratio index (APRI), currently recommended by the WHO, are not ideal for decision making on the initiation of treatment although probably adequate for the detection of cirrhosis⁵⁷. In a perspective of healthcare decentralization, healthcare workers urgently need reliable and inexpensive alternative methods for identifying the most severe patients in Africa. A new simple biochemical index, the Gamma-glutamyl transpeptidase to Platelet ratio (GPR)⁶⁶ has been developed in HBV-monoinfected subjects in West Africa, with relatively better performances for the diagnosis of extensive fibrosis and cirrhosis than APRI and Fib-4. Its good performances have been also confirmed in HCV-infected Egyptian patients. However, such findings have been controversial in HIV-HBV coinfecting patients^{67,68}. This

355 simple marker of fibrosis deserves to be evaluated in other cohorts of HBV or HCV African
356 patients.

357 **Selection of patients for treatment**

358 Where diagnostic facilities are limited, and particularly where viral load, liver biopsy and
359 Fibroscan are unavailable the selection of patients who require treatment is challenging. This
360 issue has been addressed in the WHO guidelines for treatment of HBV ⁵⁷ which recommend
361 treatment in the following patient groups: 1/ any patient who is HBsAg positive and has
362 cirrhosis and 2/ patients with HBsAg who are over 30 and have persistently raised ALT levels.

363 It is likely that these recommendations would be considered conservative by many
364 hepatologists but it is difficult to formulate guidelines for use in resource constrained settings
365 which can be safely deployed by medical and non-medical staff without specific expertise.

366 **Surveillance for HCC in cirrhotic patients**

367 Cirrhosis is the most significant risk of HCC and about 85% of HCC occur in a background of
368 cirrhosis. However, the diagnosis of cirrhosis in sub-Saharan Africa is uncommon due to lack of
369 expertise and lack of diagnostic tests. Even in developed countries the cost-effectiveness and
370 surveillance interval for HCC surveillance have been controversial. The recommended interval
371 surveillance is 6 months, based on the median doubling time of HCC. Han et al. showed that a
372 surveillance every 6 months lead to higher survival in cirrhotic patients compared with a annual
373 surveillance ⁶⁹. A French team showed that reducing the screening interval to 3 months did not
374 increase the survival in cirrhotic patients ⁷⁰. Although this surveillance has been widely
375 recommended by international groups, it is estimated that even in rich countries, more than half
376 of the cirrhotic patients do not benefit such a screening programme ⁷¹. Currently the authors
377 are not aware of any national surveillance programmes for the early detection of HCC in Africa.
378 It is urgent to train healthcare workers and implement simple and inexpensive surveillance
379 system. To date, liver ultrasound remains the best option for HCC screening in cirrhotic

380 subjects but it is not available in rural areas and highly depends on the operator's experience.
381 To date, there are no robust alternatives to liver ultrasound for HCC screening. Serum AFP
382 measurement lack sufficient sensitivity (around 60%) for detection of HCC and remains
383 expensive ⁷². Urinary biomarkers of HCC have been suggested to perform better than serum
384 AFP for the diagnosis of HCC in Africa ⁷³ and may open the way for the development of urinary
385 rapid diagnostic tests.

386 Finally, the international criteria and scores which are currently proposed for HCC screening
387 (e.g REVEAL-B) have been mainly developed and validated in Asian population and some of
388 them still rely on parameters which cannot be assessed routinely in Africa. As a result, a simple
389 scoring system for HCC screening should be assessed in Africa. Screening for HBV/HCV and
390 cirrhosis using simple tests should be integrated in general health services, access to liver
391 ultrasound should be scaled up in rural and semi-rural areas and physicians should be trained
392 on liver ultrasound.

393 **Treatment of HCC and palliative care**

394 In Africa, the majority of tumours presents at a late stage where effective treatment would be
395 challenging in any healthcare system. Within the PROLIFICA programme, we found that in 69
396 patients with diagnostic of HCC, the median size of the tumour size was 12.25 cm (1.5-32) and
397 61 (88.4%) had a mean size ≥ 5 cm at time of diagnosis (preliminary unpublished data). This
398 underlines the need for improving cirrhosis and HCC screening.

399 There are surgeons with hepatobiliary expertise in Africa who will operate on the small
400 proportion of resectable tumours but this is mainly available in the private healthcare sector.
401 There is very limited access to radiofrequency ablation or transarterial chemoembolization and
402 no liver transplantation programmes apart from some North African countries (Egypt, Tunisia,
403 Algeria).

404 Palliative care and access to opioid therapy are an additional important issue in Africa. In The
 405 Gambia, a cross sectional analysis reported that less than half of the patients with HCC
 406 received analgesics and none had morphine although pain was reported by all the patients ⁷⁴.
 407 Other common symptoms in HCC patients were also not treated and importantly the level of
 408 knowledge on palliative care amongst healthcare workers was poor. Lack of healthcare
 409 infrastructures and workers associated to regulatory restrictions for procuring opioid analgesics
 410 are a major barrier to provide good quality care to patients with end-stage liver disease in
 411 Africa ⁷⁵.

412 **Aflatoxin control**

413 Reducing aflatoxin exposure to non-detectable levels could reduce HCC cases in high risk
 414 areas by 23% ³². Reducing exposure to aflatoxin can be done through the implementation of
 415 protective and educative measures in collaboration with the local farming services: for
 416 example safer application of pesticides and dry storage. Developing reliable, simple and cheap
 417 methods to measure the exposure to AFB1 in the blood is also critical to improve 1) the
 418 assessment of human exposure in the different African sub-regions and 2) the prevention of
 419 exposure. To date, most of the techniques rely on genetic methods that indirectly measure
 420 exposure to the toxin ⁷⁶. New techniques such as High Performance Liquid Chromatography or
 421 isotopic mass spectrometry are promising methods to collect the exact exposure to Aflatoxin.
 422 Preventive chemotherapy (e.g oltipraz) has been proposed to reduce the metabolism of
 423 aflatoxins and their toxicity ⁷⁷

424 **Awareness and political support**

425 Chronic HBV infection is invariably asymptomatic until the onset of end-stage liver disease
 426 when intervention is often futile. Early diagnosis and treatment is essential to prevent HBV-
 427 related morbidity and mortality but this requires a high level of public awareness about the
 428 disease and the availability of diagnostic testing. Very little data is available on levels of public

429 awareness about HBV and its sequelae in Africa but in the PROLFICA study we found that less
 430 than less than 1% of people tested in the community had heard of the virus despite the high
 431 incidence rate of HCC ¹⁹. In contrast HIV is recognised by the majority of the population, which
 432 is the result of a concerted and well-funded programme to educate the public and to encourage
 433 testing. Improving education and knowledge on HCC and viral hepatitis represent an important
 434 part of the interventions to fight against viral hepatitis and HCC.
 435 The success of the Taiwanese programme has been possible thanks to the determination of
 436 the government and ministry of health to controlling the epidemic. In addition, the medical
 437 community and academic institutions have been fully committed and the programme has been
 438 implemented step by step with strong education programmes including activities to sensitize
 439 the general population ⁷⁸. African governments, have to take a stronger position to improve 1)
 440 HBV vaccine coverage at birth and 2) screening and treatment interventions in the general
 441 population.
 442 According to the Global Burden of Disease Study 2010, the annual number of deaths from viral
 443 hepatitis (1.44 million deaths per year) are almost similar to those attributable to HIV (1.47
 444 million deaths) and higher than those due to malaria (1.17 million) or tuberculosis (1.2 million)
 445 ⁷⁹. These deaths mainly occur in resource-poor countries. Yet, viral hepatitis and liver cancer
 446 have been long neglected. Only recently the WHO and African governments acknowledge the
 447 urgent need to improve care and treatment for the millions people infected with viral hepatitis.
 448 HIV, Tuberculosis and malaria remain important killers in Africa. Responses to fight against
 449 these epidemics have been highly deployed over the decades. Since the start of their
 450 operations in early 2000's, the President's Emergency Plan for AIDS Relief (PEPFAR) and
 451 Global Fund have been spending billions of US dollars each year to combat HIV and AIDS,
 452 tuberculosis, malaria and other opportunistic infections globally. Unfortunately viral hepatitis
 453 have never been considered as a health priority for Africa. Integrating viral hepatitis "screen-

454 and-treat” interventions within the existing HIV/TB/Malaria programmes is critical and tenofovir
455 mainly provided by the Global Fund in Africa, should not be restricted to HIV-infected subjects,
456 and its access for HBV-monoinfected in Africa should be now urgently considered.

457 Tenofovir, mainly provided by the Global Fund in Africa, should not be restricted to HIV-
458 infected subjects, and access to tenofovir for HBV-monoinfected in Africa should be now
459 urgently considered. African governments should now seriously consider to provide the HBV
460 vaccine birth dose (accessible at very low price). For example, the Senegalese government
461 recently agreed to integrate the monovalent hepatitis B birth dose into its EPI in January 2016.
462 This is a remarkable advance. The 2014 WHO African Regional Committee adopted a
463 resolution to control viral hepatitis B infection by reducing chronic hepatitis B prevalence to less
464 than 2% in children under the age of five in all member states by 2020. Prevention of HBV
465 MTCT through timely delivery of hepatitis B vaccine at birth has been recognized as a critical
466 step for African countries.

467 Although these last years, political advances have been observed greater efforts and
468 commitments are still needed in Africa.

469

470 **Conclusion**

471 Many barriers contribute to epidemic of HBV infection and HCC in Africa. In order to reduce the
472 number of deaths due to chronic hepatitis B and HCC in Africa, it is urgent to 1) improve HBV
473 vaccine coverage in particular its birth dose, 2) implement HBV “screen and treat” interventions
474 at low cost and 3) simplify the management of chronic hepatitis B using inexpensive and simple
475 diagnostic methods and 4) develop simple tools for early HCC screening and treatment.

476 Despite recent few advances from the WHO and African governments, this challenge requires
477 stronger commitment from the African ministries of health and healthcare workers, as well as
478 the whole international health community.

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504 **References**

- 505 1. Stanaway JD, Flaxman AD, Naghavi M, et al. The global burden of viral
506 hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study
507 2013. *Lancet* 2016.
- 508 2. IARC. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Last access
509 23 January 2016. 2012.
- 510 3. Jemal A, Bray F, Forman D, et al. Cancer burden in Africa and
511 opportunities for prevention. *Cancer* 2012.
- 512 4. Parkin DM, Sitas F, Chirenje M, Stein L, Abratt R, Wabinga H. Part I: Cancer
513 in Indigenous Africans--burden, distribution, and trends. *Lancet Oncol* 2008;
514 **9**(7): 683-92.
- 515 5. Shimakawa Y, Bah E, Wild CP, Hall AJ. Evaluation of data quality at the
516 Gambia national cancer registry. *International journal of cancer Journal*
517 *international du cancer* 2013; **132**(3): 658-65.
- 518 6. [www.prolifica.org.uk NCT02129829 clinicaltrialsorg](http://www.prolifica.org.uk/NCT02129829/clinicaltrialsorg)
519 Last accessed 15 August 2016.
- 520 7. Shimakawa Y, Njai HF, Takahashi K, et al. Hepatitis E virus infection and
521 acute-on-chronic liver failure in West Africa: a case-control study from The
522 Gambia. *Alimentary pharmacology & therapeutics* 2016; **43**(3): 375-84.
- 523 8. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F.
524 The burden of liver disease in Europe: a review of available epidemiological data.
525 *Journal of hepatology* 2013; **58**(3): 593-608.
- 526 9. Kirk GD, Lesi OA, Mendy M, et al. The Gambia Liver Cancer Study:
527 Infection with hepatitis B and C and the risk of hepatocellular carcinoma in West
528 Africa. *Hepatology* 2004; **39**(1): 211-9.
- 529 10. Yang JD, Gyedu A, Afihene MY, et al. Hepatocellular Carcinoma Occurs at
530 an Earlier Age in Africans, Particularly in Association With Chronic Hepatitis B.
531 *The American journal of gastroenterology* 2015; **110**(11): 1629-31.
- 532 11. de Martel C, Maucourt-Boulch D, Plummer M, Franceschi S. World-wide
533 relative contribution of hepatitis B and C viruses in hepatocellular carcinoma.
534 *Hepatology* 2015; **62**(4): 1190-200.
- 535 12. Shafritz DA, Shouval D, Sherman HI, Hadziyannis SJ, Kew MC. Integration
536 of hepatitis B virus DNA into the genome of liver cells in chronic liver disease and

- 537 hepatocellular carcinoma. Studies in percutaneous liver biopsies and post-
538 mortem tissue specimens. *The New England journal of medicine* 1981; **305**(18):
539 1067-73.
- 540 13. Kew MC, Welschinger R, Viana R. Occult hepatitis B virus infection in
541 Southern African blacks with hepatocellular carcinoma. *Journal of*
542 *gastroenterology and hepatology* 2008; **23**(9): 1426-30.
- 543 14. Shaker MK, Abdella HM, Khalifa MO, El Dorry AK. Epidemiological
544 characteristics of hepatocellular carcinoma in Egypt: a retrospective analysis of
545 1313 cases. *Liver international : official journal of the International Association*
546 *for the Study of the Liver* 2013; **33**(10): 1601-6.
- 547 15. Andoulo FA, Noah DN, Djapa R, et al. Epidemiology of hepatitis C: related
548 hepatocellular carcinoma in Cameroon. *The Pan African medical journal* 2014;
549 **19**: 379.
- 550 16. **Shi Y, Wu YH, Wu W, Zhang WJ, Yang J, Chen Z.** Association between
551 occult hepatitis B infection and the risk of hepatocellular carcinoma: a meta-
552 analysis. *Liver international : official journal of the International Association for*
553 *the Study of the Liver* 2012; **32**(2): 231-40.
- 554 17. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of
555 worldwide prevalence of chronic hepatitis B virus infection: a systematic review
556 of data published between 1965 and 2013. *Lancet* 2015.
- 557 18. Whittle H, Inskip H, Bradley AK, et al. The pattern of childhood hepatitis B
558 infection in two Gambian villages. *The Journal of infectious diseases* 1990;
559 **161**(6): 1112-5.
- 560 19. **Lemoine M, Shimakawa Y, Njie R,** et al. Acceptability and feasibility of a
561 screen-and-treat programme for hepatitis B virus infection in The Gambia: the
562 Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) study. *Lancet Glob*
563 *Health* 2016; **4**(8): e559-67.
- 564 20. Shimakawa Y, Bottomley C, Njie R, Mendy M. The association between
565 maternal hepatitis B e antigen status, as a proxy for perinatal transmission, and
566 the risk of hepatitis B e antigenaemia in Gambian children. *BMC public health*
567 2014; **14**: 532.
- 568 21. Bernier RH, Sampliner R, Gerety R, Tabor E, Hamilton F, Nathanson N.
569 Hepatitis B infection in households of chronic carriers of hepatitis B surface

- 570 antigen: factors associated with prevalence of infection. *American journal of*
571 *epidemiology* 1982; **116**(2): 199-211.
- 572 22. Crook PD, Jones ME, Hall AJ. Mortality of hepatitis B surface antigen-
573 positive blood donors in England and Wales. *International journal of*
574 *epidemiology* 2003; **32**(1): 118-24.
- 575 23. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a
576 biological gradient of serum hepatitis B virus DNA level. *JAMA : the journal of the*
577 *American Medical Association* 2006; **295**(1): 65-73.
- 578 24. Evans AA, O'Connell AP, Pugh JC, et al. Geographic variation in viral load
579 among hepatitis B carriers with differing risks of hepatocellular carcinoma.
580 *Cancer Epidemiol Biomarkers Prev* 1998; **7**(7): 559-65.
- 581 25. **Shimakawa Y, Lemoine M**, Njai HF, et al. Natural history of chronic HBV
582 infection in West Africa: a longitudinal population-based study from The Gambia.
583 *Gut* 2015.
- 584 26. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic
585 hepatitis B and advanced liver disease. *The New England journal of medicine*
586 2004; **351**(15): 1521-31.
- 587 27. Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of
588 hepatocellular carcinoma. *The New England journal of medicine* 2002; **347**(3):
589 168-74.
- 590 28. Tang B, Kruger WD, Chen G, et al. Hepatitis B viremia is associated with
591 increased risk of hepatocellular carcinoma in chronic carriers. *Journal of medical*
592 *virology* 2004; **72**(1): 35-40.
- 593 29. Kew MC, Kramvis A, Yu MC, Arakawa K, Hodgkinson J. Increased
594 hepatocarcinogenic potential of hepatitis B virus genotype A in Bantu-speaking
595 sub-saharan Africans. *Journal of medical virology* 2005; **75**(4): 513-21.
- 596 30. Yousif M, Mudawi H, Hussein W, et al. Genotyping and virological
597 characteristics of hepatitis B virus in HIV-infected individuals in Sudan. *Int J*
598 *Infect Dis* 2014; **29**: 125-32.
- 599 31. Shimakawa Y, Lemoine M, Bottomley C, et al. Birth order and risk of
600 hepatocellular carcinoma in chronic carriers of hepatitis B virus: a case-control
601 study in The Gambia. *Liver international : official journal of the International*
602 *Association for the Study of the Liver* 2015.

- 603 32. Liu Y, Chang CC, Marsh GM, Wu F. Population attributable risk of
604 aflatoxin-related liver cancer: systematic review and meta-analysis. *European*
605 *journal of cancer* 2012; **48**(14): 2125-36.
- 606 33. Montella M, D'Arena G, Crispo A, et al. Role of Sex Hormones in the
607 Development and Progression of Hepatitis B Virus-Associated Hepatocellular
608 Carcinoma. *International journal of endocrinology* 2015; **2015**: 854530.
- 609 34. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L.
610 Body-mass index and risk of 22 specific cancers: a population-based cohort
611 study of 5.24 million UK adults. *Lancet* 2014; **384**(9945): 755-65.
- 612 35. Chen CL, Yang HI, Yang WS, et al. Metabolic factors and risk of
613 hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in
614 Taiwan. *Gastroenterology* 2008; **135**(1): 111-21.
- 615 36. WHO.
616 http://apps.who.int/iris/bitstream/10665/112736/1/9789240692763_engpdf Last
617 access 28th January 2016.
- 618 37. Hall AJ, Roberston RL, Crivelli PE, et al. Cost-effectiveness of hepatitis B
619 vaccine in The Gambia. *Transactions of the Royal Society of Tropical Medicine and*
620 *Hygiene* 1993; **87**(3): 333-6.
- 621 38. Beutels P. Economic evaluations of hepatitis B immunization: a global
622 review of recent studies (1994-2000). *Health economics* 2001; **10**(8): 751-74.
- 623 39. WHO.
624 http://www.who.int/immunization/monitoring_surveillance/Global_Immunizat
625 [ion_Data.pdf?ua=1](http://www.who.int/immunization/monitoring_surveillance/Global_Immunizat). Last accessed 1st February 2016. 2015.
- 626 40. Chen DS, Hsu NH, Sung JL, et al. A mass vaccination program in Taiwan
627 against hepatitis B virus infection in infants of hepatitis B surface antigen-carrier
628 mothers. *JAMA : the journal of the American Medical Association* 1987; **257**(19):
629 2597-603.
- 630 41. Hsu HM, Chen DS, Chuang CH, et al. Efficacy of a mass hepatitis B
631 vaccination program in Taiwan. Studies on 3464 infants of hepatitis B surface
632 antigen-carrier mothers. *JAMA : the journal of the American Medical Association*
633 1988; **260**(15): 2231-5.

- 634 42. Hsu HM, Lu CF, Lee SC, Lin SR, Chen DS. Seroepidemiologic survey for
635 hepatitis B virus infection in Taiwan: the effect of hepatitis B mass immunization.
636 *The Journal of infectious diseases* 1999; **179**(2): 367-70.
- 637 43. Harpaz R, McMahon BJ, Margolis HS, et al. Elimination of new chronic
638 hepatitis B virus infections: results of the Alaska immunization program. *The*
639 *Journal of infectious diseases* 2000; **181**(2): 413-8.
- 640 44. Liang X, Bi S, Yang W, et al. Epidemiological serosurvey of hepatitis B in
641 China--declining HBV prevalence due to hepatitis B vaccination. *Vaccine* 2009;
642 **27**(47): 6550-7.
- 643 45. The Gambia Hepatitis Intervention Study. The Gambia Hepatitis Study
644 Group. *Cancer research* 1987; **47**(21): 5782-7.
- 645 46. Peto TJ, Mendy ME, Lowe Y, Webb EL, Whittle HC, Hall AJ. Efficacy and
646 effectiveness of infant vaccination against chronic hepatitis B in the Gambia
647 Hepatitis Intervention Study (1986-90) and in the nationwide immunisation
648 program. *BMC Infect Dis* 2014; **14**: 7.
- 649 47. Rey-Cuille MA, Njouom R, Bekondi C, et al. Hepatitis B virus exposure
650 during childhood in Cameroon, Central African Republic and Senegal after the
651 integration of HBV vaccine in the expanded program on immunization. *The*
652 *Pediatric infectious disease journal* 2013; **32**(10): 1110-5.
- 653 48. Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in
654 Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan
655 Childhood Hepatoma Study Group. *The New England journal of medicine* 1997;
656 **336**(26): 1855-9.
- 657 49. Chiang CJ, Yang YW, You SL, Lai MS, Chen CJ. Thirty-year outcomes of the
658 national hepatitis B immunization program in Taiwan. *JAMA : the journal of the*
659 *American Medical Association* 2013; **310**(9): 974-6.
- 660 50. Chien YC, Jan CF, Chiang CJ, Kuo HS, You SL, Chen CJ. Incomplete hepatitis
661 B immunization, maternal carrier status, and increased risk of liver diseases: a
662 20-year cohort study of 3.8 million vaccinees. *Hepatology* 2014; **60**(1): 125-32.
- 663 51. Wichajarn K, Kosalaraksa P, Wiangnon S. Incidence of hepatocellular
664 carcinoma in children in Khon Kaen before and after national hepatitis B vaccine
665 program. *Asian Pacific journal of cancer prevention : APJCP* 2008; **9**(3): 507-9.

- 666 52. Hadler SC, Fuqiang C, Averhoff F, et al. The impact of hepatitis B vaccine in
667 China and in the China GAVI Project. *Vaccine* 2013; **31 Suppl 9**: J66-72.
- 668 53. Edmunds WJ, Medley GF, Nokes DJ, Hall AJ, Whittle HC. The influence of
669 age on the development of the hepatitis B carrier state. *Proc Biol Sci* 1993;
670 **253**(1337): 197-201.
- 671 54. WHO. Hepatitis B vaccines. WHO position paper. *Wkly Epidemiol Rec*.
672 2009;84(40):405-420.). *Wkly Epidemiol Rec* 2009; **84**(40): 405-20.
- 673 55. GAVI. Hepatitis B vaccine at birth GAVI responds to MSF. 2014. Available
674 at: [http://www.gavi.org/Library/News/Statements/2014/Hepatitis-B-vaccine-](http://www.gavi.org/Library/News/Statements/2014/Hepatitis-B-vaccine-at-birth-GAVI-responds-to-MSF/)
675 [at-birth-GAVI-responds-to-MSF/](http://www.gavi.org/Library/News/Statements/2014/Hepatitis-B-vaccine-at-birth-GAVI-responds-to-MSF/). 2014.
- 676 56. Ekra D, Herbinger KH, Konate S, et al. A non-randomized vaccine
677 effectiveness trial of accelerated infant hepatitis B immunization schedules with
678 a first dose at birth or age 6 weeks in Cote d'Ivoire. *Vaccine* 2008; **26**(22): 2753-
679 61.
- 680 57. WHO. World Health Organization. Guidelines for the Prevention, Care and
681 Treatment of Persons with chronic Hepatitis B infection.
682 <http://whoint/hiv/pub/hepatitis/hepatitis-b-guidelines/en/>
683 2015; March. *Last accessed July 2016*
- 684 58. Brown RS, Jr., McMahon BJ, Lok AS, et al. Antiviral therapy in chronic
685 hepatitis B viral infection during pregnancy: A systematic review and meta-
686 analysis. *Hepatology* 2016; **63**(1): 319-33.
- 687 59. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment
688 with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label
689 follow-up study. *Lancet* 2012.
- 690 60. Wu CY, Lin JT, Ho HJ, et al. Association of Nucleos(t)ide Analogue Therapy
691 with Reduced Risk of Hepatocellular Carcinoma in Patients with Chronic
692 Hepatitis B-a Nationwide Cohort Study. *Gastroenterology* 2014.
- 693 61. Papatheodoridis GV, Chan HL, Hansen BE, Janssen HL, Lampertico P. Risk
694 of hepatocellular carcinoma in chronic hepatitis B: Assessment and modification
695 with current antiviral therapy. *Journal of hepatology* 2015.
- 696 62. Buti M, Brosa M, Casado MA, Rueda M, Esteban R. Modeling the cost-
697 effectiveness of different oral antiviral therapies in patients with chronic
698 hepatitis B. *Journal of hepatology* 2009; **51**(4): 640-6.

63. Lemoine M, Eholie S, Lacombe K. Reducing the neglected burden of viral hepatitis in Africa: Strategies for a global approach. *Journal of hepatology* 2015; **62**(2): 469-76.
64. Nayagam S, Conteh L, Sicuri E, et al. Cost-effectiveness of community-based screening and treatment for chronic hepatitis B in The Gambia: an economic modelling analysis. *Lancet Glob Health* 2016; **4**(8): e568-78.
65. Nyan DC, Ulitzky LE, Cehan N, et al. Rapid detection of hepatitis B virus in blood plasma by a specific and sensitive loop-mediated isothermal amplification assay. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014; **59**(1): 16-23.
66. 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* 2015.
67. Boyd A, Bottero J, Lacombe K. The gamma-glutamyl transpeptidase-to-platelet ratio as a predictor of liver fibrosis in patients co-infected with HBV and HIV. *Gut* 2015.
68. Stockdale AJ, Phillips RO, Geretti AM, Group HS. The gamma-glutamyl transpeptidase to platelet ratio (GPR) shows poor correlation with transient elastography measurements of liver fibrosis in HIV-positive patients with chronic hepatitis B in West Africa. Response to: 'The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa' by Lemoine et al. *Gut* 2016.
69. Han KH, Kim do Y, Park JY, et al. Survival of hepatocellular carcinoma patients may be improved in surveillance interval not more than 6 months compared with more than 6 months: a 15-year prospective study. *Journal of clinical gastroenterology* 2013; **47**(6): 538-44.
70. Trinchet JC, Chaffaut C, Bourcier V, et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. *Hepatology* 2011; **54**(6): 1987-97.
71. Davila JA, Henderson L, Kramer JR, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. *Annals of internal medicine* 2011; **154**(2): 85-93.

- 732 72. Daniele B, Bencivenga A, Megna AS, Tinessa V. Alpha-fetoprotein and
733 ultrasonography screening for hepatocellular carcinoma. *Gastroenterology* 2004;
734 **127**(5 Suppl 1): S108-12.
- 735 73. Ladep NG, Dona AC, Lewis MR, et al. Discovery and validation of urinary
736 metabotypes for the diagnosis of hepatocellular carcinoma (HCC) in West
737 Africans. *Hepatology* 2014.
- 738 74. Shimakawa Y, Takao Y, Anderson ST, et al. The prevalence and burden of
739 symptoms in patients with chronic liver diseases in The Gambia, West Africa.
740 *Palliative medicine* 2015; **29**(2): 184-5.
- 741 75. Colebunders R, John L, Muganzi A, Lynen L, Kambugu A. Palliative care in
742 sub-Saharan Africa. *Lancet* 2005; **366**(9485): 546-7.
- 743 76. Magnussen A, Parsi MA. Aflatoxins, hepatocellular carcinoma and public
744 health. *World journal of gastroenterology* 2013; **19**(10): 1508-12.
- 745 77. Wild CP, Hall AJ. Primary prevention of hepatocellular carcinoma in
746 developing countries. *Mutation research* 2000; **462**(2-3): 381-93.
- 747 78. Kao JH, Chen DS. Global control of hepatitis B virus infection. *The Lancet*
748 *Infectious diseases* 2002; **2**(7): 395-403.
- 749 79. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from
750 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis
751 for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2095-
752 128.

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754 Author names in bold designate shared co-first authorship

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Fig. 1: Estimated liver cancer mortality in men worldwide (2012). From GLOBOCAN 2012.

Fig 2: Number of HCC cases per 5-year age range in Africa. Data from a consortium of collaborating Centers on HCC (Yang et al. Am J Gastro 2015)

Fig.3: Global coverage of HBV vaccine birth dose. WHO/UNICEF coverage estimates 2012 revision, July 2013.