**Report to the Myre Sim Committee, Royal College of Physicians of Edinburgh**

**Project: Hepatitis B in Kumasi (HEPIK)**

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## Background to the Project

In 2010, the Hepatitis B in Kumasi (HEPIK) project commenced in Kumasi, Ghana. This study was a partnership between Prof AM Geretti's research group at the University of Liverpool, United Kingdom (UK) and Dr Richard Odame Phillips and colleagues from Kumasi, the University of London, and the University of Middlesborough, UK.

The HEPIK study is a longitudinal prospective cohort study of hepatitis B-HIV co-infected individuals from Ghana, who were antiretroviral therapy (ART) experienced at study entry, looking at liver-related and virological outcomes of introducing tenofovir.

Support from the Myre Sim fund has facilitated travel to, and participation in further follow up of the HEPIK study cohort and we are very grateful for this support.

## Introduction

Chronic HBV infection is the principal cause of cirrhosis and liver cancer in sub-Saharan Africa.[1] Liver-related deaths are increasing in the region, reflecting high HBV endemicity, limited HBV screening and treatment programmes, and declining HIV-associated mortality through increasing provision of ART. Between 2005 and 2015, the proportion of adult deaths due to cirrhosis or liver cancer increased from 3.2% to 4.0%.[2] HIV and HBV infection commonly co-exist, and global HBV prevalence is estimated at 7.4% among people living with HIV.[3] In HIV/HBV co-infection, progression of liver fibrosis is accelerated and liver-related mortality is higher compared with HBV infection alone.[4]

In view of the rapid emergence of drug resistance when HBV infection is treated with lamivudine alone,[5] since 2009 the World Health Organisation (WHO) has recommended that ART regimens for HIV/HBV co-infected patients should include tenofovir, typically alongside lamivudine or emtricitabine.[6] However, treatment programmes in sub-Saharan Africa for many years provided ART without systematic hepatitis B surface antigen (HBsAg) screening and therefore blind to HBV status.[7] Since 2013, WHO has recommended tenofovir as a preferred ART component for all HIV-1 positive patients regardless of HBV status. Use of tenofovir in first-line regimens in low- and middle-income countries increased accordingly from 39% to 72% between 2013 and 2015.[8] In high income countries, even among patients with established cirrhosis, treatment with tenofovir disoproxil fumarate (TDF) over five years resulted in histological regression of liver fibrosis, without emergent HBV drug resistance. [9]

We previously reported the short-term outcomes of introducing TDF in a HIV/HBV co-infected population in Ghana who had previously received four years of ART with lamivudine as the sole HBV-active agent.[10] Prior to introducing TDF, there was evidence of ongoing HBV replication and extensive lamivudine resistance. After a median of 7 months of TDF, usually with continuation of

lamivudine, we observed improved HBV DNA suppression and a reduction in liver stiffness by transient elastography. To date, there are limited data demonstrating the long-term effect of TDF on liver stiffness and virologic status of HIV/HBV co-infected individuals in typical ART programmatic settings in sub-Saharan Africa.[11, 12] Here, we report long-term outcome data after four years of TDF plus lamivudine among HIV/HBV co-infected individuals in Ghana.

Support from the Myre Sim Fund facilitated an exchange between the University of Liverpool and the Komfo Anoke Teaching Hospital, Kumasi Ghana to continue the HEPIK study and provide much-needed follow up of participants in the study to report on the long-term outcomes from introducing tenofovir in this previously treatment-experienced population.

Together with colleagues from Liverpool we travelled to Kumasi, Ghana and working with colleagues from Kumasi, led by Dr Richard Odame Phillips, invited participants in the study for follow up visits, obtaining additional data on liver stiffness, clinical outcomes and patient-specific factors via participant questionnaires and collection of samples for further virological outcome analysis.

## Study Abstract:

**Long-term effect of tenofovir disoproxil fumarate (TDF) on liver stiffness and virologic outcomes in lamivudine-experienced patients with HIV and hepatitis B virus (HBV) co-infection in a HIV programmatic setting in sub-Saharan Africa**


### Background

In lamivudine-experienced HIV/HBV co-infected patients in sub-Saharan Africa, introducing TDF as part of antiretroviral therapy improves control of HBV replication and reduces liver stiffness in the short-term. This study determined the long-term effects of TDF in a prospective observational cohort in Ghana.

### Methods

Study visits occurred in 2011-2012 (T0/T1) and 2015 (T2), when participants underwent liver stiffness measurement (LSM) by transient elastography and blood sampling. HBV DNA load, surface antigen (HBsAg), and e antigen (HBeAg) were measured retrospectively. HBV drug resistance was detected by deep sequencing.

### Results

After a median of 4 years of TDF (IQR 3.8-4.1), among 94 subjects with paired T0/T1 and T2 evaluations, HBV DNA suppression rates increased from 58.7% to 81.9% ($p=0.0002$) and median LSM declined from 5.5 kPa to 4.5 kPa ($p<0.0001$), reducing proportions with ≥F2 fibrosis from 45% to 23% ($p=0.001$). LSM declined by 1.1 kPa/year in the first year and by 0.2 kPa/year in the subsequent three years. Female gender, greater adherence and no significant alcohol consumption predicted larger LSM reductions. Median HBsAg concentrations declined from 3.7 to 3.3 log10 IU/ml ($p=0.0001$). Annualised HBsAg and HBeAg seroclearance rates were 2.4% and 11.6% respectively. Three subjects with detectable HBV DNA showed mutations with potential TDF resistance effects (rsS78T; I233V; rtN236T).

### Conclusions

Introducing TDF improved HBV suppression and liver stiffness at four years. Systematic HBsAg screening, use of potent antiviral agents, and gender-stratified interventions to improve adherence and reduce alcohol consumption are needed to reduce avoidable liver disease in this population.

**Research Output**

- A selection of the data from this project were presented at the American Association for the Study of Liver Diseases (AASLD) in Boston, USA in November 2016 and at the European AIDS Clinical Society conference in Milan, Italy in October 2017.
- A subset of data from this study concerning the use of biomarkers for liver fibrosis prediction have also been published in Gut.[13]
- We are currently in the final stages of preparation of the main outcome data for publication and will be pleased to forward the final manuscript to the Myre Sim committee.

**Learning Outcomes from the Project**

- The project allowed me to gain vital experience in the planning and project management of an observational cohort study in sub-Saharan Africa. I developed new skills in statistical analysis and in virology including the use of next generation sequencing and in bioinformatics analysis of minority quasispecies.
- Experience gained from this project contributed to a successful application for a Wellcome Trust Clinical PhD Fellowship. As a result, I am currently studying hepatitis B at the Malawi-Liverpool Wellcome Trust Clinical Research Programme in Blantyre, Malawi.

## References


1. Lemoine M, Thursz MR. Battlefield against hepatitis B infection and HCC in Africa. Journal of Hepatology **2017**; 66(3): 645-54.
2. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet **2016**; 388(10053): 1459-544.
3. World Health Organisation. Global Hepatitis Report. Geneva, Switzerland, **2017**.
4. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet **2002**; 360(9349): 1921-6.
5. Aoudjane S, Chaponda M, Gonzalez Del Castillo AA, et al. Hepatitis B virus sub-genotype A1 infection is characterized by high replication levels and rapid emergence of drug resistance in HIV-positive adults receiving first-line antiretroviral therapy in Malawi. Clin Infect Dis **2014**; 59(11): 1618-26.
6. Organisation WH. Rapid advice: Antiretroviral therapy for HIV infection in adults and adolescents. Geneva, Switzerland, **2009**.
7. Coffie AP, Egger M, Vinikoor MI, et al. Abstract 565: Changes in Viral Hepatitis Screening Practices Over Time in African HIV Clinics. In: Conference on Retroviruses and Opportunistic Infections. Seattle, Washington, USA, 2016.
8. Initiative CHA. ARV Market Reprt: The state of the antiretroviral drug market in low- and middle-income countries 2015-2020. Boston, MA, USA, **2016**.
9. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet **2013**; 381(9865): 468-75.

10. Stockdale AJ, Phillips RO, Beloukas A, et al. Liver Fibrosis by Transient Elastography and Virologic Outcomes After Introduction of Tenofovir in Lamivudine-Experienced Adults With HIV and Hepatitis B Virus Coinfection in Ghana. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2015**; 61(6): 883-91.
11. Vinikoor MJ, Sinkala E, Chilengi R, et al. Impact of antiretroviral therapy on liver fibrosis among HIV-infected adults with and without HBV coinfection in Zambia. Clin Infect Dis **2017**; 64(10): 1343-9.
12. Grant J, Agbaji O, Muhammad M, et al. Long-Term Changes in Liver Fibrosis in HIV and HIV/HBV Infected Nigerians on ART. Conference on Retroviruses and Opportunistic Infections. Boston, MA, USA, **2016**:564.
13. Stockdale AJ, Phillips RO, Geretti AM. 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**.