New insights on long-term hepatitis B virus responses in HIV-HBV co-infected patients: implications for antiretroviral management in HBV-endemic settings

David Dunn[ab] , Huw Price[a], Tobias Vudriko[c], Cissy Kityo[d], Godfrey Musoro[e], James Hakim[e], Charles Gilks[f], Pontiano Kaleebu[c], Deenan Pillay[g], Richard Gilson[a], DART Virology Group.

DD and HP made an equal contribution

a. Institute for Global Health, University College London

b. MRC Clinical Trials Unit, University College London

c. MRC/UVRI & LSHTM Uganda Research Unit, Entebbe, Uganda

d. Joint Clinical Research Centre, Kampala, Uganda

e. University of Zimbabwe Clinical Research Centre, Harare, Zimbabwe

f. School of Public Health, University of Queensland, Brisbane, Australia

g. Division of Infection and Immunity, University College London

Corresponding author: Professor David Dunn, UCL Centre for Clinical Research in Infection and Sexual Health, Mortimer Market Centre, Mortimer Market Centre, Capper Street, London WC1E 6JB. Email: d.dunn@ucl.ac.uk

Conflicts of Interest and Funding

No conflicts of interest are declared. DART was funded by the UK Medical Research Council (grant number G0600344), the UK Department for International Development (DFID), and the Rockefeller Foundation. Gilead Sciences funded the HBV immunological

and virological assays. HP was funded by a UK Medical Research Council Clinical Research Training Fellowship.

ABSTRACT

Background

WHO treatment guidelines recommend tenofovir plus lamivudine or emtricitabine as the NRTI backbone in first-line regimens for HIV-infected adults. Lamivudine-alone is not recommended, because of the risk of HBV resistance. We studied HBV responses in a large cohort of co-infected patients in a resource-limited setting.

Setting

Clinical centres in Uganda and Zimbabwe

Methods

DART was a randomised trial of monitoring practices in HIV-infected adults starting antiretroviral therapy. Baseline samples were tested retrospectively for HBV serological markers and HBV-DNA. Longitudinal HBV DNA testing, at 48 weeks and the last available sample before HBV-relevant modification of antiretroviral therapy, was performed on patients with detectable HBV-DNA at baseline.

Results

224 HBsAg-positive patients were followed for up to 4.8 years. Of the drugs with anti-HBV activity, 166 were prescribed lamivudine-tenofovir and 58 lamivudine-alone. 98%(96/98) patients with baseline HBV-DNA <6 $\log_{10}$IU/mL achieved viral suppression at 48 weeks (HBV DNA <48 IU/ml), regardless of regimen, compared with 50%(26/52) for HBV-DNA >6 $\log_{10}$ IU/mL, Of the 83 patients suppressed at 48 weeks and with follow-up data, only 7(8%) experienced viral rebound (range 200-3,460 IU/mL). Of the 20 patients not suppressed at 48 weeks and with follow-up data, HBV-DNA levels generally declined with lamivudine-

tenofovir, but increased with lamivudine-alone. ALT flares were not observed in any patient who experienced viral rebound.

Conclusions

The suppressive effect of lamivudine-alone was highly durable (up to 5 years) in HIV-HBV co-infected patients with baseline HBV-DNA <6 $\log_{10}$IU/mL. It may be feasible to develop stratified approaches using lamivudine as the only drug with anti-HBV activity.

Keywords: HIV; Hepatitis B; co-infection; antiretroviral therapy; HBV DNA; lamivudine

INTRODUCTION

Of the 35 million persons living with HIV, an estimated 2.6 million (6%) are also chronically infected with hepatitis B virus (HBV), with most cases (1.9 million) occurring in Sub-Saharan Africa.[1] Fortuitously, several antiretroviral drugs are highly active against both viruses: tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), lamivudine (3TC), and emtricitabine (FTC).[2 3] Regimens containing 3TC alone achieve a large initial reduction in HBV DNA but is perceived to be ineffective in the long-term because of the inevitable development of resistance.[2-4] In contrast, HBV response to TDF is remarkably durable with no documented resistance in a group of 585 patients followed for up to 10 years.[5]

Current WHO HIV treatment guidelines recommend TDF plus 3TC/FTC as part of the preferred first-line regimen for adults.[6] Thus, there is no compelling rationale for HBV screening (which is rarely used in most resource-limited settings) unless it is intended to monitor HBV virological response.[7] However, an estimated 2.4 million patients are still receiving a first-line regimen that does not contain TDF or TAF,[8] TDF/TAF may be contra-indicated in some cases, and an HIV regimen comprising only dolutegravir and 3TC was recently approved for first-line treatment and may be incorporated into treatment guidelines.[9]

DART was a randomised open-label trial of monitoring practices in HIV-infected adult patients starting antiretroviral therapy with a CD4 cell count less than 200 cells/μL.[10] We previously presented an analysis of serological markers and plasma HBV DNA viral load measured on baseline samples.[11] This identified more than 300 HBV co-infected (HBsAg-positive) patients, on whom we undertook further longitudinal testing of HBV DNA, the

findings of which are reported here. All patients were prescribed 3TC and most, but not all, were also prescribed TDF. Although treatment regimen was not randomised, this still provided an exceptional opportunity to compare the long-term effectiveness of lamivudine-tenofovir versus lamivudine alone in terms of anti-HBV activity.

METHODS

The DART trial enrolled 3,316 patients between January 2003 and October 2004 from three clinical centres in Uganda [Medical Research Council/Uganda Virus Research Institute (UVRI) Uganda Research Unit on AIDS, Entebbe; Joint Clinical Research Centre (JCRC), Kampala; and Infectious Diseases Institute, Kampala] and from one centre in Zimbabwe (University of Zimbabwe, Harare).[10] Follow-up continued until September 2009. The trial was approved by research ethics committees in Uganda, Zimbabwe, and the UK. All patients provided written, informed consent. Exclusion criteria included an alanine transaminase (ALT) value greater than five times the upper limit of normal. All patients started first-line ART with co-formulated zidovudine (ZDV) with 3TC, and either TDF, nevirapine (NVP), or abacavir (ABC). Drug allocation was not randomised, except for a 1:1 randomisation to ABC or NVP in a sub-study of 600 patients in Uganda.[12] A further sub-study randomised 813 participants with a good CD4 response to structured treatment interruptions or continuous therapy from 48 or 72 weeks after randomisation.[12]

Plasma samples were stored at screening, enrolment, and each scheduled 3-monthly clinic visit. All tests for HBV, both serological and virological, were performed retrospectively after trial closure. For each patient a screening or enrolment sample was tested for hepatitis B surface antigen (HBsAg) and antibody to HBV core (anti-HBc), and samples with detectable HBsAg were further tested for HBV e-markers (HBeAg, anti-HBe), and HBV DNA. An analysis of baseline findings has been reported previously.[11]

Follow-up testing at later time-points was restricted to patients with detectable/quantifiable HBV DNA at baseline. It was further limited to samples taken before any change in antiretroviral therapy with altered anti-HBV activity, defined as stopping or interrupting

either 3TC or TDF for ≥30 days or switching to TDF if treated initially with NVP or ABC; this included the participants who were randomised to structured treatment interruptions. From each patient, we attempted to retrieve and test a week 48 sample and the last available sample, provided this was after week 96. These samples were tested for HBV DNA but not serology, and no viral resistance tests were conducted.

Laboratory methods

Details of serological tests have been described elsewhere.[11] HBV DNA viral load assays were performed at either JCRC (Roche Cobas Ampliprep/Cobas TaqMan, lower limit of detection 12 IU/ml, upper limit of quantification $110x10^6$ IU/ml) or University of Harare (Abbott RealTime HBV, lower limit of detection 10 IU/ml, upper limit of quantification $1x10^9$ IU/ml). Due to low sample volumes, samples at JCRC were diluted (either 1:2 in 1:4), giving an effective lower limit of detection of 24 or 48 IU/ml. Both laboratories participated in the United Kingdom National External Quality Assessment Service (UK NEQAS) scheme. For the purpose of analysis, viral suppression was defined as HBV DNA <48 IU/ml. CD4 counts (routinely performed on all patients) and HIV viral load levels (available on selected patients) were examined in patients with a suboptimal HBV response for evidence of non-compliance.

Statistical methods

Statistical approaches were mainly descriptive based on the observed data (i.e. missing=excluded). Proportions were compared by Fisher's Exact Test. Logistic regression was used to examine predictors of viral suppression at week 48, excluding patients whose baseline HBV DNA was less than 6 $\log_{10}$ IU copies/ml since this was almost a perfect predictor of a successful outcome. ZDV/3TC/NVP and ZDV/3TC/ABC regimens were

combined in some analyses due to small numbers, although there is limited evidence that ABC may have some anti-HBV activity.[13] All analyses were performed in STATA version 15.1.

RESULTS

Baseline HBV DNA findings

308 (9.3%) patients were HBsAg-positive at baseline, with a significantly higher rate observed in Zimbabwe (16.7%,167/998) than in Uganda (6.1%,141/2317) (P<0.001). These rates are broadly consistent with data reported in other surveys.[1 14] Among HBsAg-positive patients, 282 (91.6%) had an available baseline sample tested for HBV DNA. 58 (20.6%) patients had undetectable DNA, 33 (11.7%) had detectable DNA below the level of quantification (BLQ), and 191 (67.7%) had quantifiable DNA (Figure 1). 143 (50.7%) patients had a HBV DNA level greater than 2000 IU/ml, the threshold for initiating HBV therapy in some treatment guidelines for mono-infected patients,[2 3] and 90 (31.92%) patients had a value greater than 6 $\log_{10}$ IU/mL.

The remaining analyses relate to the 224 patients with detectable or quantifiable DNA at baseline, in whom follow-up testing was performed (Table 1). 41% of patients were HBeAg-positive. ALT levels were at most moderately raised (maximum value = 148 IU/L) despite advanced immunosuppression (median CD4 count = 88 cells/ cells/μl). 166 patients initiated antiretroviral therapy with ZDV/3TC/TDF, 41 with ZDV/3TC/NVP, and 17 with ZDV/3TC/ABC.

Follow-up

A flow diagram of participant follow-up is shown in Figure 2. Antiretroviral treatment (related to anti-HBV activity) was modified for 23 patients before 48 weeks, mainly due to patient decision, failure to attend, an adverse reaction, or participation in the STI sub-study. Treatment was modified for a further 28 patients between 48 and 96 weeks, mainly due to participation in the STI sub-study or initiating second-line therapy. 21 patients died, mostly

soon after antiretroviral initiation (14 before 20 weeks).[15] None of the deaths were judged to be liver-related by an Endpoint Review Committee. HBV DNA was assessed on 114 patients after 96 weeks, at a median (range) of 252 (96, 289) weeks, or 4.8 (1.8, 5.6) years.

HBV DNA response at week 48

150 (82.4%) of 182 patients had an available sample tested for HBV DNA at 48 weeks. 83 (55.3%) patients had undetectable DNA, 29 (19.3%) had detectable DNA BLQ, and 38 (25.3%) had quantifiable DNA, with a median (IQR) value of 2.47 (2.16, 3.20) $\log_{10}$ IU/ml. 16 (10.7%) patients had a HBV DNA level greater than 2000 IU/ml.

Figure 3 shows HBV DNA at 48 weeks plotted against baseline HBV DNA, stratified by antiretroviral regimen. Overall, 98% (96/98) of patients with baseline HBV DNA <6 $\log_{10}$IU/mL achieved viral suppression at 48 weeks. One patient (who received ZDV/3TC/TDF) showed no discernible change in HBV DNA (350 IU/mL at baseline, 260 IU/mL at 48 weeks) despite laboratory evidence of good compliance and normalisation of ALT levels (126 IU/L at baseline, 17 IU/L at baseline at 48 weeks) (Appendix, page 8). In the other non-suppressor (who received ZDV/3TC/NVP), HBV DNA declined from 126,000 IU/mL at baseline to 150 IU/mL at 48 weeks. In contrast, only 26 (50%) of the 52 patients with baseline HBV DNA level greater than 6 $\log_{10}$ IU/mL achieved viral suppression, although all achieved a reduction of at least 3.26 $\log_{10}$ IU/mL (i.e. ~2000-fold). Viral suppression was more frequent among patients who received lamivudine-tenofovir (58%; 23/40) than lamivudine alone (25%; 3/12) (P=0.05).

As expected, a close relationship was observed between HBeAg status and baseline HBV DNA level (Appendix, page 5): 88% of HBeAg-negative patients and 28% of HBeAg-

positive patients had a baseline HBV DNA less than 6 $\log_{10}$ IU/mL Graphs analogous to Figure 3 but showing the effect of HBeAg status are provided in the Appendix.

HBV DNA response at last time point

114 (75.0%) of 152 patients had an available sample tested for HBV DNA at the last time point. 79 (69.3%) patients had undetectable DNA, 18 (15.8%) had detectable DNA BLQ, and 17 (14.9%) had quantifiable DNA, with a median (IQR) value of 3.08 (2.47, 6.24) $\log_{10}$ IU copies/ml.

103 of the 114 patients whose HBV DNA was assessed at the last time point had a paired value at 48 weeks. Of the 83 patients with HBV DNA<48 IU/mL at 48 weeks, 7 (8%) patients subsequently experienced viral rebound, all to a relatively low level (range 200-3,460 IU/mL) (Figure 4). The frequency of rebound was similar for patients who were prescribed lamivudine-tenofovir (10%, 6/61) and those prescribed lamivudine-alone (5%, 1/21) (P=0.67). HBV DNA profiles for the 20 patients with non-suppressed HBV DNA at week 48 are shown in Figure 5. Five of six patients prescribed lamivudine-alone showed substantial increases in HBV DNA (to greater than 10^6 IU/mL). In contrast, HBV DNA declined to <48 IU/mL in all but two of 14 patients prescribed lamivudine-tenofovir.

A total of 14 patients either experienced viral rebound from undetectable or BLQ at 48 weeks, or an increase in HBV DNA after 48 weeks, having never fully suppressed viral replication. With four possible exceptions (patients 005, 006, 013, 014), HIV viral load and CD4 count data indicated good compliance to therapy, suggesting the development of HBV resistance as the most likely explanation for the increases in HBV DNA level (Appendix, page 8). Noteworthy findings were observed on patients 007 and 008, both of whom

experienced HBV DNA rebound while receiving lamivudine-tenofovir while maintaining HIV suppression. None of the 14 patients experienced an ALT flare, despite some substantial rebounds in HBV DNA levels.

DISCUSSION

This is the largest published cohort study of HIV-HBV co-infected patients with the longest follow-up, and provides novel and important insights on HBV DNA response during first-line antiretroviral therapy. Response at 48 weeks was strongly influenced by two factors, HBV DNA level at baseline and whether the antiretroviral regimen contained lamivudine alone or lamivudine-tenofovir. These factors need to be considered in conjunction.

If baseline HBV DNA was less than approximately 6 $\log_{10}$ IU/mL, viral suppression at 48 weeks was almost ubiquitous, regardless of the antiretroviral regimen received. Further, if this outcome was achieved, over 90% of patients remained virally suppressed at the latest time-point, almost five years, on average, after initiating therapy. These findings contradict the widespread belief that lamivudine monotherapy has severely time-limited activity against HBV in the context of HIV-HBV co-infection. This view is mainly derived from a French cohort study from the 1990s: this reported that 3TC-resistant HBV emerged in 20% of patients per year and that, following virological breakthrough, HBV DNA levels rapidly returned to pre-treatment levels.[16] However, the cohort comprised of only 66 patients, of whom only 12 were followed beyond two years and 6 beyond three years. Other studies, although in mono-infected patients, found a much higher rate of sustained HBV DNA response (>90% at 2 years) and reduced HBV DNA concentrations compared with baseline despite the emergence of resistant virus.[17 18]

A more complex picture was apparent if baseline HBV DNA was greater than 6 $\log_{10}$ IU/mL, with one half of patients failing to achieve viral suppression at 48 weeks. In this group, HBV DNA levels in patients who received lamivudine-tenofovir generally continued to decline beyond 48 weeks, whereas they tended to increase, although to well below pre-treatment

levels, if they received lamivudine alone. A striking finding was the absence of ALT flares regardless of a favourable or unfavourable HBV DNA response.

Our results are broadly consistent with an earlier report on HIV-HBV co-infected participants from two ACTG trials, although our study is three times larger with two years additional follow-up.[19] These authors also found that lamivudine alone was effective in patients with a low baseline HBV DNA level, defined a priori as less than 20,000 IU/ml. As previously noted, our analysis identified a much higher threshold value, around 6-7 $\log_{10}$ IU/mL. Overall, 68% of HBsAg-positive patients in our study had a baseline HBV DNA less than 6 $\log_{10}$ IU/mL, for whom lamivudine alone was likely to have been effective. The ACTG analysis identified two other baseline predictors of a favourable HBV response, very low baseline CD4 cell count and high ALT levels; our findings support the latter but not the former association.

Several limitations of our study are acknowledged. First, the allocation of antiretroviral regimen was not randomised, although any bias is likely to be small as the HBV status of participants was not known at the time of allocation. Second, limited resources constrained the number of longitudinal samples that we were able to test, and no virological data were generated on patients with undetectable HBV DNA at baseline or after a switch to a second-line regimen. Third, neither follow-up HBV serology nor HBV resistance testing was performed, which limits our understanding of the causes of viral breakthrough. Fourth, the cohort is susceptible to survivorship bias through deaths and modification of antiretroviral therapy, although both factors appeared to be unrelated to HBV infection. Finally, as most of the study population are likely to have acquired HBV infection in early childhood, the results

may not generalise to populations where the predominant mode of transmission is through sexual contact or injection drug use.

Our findings have important implications for clinical management, particularly in settings where HBV screening is not routinely performed. First, recently approved two-drug HIV treatment regimens are generally considered to be unsuitable for resource-limited settings with a high prevalence of HBV infection as this would result in lamivudine being the only drug with HBV-activity in patients who may have unrecognised HBV infection.[20] However, our findings suggest that this concern may have been overly emphasised, other than in patients with high baseline HBV concentrations. Even in this group, we found no evidence of ALT flares and a remarkably low rate of liver-related morbidity in the cohort overall. The strong correlation between HBV DNA level and HBeAg-status suggests a potential role for point-of-care HBe tests to identify patients with high level HBV DNA replication.[21 22]

Second, HIV treatment guidelines recommend that both TDF and 3TC or FTC should be continued in second-line regimens (adding ZDV as a third NRTI) for HIV-HBV co-infected patients.[6] However, because HBV DNA levels would be expected to be low at the point of switching to second-line ART (provided non-compliance is excluded), 3TC/FTC alone as part of a new ART regimen may be sufficient to suppress HBV replication. 3TC/FTC also appear to have a continued benefit against HIV, even in the presence of the highly resistant M184V mutation.[23 24] Thus a compromise strategy in areas with high HBV endemicity could be to include 3TC/FTC indefinitely in all antiretroviral regimens.

Finally, excellent HBV viral outcomes were observed despite the absence of real-time testing, mirroring findings for HIV outcomes in the DART trial.[25] Consideration of cost-

effectiveness and a broader perspective of health system utilisation are important before implementing routine monitoring for the treatment of either virus in resource-limited settings.[26-28]

ACKNOWLEDGEMENTS

DART Virology Group

P. Kaleebu, D. Pillay, P. Awio, M. Chirara, D. Dunn, D.M. Gibb, C. Gilks, R. Goodall, A. Kapaata, M. Katuramur, F. Lyagoba, B. Magambo, K. Mataruka, L. Mugarura, T. Musunga, M. Nabankkema, J. Nkalubo, P. Nkurunziza, C. Parry, V. Robertson, M. Spyer, D. Mulima, D.E. Williams, I. Nankya, S. Nassimbwa, E. Ndashimye, E. Nabulime, M. Phiri, K. Mutasa, and S. Mukasa.

This study was built upon the main DART study. A full list of contributors is given in reference 10.

AUTHORS' CONTRIBUTIONS

RG, DD, and DP developed the sub-study protocol. HP and DD conducted the statistical analyses. TV performed laboratory testing. DD and RG wrote the first draft of the manuscript and made subsequent edits. All other authors commented on the manuscript.

Table 1. Characteristics of study cohort with follow-up HBV DNA testing

Factor	Number (%) or median (IQR)
Total	224 (100)
Country	
Uganda	107 (48)
Zimbabwe	117 (52)
Female	115 (51)
Age, years	37 (32,42)
CD4 count, cells/μl	88 (33,138)
ALT, IU/L	29 (22,42)
HBeAg status	
Negative[1]	121 (59)
Positive[1]	85 (41)
Unknown	18
Initial ART regimen	
ZDV/3TC/TDF	166 (74)
ZDV/3TC/NVP	41 (18)
ZDV/3TC/ABC	17 (8)

1. Percentages exclude patients with unknown HBeAg status

FIGURES

Figure 1

HBV DNA findings at baseline and definition of study cohort

Figure 2

Participant follow-up and disposition

Figure 3

HBV DNA level at week 48 versus baseline, stratified by first-line ART regimen

Legend: ZDV/3TC/TDF, red circles; ZDV/3TC/NVP, blue circles; ZDV/3TC/ABC, green circles.

Footnote: Values below level of quantification (48 IU/mL) shown as random value between 0 and 1. Dotted line corresponds to no change.

Figure 4

Panel A: HBV DNA profiles of patients with suppressed HBV DNA at week 48 who subsequently re-bounded

Legend: ZDV/3TC/TDF, red lines ; ZDV/3TC/ABC, green lines

Footnote: Values below level of quantification (48 IU/mL) shown as random value between 0 and 1.

Panel B: HBV DNA profiles of patients with non-suppressed HBV DNA at week 48

Legend: ZDV/3TC/TDF, red lines; ZDV/3TC/NVP, blue lines; ZDV/3TC/ABC, green lines

REFERENCES

1. Platt L, French CE, McGowan CR, et al. Prevalence and burden of HBV co-infection among people living with HIV: A global systematic review and meta-analysis. Journal of Viral Hepatitis 2020;**27**(3):294-315
2. European Association for the Study of the Liver. 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatology 2017;**67**(2):370-98
3. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;**67**(4):1560-99
4. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006;**354**(10):1001-10
5. Marcellin P, Wong DK, Sievert W, et al. Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. Liver International 2019;**39**(10):1868-75
6. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013
7. Wiersma ST, McMahon B, Pawlotsky JM, et al. Treatment of chronic hepatitis B virus infection in resource-constrained settings: expert panel consensus. Liver International 2011;**31**(6):755-61
8. Clinton Health Access Initiative. HIV Market Report. The state of the HIV testing and prevention markets in low- and middle-income countries 2017-2022. Issue 9, September 2018. https://www.clintonhealthaccess.org/2018-hiv-market-report/
9. Radford M, Parks DC, Ferrante S, Punekar Y. Comparative efficacy and safety and dolutegravir and lamivudine in treatment naive HIV patients. AIDS 2019;**33**(11):1739-49
10. DART Trial Team. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. Lancet 2010;**375**(9709):123-31
11. Price H, Dunn D, Zachary T, et al. Hepatitis B serological markers and plasma DNA concentrations: baseline results from a treatment-monitoring practices trial. AIDS 2017;**31**(8):1109-17
12. DART Trial Team. Fixed duration interruptions are inferior to continuous treatment in African adults starting therapy with CD4 cell counts < 200 cells/microl. AIDS 2008;**22**(2):237-47
13. McGuigan C, Harris SA, Daluge SM, et al. Application of phosphoramidate pronucleotide technology to abacavir leads to a significant enhancement of antiviral potency. Journal of Medicinal Chemistry 2005;**48**(10):3504-15
14. Barth RE, Huijgen Q, Taljaard J, Hoepelman AI. Hepatitis B/C and HIV in sub-Saharan Africa: an association between highly prevalent infectious diseases. A systematic review and meta-analysis. Int J Infect Dis 2010;**14**(12):e1024-31
15. Walker AS, Prendergast AJ, Mugyenyi P, et al. Mortality in the year following antiretroviral therapy initiation in HIV-infected adults and children in Uganda and Zimbabwe. Clin Infect Dis 2012;**55**(12):1707-18
16. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. Hepatology 1999;**30**(5):1302-6.

17. Liaw YF, Leung NW, Chang TT, et al. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. Gastroenterology 2000;**119**(1):172-80
18. Chang TT, Lai CL, Chien RN, et al. Four years of lamivudine treatment in Chinese patients with chronic hepatitis B. Journal of Gastroenterology and Hepatology 2004;**19**(11):1276-82
19. Thio CL, Smeaton L, Hollabaugh K, et al. Comparison of HBV-active HAART regimens in an HIV-HBV multinational cohort: outcomes through 144 weeks. AIDS 2015;**29**(10):1173-82
20. Calmy A. Positioning 2-drug ART in two key treatment settings. Clinical Care Options 2020. https://www.clinicaloptions.com/hiv/programs/art-advances/clinicalthought/ct3/page-1
21. Peeling RW, Boeras DI, Marinucci F, Easterbrook P. The future of viral hepatitis testing: innovations in testing technologies and approaches. BMC Infectious Diseases 2017;**17**(Suppl 1):699
22. Chevaliez S, Pawlotsky JM. New virological tools for screening, diagnosis and monitoring of hepatitis B and C in resource-limited settings. Journal of Hepatology 2018;**69**(4):916-26
23. Quan Y, Brenner BG, Oliveira M, Wainberg MA. Lamivudine can exert a modest antiviral effect against human immunodeficiency virus type 1 containing the M184V mutation. Antimicrob Agents Chemother 2003;**47**(2):747-54
24. Castagna A, Danise A, Menzo S, et al. Lamivudine monotherapy in HIV-1-infected patients harbouring a lamivudine-resistant virus: a randomized pilot study (E-184V study). AIDS 2006;**20**(6):795-803
25. Kityo C, Gibb DM, Gilks CF, et al. High level of viral suppression and low switch rate to second-line antiretroviral therapy among HIV-infected adult patients followed over five years: retrospective analysis of the DART trial. PLoS One 2014;**9**(3):e90772
26. Medina Lara A, Kigozi J, Amurwon J, et al. Cost effectiveness analysis of clinically driven versus routine laboratory monitoring of antiretroviral therapy in Uganda and Zimbabwe. PLoS One 2012;**7**(4):e33672
27. Hosseinipour MC, Schechter M. Monitoring antiretroviral therapy in resource-limited settings: balancing clinical care, technology, and human resources. Curr HIV/AIDS Rep 2010;**7**(3):168-74
28. Harries AD, Schouten EJ, Libamba E. Scaling up antiretroviral treatment in resource-poor settings. Lancet 2006;**367**(9525):1870-2