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Review

Hepatitis B virus genetic multiplicity and the associated HBV lamivudine resistance mutations in HBV/HIV co-infection in Western Kenya: A review article

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ABSTRACT

Background: Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) co-infections are common as the two viruses use same routes of transmission. Studies show that HIV infection modifies the natural course of chronic HBV infection, leading to more severe and progressive liver disease, and a higher incidence of cirrhosis, liver cancer and mortality. Therefore, determining HBV status and genotypes among HIV co-infected patients would improve their therapeutic management.

Objective: This article reviewed the HBV genetic multiplicity and the associated HBV Lamivudine resistance mutations in HBV/HIV co-infection in western Kenya.

Methods: Comprehensive literature searches and analysis were performed in peer-reviewed journals in the National council for biotechnology information (NCBI), PubMed, and Web of science using key words of HIV, Hepatitis B genotypes, HBV/HIV co-infection and Lamivudine resistance.

Results: HBV genotype A is predominant. D and E are also present in Kenya and neighboring countries in the region. HBV polymerase rtV173L, rtL180M, and rtM204V major substitutional mutations were identified. Currently, TDF + 3TC + DTG are recommended for treatment of HBV/HIV co-infection.

Conclusion: Evidence shows that HBV/HIV co-infection places a heavy burden to the society. Along with ART regimen, HBV genotype is a major factor determining the course of disease and treatment outcome. Treating HIV in HBV/HIV co-infection with antiretroviral agents may result in a very high prevalence of HBV 3TC-resistance mutations. Therefore, improved screening for HBV and extended follow-up of HBV/HIV co-infected individuals is needed to better understand the impact of different ART regimens on clinical outcomes.

1. Introduction

Hepatitis B virus infection in HIV positive people is associated with increased risk of chronicity, reduced chances of spontaneous clearance, higher rates of replication and reactivation and therefore increased incidence of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC) (ICAP_CQUIN_Kenya-ARV-Guidelines-2018-Final_20thAug2018, n.d.). Additionally, HBV/HIV co-infection has been associated with rapid HIV disease progression and poorer HIV treatment outcomes. Other complications of HBV/HIV co-infection include increased incidence of drug-related hepatotoxicity, drug-toxin interactions and ART-related immune reconstitution hepatitis (ICAP_CQUIN_Kenya-ARV-Guidelines-2018-Final_20thAug2018, n.d.; NASCOP, 2018). Since HBV and HIV share common routes of transmission, the prevalence of hepatitis B markers [anti- hepatitis B core antibodies (anti-HBcAb) or hepatitis B surface antigen (HBsAg)] in HIV-infected patients is remarkably high, (Lacombe et al., 2009). The risk of acquiring HBV infection in HIV-infected patients is increased by 40% compared to HIV-

Abbreviations: HBV, hepatitis B virus; HIV, human immunodeficiency virus; DNA, deoxyribonucleic acid; WHO, world health organization; CCC, comprehensive care clinic; NCBI, national council for biotechnology information; PLHIV, people living with HIV; ALT, alanine aminotransferase; ART, antiretroviral therapy; 3TC, lamivudine; DTG, dolutegravir; TDF, tenofovir disoproxil fumarate; EFV, efavirenz; NASCOP, national AIDS and STI control program; ATV/r, atazanavir/ritonavir; DRMs, drug resistance mutations; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B envelope antigen; HBcAb, hepatitis B core antibody..

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negative individuals (Weldemhret, 2021). In high endemicity areas, about 10% of HIV-infected individuals have been found to be concurrently infected with HBV (Cheng et al., 2021; Archampong et al., 2017; Yousif et al., 2014; Ranjbar et al., 2011). HBV co-infection causes increased morbidity and mortality among people living with HIV (Weldemhret, 2021). According to the World Health Organization (WHO) global progress report 2021, HIV, viral hepatitis, and sexually transmitted infections account for 2.3 million deaths per year, which represents 14% of deaths from infectious and parasitic diseases, digestive diseases and cancer and 4% of deaths from all causes worldwide. They result in 1 million people newly infected per day and 1.2 million people developing cancer per year and continue to be a major public health burden in terms of mortality, morbidity and quality of life, (World Health Organisation, 2021). Although some current therapeutic strategies are considered effective options in treating single virus infections, HBV/HIV coinfection has altered the natural history of the virus, requiring novel individualized therapeutic forms (Cheng et al., 2021). Although there has been great progress in HIV care, universal HBV vaccination and care is lacking, then again, HBV status of most HIV patients is usually not determined hence most HIV care does not consider HBV co-infection (Deressa et al., 2017). Unfortunately, since most patients are initiated on therapy without testing for HBV and majority have been on lamivudine (for HBV or as the only anti-HBV active agent in co-infected patients) inadvertently there may be a lot of resistance in the patient population especially where the burden of both infections is high (Ocama et al., 2015). This, therefore, calls for a common public health approach along the continuum of prevention, diagnosis, treatment and care, (World Health Organisation, 2021). (See Figs. 1–2.)

2. Epidemiology

HBV, HIV and HBV/HIV co-infections are transmitted from mother to child during birth and delivery, as well as through contact with blood or other body fluids during sex with an infected partner, unsafe injections, or exposures to sharp instruments (World Health Organisation, 2021). 296 million people were living with chronic hepatitis B infection in 2019, with 1.5 million new infections each year (World Health Organisation, 2021). The prevalence varies in different geographic regions, ranging from 10 to 28%, with the greatest burden of disease in Southeast Asia and Sub-Saharan Africa (Cheng et al., 2021; Archampong et al., 2017; Deressa et al., 2017; Chotun et al., 2015). Therefore, in these regions, most individuals are often infected at early childhood (due to close contact with household members) or in the perinatal period (from mother to baby at birth), with the highest proportion of the prevalence reported in west African and south African cohorts (Ranjbar et al., 2011; Spearman et al., 2017; Mabeya et al., 2016). These rates are high compared to low endemic areas, such as in western countries, where most transmission occurs during adolescence and young adulthood due to high risk behaviors like unprotected sexual contact and injection drug use (Cheng et al., 2021; Mabeya et al., 2016). HBV/HIV-co-infected individuals have approximately five- to six-fold higher risk of hepatocellular carcinoma (HCC) incidence with the presence of liver cirrhosis (Cheng et al., 2021).

At Mama Lucy hospital in Nairobi Kenya, 5.5% of HIV, infected patients attending the clinic also had HBV co-infection (Mabeya et al., 2016). A different study in the same hospital found a 7.25% HBV/HIV co-infection rate among patients attending the comprehensive care clinic (Mabeya et al., 2017). HBV/HIV co-infection was 4.26% in a study carried out in informal urban settlements in Nairobi Kenya (Kerubo et al., 2015). However, among the high-risk group individuals at the coastal Kenya, co-infections of HBV and HIV were 9.6% (Kilongosi et al., 2015). Among HIV-1 discordant heterosexual couples, co-infection with HBV was as high as 10.2% (Njuguna et al., 2015).

At the Academic Model Providing Access to Healthcare Clinic, co-infection with HBV and HIV among patients was 5.7% (W. RJ, O. PE, M. AW, N. DW, L. R, and B. MW, 2016), whereas, at selected hospitals in Kericho County, there was 5% HBV/HIV co-infection rate among patients attending various CCC clinics (Kenyatta, 2018). However, in a cross-sectional study which was carried out to establish the burden of HBV among high-risk populations in the western Kenya region demonstrated a high prevalence of 8.8% co-infections with the two viruses (Mercy Jelagat et al., 2020). These data correlate with the findings in other countries in the same region. These include, northwest Ethiopia, where HBV/HIV co-infection was 5.5% (Deressa et al., 2017), Mulago hospital in Uganda where HBV/HIV co-infection was 6.7% (Ocama et al., 2015), at Bugando hospital in northwestern Tanzania, where co-infection with HBV and HIV was 6.6% (Kilonzo et al., 2017). In Sudanese patients, there was a 14% rate of co-infection (Yousif et al., 2014). In a retrospective laboratory based study in Cameroon, HBV/HIV co-infection was 25.5% (Magoro et al., 2016). A study on the prevalence of Occult hepatitis B virus infection in Moroccan HIV infected patients demonstrated a prevalence of 23% (Bajjou et al., 2015). The overall pooled prevalence of HBV/HIV co-infection among pregnant mothers in sub-Saharan Africa was 3.302% (Kafeero et al., 2020). These statistics narrow down to the possible HBV genotypes circulating among these population that predisposes them to HIV co-infection. The mechanistic presentation of both infections at the genetic level should leverage their epidemiological survey and management.

3. Hepatitis B virus genotypes

At least 10 hepatitis B virus (HBV) genotypes (A to J) with distinct geographic distributions and several HBV mutants, including pre-core/core promoter mutations and pre-S/S deletion mutations, have been recognized to be not only predictive of liver disease progression but also associated with response to antiviral therapy (Lin and Kao, 2015). HBV genotype–specific pathogenesis may contribute to heterogeneous clinical outcomes in chronic hepatitis B patients across the world. For example, patients with HBV genotypes C and D infection have a lower rate of spontaneous HBeAg seroconversion (Archampong et al., 2017; Lin and Kao, 2015). In addition, HBV genotypes C and D have a higher frequency of core promoter and pre-S mutations than genotypes A and B. Genotypes C and D also carry a higher lifetime risk of cirrhosis and HCC development than genotypes A and B (Lin and Kao, 2015; Vivekanandan et al., 2004). Therapeutically, genotypes A and B patients have a better response to interferon-based therapy than genotypes C and D patients, but the response to nucleos(*t*)ide analogs is comparable across different HBV genotypes (Archampong et al., 2017; Lin and Kao, 2015; Vivekanandan et al., 2004). Africa is one of the endemic regions of HBV, with five genotypes A–E identified. Genotype D is found in Tunisia, genotypes A–D in South Africa, and genotype E in Nigeria (Mabeya et al., 2017; Kilongosi et al., 2015; Lin and Kao, 2015; Zhang et al., 2015). In Cameroon, genotypes A and E are predominant (Magoro et al., 2016).

Studies carried out in Nairobi and coast provinces of Kenya demonstrated that HBV genotype A is the most predominant genotype in Kenya with both sub-type A1 and A2 present. Genotype D and E were also present in the population. This demonstrates that there could be a high genetic diversity of HBV in Kenya, that would translate to co-

Genotype	Region
A	Africa, Europe, India, America.
B	Asia, Pacific region
C	Asia, Pacific region
D	Africa, Europe, Mediterranean, India
E	West Africa
F	Central America, South America
G	France, Germany, Americas
H	Central America and Mexico
I	Vietnam, Laos
J	Japan

Fig. 1. Summary table of HBV genotypes distribution (Lin and Kao, 2015).

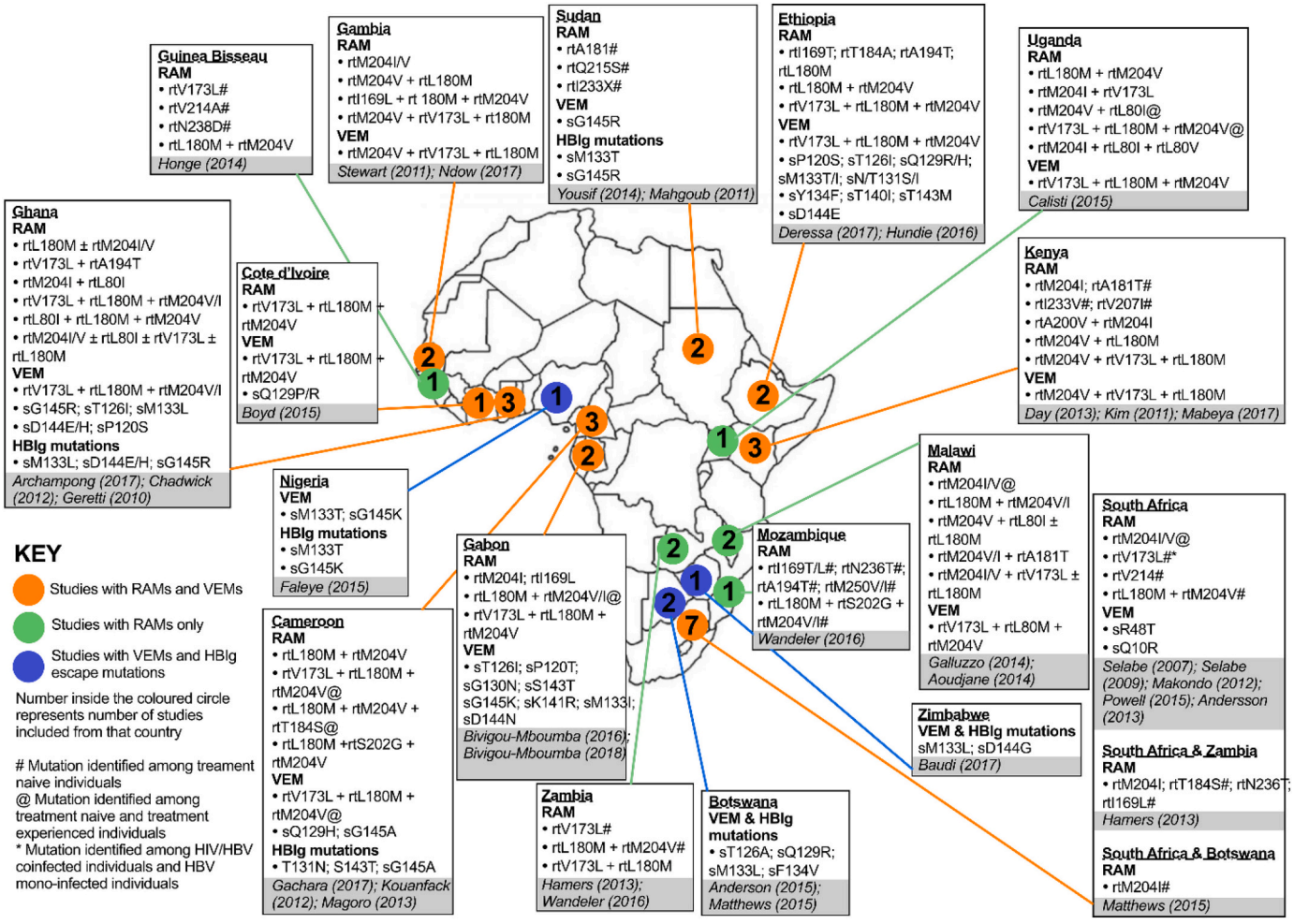

Fig. 2. Annotated map to summarized HBV drug resistance associated mutations (RAMs) and vaccine escape mutations (VEMs). Mutations identified from 33 studies of African cohorts published between 2007 and 2017 (Mokaya et al., 2018).

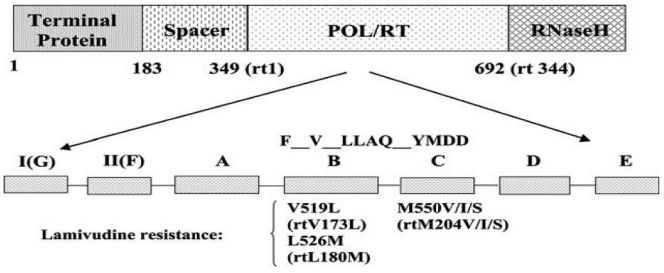

Fig. 3. Genotype-independent numbering scheme for the HBV Pol. The functional conserved domains (G-E) are shown. The B domain mutations rtV173L and rtL180M as well as the C domain mutations rtM204V/I/S associated with lamivudine resistance are highlighted (Locarnini, 2003) (Fig. 3).

existence of the genotypes in the population. When this is associated with HIV, then disease burden is compounded thus leading to difficulty in management (Kilongosi et al., 2015; Mwangi et al., 2009). In a study which recruited patients presenting with jaundice in four selected referral hospitals in Kenya demonstrated predominance of HBV genotype A followed by D and E (Ochwoto et al., 2016). In western Kenya, it was demonstrated that there is a heavy burden of Hepatitis among the high risk groups, with as high as 10.7% prevalence rate (Mercy Jelagat et al., 2020). This, therefore, calls for more genotypic studies in the region with the possibility of identifying new HBV genotypes, and their association with HIV prognosis. However, the information on HBV genetic diversity is still limited in Kenya, even though the country is considered among the endemic countries for these viruses (Mabeya et al., 2017). The paucity of information could be due to lack of focused studies to unravel the linking units between HBV genotypes and HIV that supports their co-existence.

4. Management of Hepatitis B and HIV infections

Antiviral therapies should be initiated for HBV/HIV co-infected patients as soon as possible regardless of clinical stage of the disease, the count of CD4+ cells and the stage of liver disease, since the effects of anti-HBV treatment might be reduced following the deterioration of immunodeficiency (Cheng et al., 2021). However, new data shows that HIV testing and prevention, as well as Hepatitis B care services, are among the most frequently disrupted services caused by COVID-19. (World Health Organisation, 2021). The general recommendations for treatment preparation, adherence counselling and support and monitoring of therapy for people living with HIV (PLHIV) apply. However, because HBV positive patients are at higher risk of hepatotoxicity, closer monitoring of liver function (with ALT) is advised (ICAP_CQUIN_Kenya-ARV-Guidelines-2018-Final_20thAug2018, n.d.).

5. Recommended first line ART in HBV/HIV co-infection

The recommended first-line ART in adolescents and adults with HBV/HIV co- infection is TDF + 3TC + DTG (or TDF + 3TC + EFV for

women and adolescent girls of childbearing potential), (ICAP_CQUIN_-Kenya-ARV-Guidelines-2018-Final_20thAug2018, n.d.). Utilization of agents against HBV/HIV only can lead to drug resistance. Therefore, the optimal therapeutic options should include agents possessing dual anti-HBV and anti-HIV activity. Treatment with both TDF and 3TC is recommended, as 3TC alone will result in rapid emergence of resistance (Cheng et al., 2021). However, TDF could not completely suppress HBV replication (Jia et al., 2018). Therefore, a thorough search for drug interactions that would benefit the patient from both frontiers is encouraged.

6. Recommended second line ART in HBV/HIV co-infection

The recommended second-line ART regimen in HBV/HIV co-infection is TDF + 3TC + ATV/r (ICAP_CQUIN_Kenya-ARV-Guidelines-2018-Final_20thAug2018, n.d.; NASCOP, 2018). However, the efficacy and safety of many strategies for the treatment of HBV/HIV coinfection are being assessed in clinical trials. Several agents remain at the preclinical phase and are not yet available for the clinical treatment of HBV/HIV coinfection. More research and clinical trials are required to definitively establish the value of such agents for the therapy of HBV/HIV coinfection (Cheng et al., 2021). This study recommended apart from animal model drug testing stages, computer simulations and bioinformatics analysis need to be considered for a holistic approach into the management of both infections.

7. HBV Lamivudine (3TC) resistance associated mutations

HBV drug resistance is very common in HBV/HIV-1 co-infected patients receiving lamivudine-containing ART without tenofovir (Mabeya et al., 2017; Locarnini, 2003). In Nairobi, Nucleos(*t*)ide drug resistance mutations were found in 6 patients. Five subjects had rtV173L, rtL180M, and rtM204V and one with rtL180M and rtM204V major mutations (Mabeya et al., 2017). This data correlates with the findings in neighboring countries in the region. In Ethiopia for instance, all HBV/HIV positive cases that were on ART with anti-HBV activity (i.e., 3TC) had 3TC associated HBV drug resistance mutations (DRMs) (i.e., rtV173L, rtL180M, and rtM204V) detected in 7/13 (53.8%) subjects (Deressa et al., 2017). In Ghana, of the 100 HBV/HIV co-infected study patients, 75 were successfully PCR-amplified, and 63 were successfully sequenced. Of these 63 patients, 27 (42.9%) were ART-experienced, and 58 (92.1%) had HBV genotype E. No resistance mutations were observed in the 36 ART-naïve patients, while 21 (77.8%) of 27 treatment-experienced, patients had resistance mutations. All patients with resistance mutations had no tenofovir (TDF) in their regimens. The 3TC resistance mutations rtL180M and rtM204V were observed in 10 (47.6%) of the 21 patients, while 5 patients (23.8%) had rtV173, rtL80I, and rtM204V mutations (Archampong et al., 2017). In Cameroon, HBV polymerase mutations associated with resistance to lamivudine and other drugs used in treatment were determined. These mutations were detected in seven patients. Six among genotype A and one among genotype E. Mutations rtV173L, rtL180M, rtM204V conferring resistance to lamivudine and other ʟ-nucleoside analogues were identified in six patients while one patient had the rtL180M + rtM204V + rtT184S mutations, associated with resistance to both ʟ-nucleoside analogues and entecavir (Magoro et al., 2016). In addition, drug resistance findings support the use of TDF based ART regimens among HBV/HIV co-infected persons (Magoro et al., 2016). Elsewhere, in China, The major pattern of lamivudine (3TC)-resistant mutations was L180M + M204I + L80I (35.7%). In total, 95% of subjects with resistant mutations had cross-resistance to telbivudine and entecavir. No putative TDF resistance change was found (Jia et al., 2018). In another study in China, different HBV genotypes demonstrated varying resistance to ART among different ethnic groups as follows; Genotype B and C were common in Han population, while genotype D was predominant in Uygurs. Genotype C was the major genotype in both Tibetans and Yis, and recombinant C/D was found in Tibetans only. Lamivudine resistance was common in all populations, especially in Hans with prevalence of 42.8%. Entecavir resistance was barely observed regardless of ethnicity. Genotype C isolates had higher rates of rtA181T/V than genotype B (Zhang et al., 2015). This is an indication that varied HBV genotypes circulate among the population that may be drug resistance induced, and this could be exuberated by the HIV co-infection.

8. Conclusion

Accumulating evidence indicates that the co-infection of HBV and HIV place a heavy burden to the society (Cheng et al., 2021). Co-infection is capable of accelerating the progression of liver diseases due to mixed management strategies (NASCOP, 2018). Treating HIV in HBV/HIV co-infection with antiretroviral agents may result in a very high prevalence of HBV 3TC-resistant mutations. There were no resistance changes noted in patients treated with TDF (Jia et al., 2018). Improved screening for HBV and extended follow-up of HBV/HIV-1 co-infected individuals is needed to better understand the impact of different ART regimens on clinical outcomes in the population (C. and V. O. of H. B. V. C.-I. in H.-1 P. K. W. on A. T. Prevalence, 2013). Taken together, HBV genotype A is the most prevalent in Kenya followed by D and E (Mabeya et al., 2017). There is paucity of data on HBV genotypes and HBV/HIV co-infection in western Kenya, however, different genotypes exhibit different resistance rates to ART (Zhang et al., 2015). Therefore, these findings underscore the importance of integrating HBV screening and genotyping to the HIV treatment guidelines for better management and prevention of HBV-related liver disease, and drug resistance mutations.

Declaration of Competing Interest

None.

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