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Engaging currently available tested and proven strategies to tackle Hepatitis B viral epidemic: The HBV-4-Pronged Approach (HBV4PA)

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Globally, Hepatitis B viral infection is a major epidemic and responsible for one of the commonest cancers in males reference needed because the HBsAg seroprevalence in males slightly higher than females, especially in sub-Saharan Africa. However, although its treatment is available and effective, it is out of the reach of the common person. Many have, because of cost of treatment, succumbed to the chronic effects of HBV infection, such as liver cirrhosis and primary liver cell carcinoma. In this article, we make a case for the provision of free antiviral drugs to all HBV patients by expanding the current HIV services to HBV-infected individuals using the PMTCT model. This, when implemented, will save lives, prevent unnecessary and escalating health expenditure and ensure sustainable development.

Key words: Hepatitis B viral infection, HIV PMTCT, Nigeria, expanding HIV services

INTRODUCTION

Globally, chronic hepatitis B virus (HBV) infection is a common public health problem and a major risk factor for cirrhosis and liver cancer affecting over two billion people and leading to chronic infection in about 250 to 350 million people worldwide (Ott et al., 2012; Uneke et al., 2005; Utoo, 2014; World Health Organization [WHO], 2015). Age at infection is important in determining the risk of chronic infection as chronicity follows acute infection in over 90% of neonates (particularly babies born to HBV e antigen-positive mothers not only HBV e antigen-positive mothers but mothers with active infection), 20-60% of children under the age of 5 years, but less than 2-6% when infection occurs in adulthood (Centers for Disease Control and Prevention [CDC], 2015; WHO, 2015).

HBV is the second most frequent known carcinogen after tobacco and in sub-Saharan Africa, HBV-associated liver canceris the most common cause of death amongst young men and the second most prevalent cancer

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worldwide (Harry et al., 1994; Uneke et al., 2005). In Nigeria, the global burden of cancer in 2013 shows liver cancer to be the commonest cause of cancer death (Naghavi, 2015). HBV infection is also highly endemic in Nigeria as about 75% of the Nigerian population may have been exposed to HBV at one time or the other in their life and an estimated 12% of the total population have chronic carriage of HBV (Owolabi et al., 2014; Sirisena et al., 2002) and is reported to be the most common cause of liver disease (Musa et al., 2015). With high rates of blood transfusion following road traffic accidents, pregnancy and its complications, malaria and sickle cell diseases (in addition to more recognized risk factors, such as intravenous drug usage, unprotected sexual intercourse and poor sterilization of surgical or dental equipment), it is not surprising to see the prevalence of HBV infection over 30% in some regions of the country (Luka et al., 2008; Mbaawuaga et al., 2008).

The epidemic of HBV spares no population, as a study among clergymen who presented themselves for blood donation revealed a positivity rate of 15.1% for HBV and 4.3% for HCV. HIV was found only in 2.7% of the clergy, making it a less important issue of public health concern (Egah, et al., 2007) even this low percentage (2.7%) among a non-risky group should be considered as important issue of public health. Among doctors and dentists, the prevalence was high as active infection was detected in 10/22 (45%) dentists and 19/53 (35.8%) doctors against 5/25 (20%) of local blood donors (Olubuyide et al., 1997). There are also data to suggest that HBV infection is more common in the rural than urban areas (Amazigo and Chime, 1990; Jombo et al., 2004); and also seen among adolescents (Eke et al., 2015).

As HBV is a blood-borne disease, the common drivers of this epidemic are traditional practices like tattooing, vertical transmission from mother to child, sexual practices (both heterosexual and homosexual), occupational exposures, clustering of carriers in families and institutions, behavioral factors, marital status it is not precise that marital status is a common drivers of the disease, and exposure amongst prisoners (Amazigo and Chime, 1990; Ansa et al., 2002; Jombo et al., 2004; Luka et al., 2008). However, studies have shown that HBV transmission in sub-Saharan Africa is mainly through the horizontal route in childhood rather than the perinatal route (Kiire, 1996).

For those millions of people who are chronically infected with a viral load over 2000 IU/mL and/or the presence of hepatic fibrosis, it is also treatable with current pharmaceuticals, such as Tenofovir, a drug that is familiar to many as a treatment for HIV. Although Tenofovir rarely leads to surface antigen seroconversion and virological cure, the viral suppression that it provides may lead to a reduced incidence of complications, such as cirrhosis or liver cancer (Lemoine et al., 2016).

HIV and HBV infections

Studies have shown that HBV infection commonly co-exist with HIV (Hamza et al., 2013; Unekeet al., 2005).For instance, studies by Uneke and colleagues in Jos Plateau revealed a higher incidence of HBV infection among HIV positive individuals when compared with the general population and blood donors (Uneke et al., 2005).This was collaborated by another study in Kano (Mustapha and Jibrin, 2004).In Uneke et al. (2005). This was corroborated by another study in Kano (Mustapha and Jibrin, 2004). In the study by Uneke and colleagues, although males had a slightly higher sero-prevalence than females (14.6% vs 12.9%), among the HIV subpopulation, males had a significantly higher sero-prevalence (31.8% vs. 22.1% (Uneke et al., 2005).. Apart from HBV, some individuals with HIV also had HCV infection as was demonstrated in North-Central Nigeria (Forbi et al., 2007). Taking a closer look at this, co-infection is critical as HBV negatively affects the ability of antiretroviral drugs to improve CD4 counts in patients (Idoko et al., 2009). Immunization against HBV can improve the prognosis of HIV as well as the efficacy of antiretroviral drugs (Hamza et al., 2013). Left unmanaged, HBV infection impacts negatively on disease progression in HIV-infected children, increasing morbidity and mortality (Nwolisa et al., 2013).

Current control and prevention strategies in Nigeria

HBV vaccination has recently been added to the routine vaccinations for newborn babies. Although this vaccine is effective, its effectiveness is time-bound as only children vaccinated within the first 24 hours of birth reliably develop an adequate immune response and are able to generate sufficient antibodies (WHO, 2015). But as few pregnant women deliver within the health facilities and majority of the health facilities may not even have the vaccine at the time of delivery, very few children actually have the vaccination during the correct window at birth.

Vaccination against HBV is low in many sub-Saharan African countries (Musa et al., 2015). For instance, the 2013 National Demographic Health Survey reveals that only 19.9% of infants received the HBV vaccine at birth (National Population Commission [NPC] and ICF International, 2013). Similarly, the same study revealed that only 17.3% and 14.7% received the second and third doses respectively. This is similar to the Nigerian national immunization coverage rate for the period, which was less than 25%. It therefore shows that relying on childhood vaccination for HBV infection control and prevention may be beneficial, but definitely not a sufficient approach to eliminating this virus from the population.

Unlike HBV, HIV prevention, care and treatment is well

funded. Patients with HIV have access to free testing, free counselling and free medication. In addition, they are supported to access these services. When HIV-positive individuals cannot access care and treatment due to economic difficulties, they are given financial assistance to help them live a healthier life. However, like HIV, HBV results in debilitating disease and significant end stage problems, such as liver cancer, which is a common cause of cancer deaths in young males in the sub-region (Harry et al., 1994; Yang et al., 2015).

Also HBV is known to be 50-100 times more infectious than the HIV virus (CDC, 2015). Despite the public health hazard of HBV, there is no active drive to ensure either the prevention of HBV infection, as is seen in HIV. With HIV, there are various prevention messages, behavioral change communications, and provision of condoms and other protective equipment to prevent transmission of HIV. Furthermore, while individuals infected with HIV are begged, cajoled and even supported to access care, the majorities of people with HBV infection die in ignorance of what their disease is, or discover the infection very late, or are accidently informed of their infection during blood drives or premarital screening. There is therefore the need to adopt a new approach to curtail the menace of HBV control or eliminate HBV-associated chronic liver disease. To achieve this, we propose the HBV-4-Pronged Approach (HBV4PA), which is adapted from the PMTCT program.

HBV-4-Pronged Approach (HBV4PA): *Adopting the HIV control strategies for HBV infection prevention and control*

HBV affects all age groups, and can be transmitted through sexual contact and by vertical transmission, similar to HIV. Thus, HIV prevention strategies should be up-scaled to prevent HBV infection. Like PMTCT in HIV program, HBV can benefit from the four prongs of PMTCT as defined by the World Health organization:

Primary prevention of HBV infection

Keeping a woman HBV infection-free before, during and after delivery keeps the infant free of HBV infection. Like HIV, a HBV-negative individual living in a discordant relationship has a risk of becoming HBV-infected unlike a person living in a concordant HBV negative relationship. Detecting discordant couples through couples counselling and testing will help deliver targeted intervention to spouses whose partners are infected. This will reduce the risk of cross infection. Treating discordant couples also reduced the possibility of transmission to the uninfected child.

To prevent primary infection of HBV, counselling and testing (including couples counselling), disclosure, condom distribution, and also targeted prevention programs for high risk populations, such as female sex workers, injection drug users and male who have sex with men is critical. Women who tested negative in the early part of their pregnancies can also be re-tested later, in the third trimester. These measures are in line with calls for improved efforts to promote routine screening of pregnant women and other subpopulations due to rising HBV prevalence in Nigeria (Hamza et al., 2013). Retesting allows identification of women who seroconvert during pregnancy, delivery, or even in the breastfeeding period. For those pregnant women who do test negative, then the HBV vaccine can be offered as a further primary prevention measure. The availability of rapid diagnostic testing for HBV infection makes testing easier with minimal barriers and delays. Implementing of HBV testing within the health institutions should be encouraged.

Secondly, alcohol risk reduction and biomedical interventions involving the use of routine use of HBV antivirals, such as Tenofovir for infected partners are possible avenues for disease control. This will be most easily up-scaled as the drug and associated services are distributed free to all exposed or infected individuals who HIV and therefore, the infrastructure to extend this to HBV exists. It is worthy of note that Tenofovir is currently free in sub-Saharan Africa for HIV, but not for HBV, costing patients about $US 8000 per year Furthermore, treating sexually transmitted infections are essential for primary prevention. Use of male circumcision may also reduce the rate of new infection as is seen in HIV and other sexually transmitted infections – but this need to be further studied and validated (Weiss et al., 2000, 2006).

The risk of perinatal HBV infection among infants born to mothers already infected with HBV ranges from 10%-85%, depending on the mother's hepatitis B e antigen (HBeAg) status. If the mother is positive for both hepatitis B surface antigen (HBsAg) and HBeAg, the risk of perinatal transmission is 70%-90%. By contrast, if the mother is HBsAg-positive, but HBeAg-negative, the risk of perinatal transmission is <10%. A proper birth dose vaccine with full implementation of the three vaccine doses in the first year of life can reduce neonatal infection and the potential sequelae by 95%. So, the use of routine use of HBV antivirals, such as Tenofovir (the drug that cannot cause cure and is costly) for infected partners will not add the needed value.

Thirdly, to prevent primary HBV infection, structural factors that hinder people's access to HBV testing, counselling (testing and counseling should be the first part of the primary prevention or even after the vaccine usage strategy) and drugs should be removed. This can be achieved by making testing and vaccination for negative mothers for HBV infection free, and creating relevant awareness through HBV prevention messages in social and mass media across the nations of the world.

Testing and counselling can be fully integrated into the current HIV testing and counselling drive in line with the UNAIDS 90-90-90 agenda. Drugs for HBV (Tenofovir) could be provided with ARTs in supported service delivery points. Integrating HBV services in HIV programs will be most appropriate as both diseases have a lot in common, including common treatments. An additional benefit is that it is cost effective, will not require new human resources for health, will utilize already existing structures, and if well managed, be quickly taken over by national health leaders.

Preventing unintended pregnancies among HBV infected women

To further prevent the impact, incidence and prevalence of HBV infection, there is the need to reduce unintended pregnancies among women infected with HBV. This will lead to a reduction in the number of infants born to HBV-infected mothers, and thus reduce the number of HBV-exposed infants. As family planning is critical towards the achievement of this goal, and family planning is a severely unmet need in Africa, coupling HBV with HIV will give the world another vital reason to drive improvement in access, availability and even affordability of family planning services and consumables across Africa and beyond. The use of protective equipment such as condoms for family planning will serve dual purposes – preventing pregnancies with a collateral advantage of preventing new infections in discordant couples.

To address this unmet need for family planning, governments should implement the modified United Nations Population Fund (UNFPA) recommendations of linking sexual and reproductive health with HBV interventions at the policy, systems and service-delivery levels; engaging communities, getting more men involved, engaging organizations of people living with HBV (where they exist), and ensuring the provision of nondiscriminatory services in stigma-free settings (UNFPA, 2012). Applying these steps will result in commonization of HBV services and its full integration into the healthcare delivery model in any country.

Preventing HBV Infection from HB- infected pregnant women to their children

To ensure a HBV-free generation, all pregnant women should be granted access to HBV testing and counseling (HbTC) during antenatal services; and all those that have HBV infection granted access to anti-HBV medications and supportive care**.** During labour, every effort should be made to prevent transmission of the virus to the newborn baby. This could be achieved through safe obstetric practices, judicious use of cesarean sections when appropriate and provision of intra- and immediate postpartum HBV medication (which medication could be used to prevent the postpartum transmission of the virus), and hyper-immune globulin/vaccines to the newborns. Vigilance in preventing HBV infection from HBV-infected pregnant women to their children should continue for at least the first year. Infected mothers should be followed-up and supported, counselled on child nutrition and care, and encouraged to use appropriate anti-HBV medications, while their babies receive all three vaccine doses in the first year of life. Also, early infant diagnosis for exposed babies should be developed and implemented. Breastfeeding mothers (Examination of relevant studies indicates that there is no evidence that breastfeeding poses any additional risk to infants of HBV carrier mothers) should be provided with appropriate HBV antivirals, and infants with confirmed HBV-infection should be given appropriate medications as 90% of them will go on to develop chronic infection. Even after breastfeeding, infected mothers should continue their medication until such times as they seroconvert, but being mindful of the fact that treatment for many is life-long.

In this prong, the strategy for use HBIG and the vaccination for the infant should be added and explained.

Care, treatment, and support to women living with HBV, their children and families

This is the fourth prong and it is designed to provide adequate care, treatment and support services for people living with HBV, their children and families. This will result in lower morbidity and mortality, improved overall health and quality of life of HBV positive individuals, and reduced rate of transmission. Furthermore, starting HBV antivirals early will result in better outcomes and lower risk of chronic liver diseases. Hepatitis B immunoglobulins (HBIg) will also be helpful in the management of infected patients with high viral loads. Exposed but uninfected infants should be vaccinated.

This HBV4PA plan provides a comprehensive approach to HBV prevention, treatment and control. HBV service provision can make use of the already existing HIV structures to reach millions of people who need services within a short time.

For instance, the ongoing HTC saturation drive could be up-scaled to include Rapid Diagnostic Test (RDT) for HBV. It would use the same healthcare workers, facilities, non-governmental associations and community contacts as HIV with little impact for further resource allocation.

As most studies referenced in this report are facility-based figures, testing both males and women within their communities will help document community prevalence rate of HBV. This would be compared with HIV prevalence within the same communities. Also, the prevalence of co-infection (HIV and HBV) should be

documented. Infected persons would then be linked to care, treatment and support; while the pregnant women would be provided with relevant services to ensure that the unborn child is adequately protected.

Children born to HBV-infected women with high viral loads should receive the same attention given to HIV-exposed babies and their HBV vaccine and HBIg should be given on the same day of birth. EID using DBS could be used to make early diagnosis. Thus samples collected for HIV-exposed babies should also be tested for HBV if parents were co-infected. Samples from exposed infants should also be collected for analysis at 18 months when maternal antigens capacity to produce false positive results has significantly reduced.

Riding on the success of HIV, services can be provided that covers all aspects of HBV infection at very minimal extra cost to the system.

Conclusion

Although there is a global decline in HBV infection prevalence which may be related to expanded immunization, this is not the case in Nigeria where there is an increasing overall number of individuals chronically infected with HBV (Amazigo and Chime, 1990). This widespread global difference in HBV prevalence calls for targeted approaches to tackle HBV-related mortality and morbidity (Finlayson et al., 1999).

While, HBV infection prevalence data are needed at country and sub-national level to estimate disease burden and guide health and vaccine policy, upscaling current HIV programs to include HBV is possible and making the anti-retroviral drug, Tenofovir, which is already in free circulation for HIV, free for the treatment of HBV will drastically reduce both mortality and morbidity of this disease. Governments, the WHO and the World Bank would however, have to ask the manufacturers to expand their coverage beyond HIV.

This strategy to be successful, it should be implemented in all health care institutions and even governmental or non-govermental organizations.

Furthermore, HBV services – testing, care and treatment could be integrated into hospital services. There is no moral justification for free HIV services while HBV services remain fully-paid and unsubsidised. We believe that the time to change all this is now. Let the change begin with provision of free Tenofovir for all HBV patients who require it. This strategy has been shown in recent studies to be an effective HBV control intervention (Lemoine et al, 2016)..

Conflict of Interests

The authors have not declared any conflict of interests.

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