

Treatment of Chronic Hepatitis B infection using Pegylated Interferon and Emtricitabin + Tenofovir: Preliminary Cost Burden and Policy Implications.

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Abstract

Hepatitis B infection remains a major cause of global mortality with Nigeria identified as a country with significant endemicity. Little is however known about the cost burden for managing Hepatitis B infection in this setting, or what policies exist to ensure access to care.

A sample of one hundred patients recruited at National Assembly Medical Centre was screened for Hepatitis B. The study aimed at identifying clinical outcomes and economic burden of treating Hepatitis B with a treatment regimen of Pegylated Interferon alfa-2a (PEG-INFalfa-2a) and Emtricitabine + Tenofovir (ET). Parameters evaluated include viral load (VL), sero-conversion and liver function test (LFT). Direct and indirect medical costs that were determined include laboratory investigations (HBsAg), VL, LFT, drugs and visits.

The result showed a 7.2% prevalence of HBsAg. Initial monotherapy with PEG-INFalfa-2a resulted in sero-conversion in 5 out of the 8 treated cases (62.5%) with a drop in VL to an undetected value (less than 20 copies/ml). In the rest (37.5%), VL rose to a range of 12000 - 35000 copies/ml and elevated liver enzyme [Alanine Transaminase (ALT)] increased to a range of 94-197 u/ml. Therapy switch to ET in treatment phase 2 (non-responsive in phase 1) led to a decrease of VL to 2500-3000 copies/ml. Follow up therapy with PEG-INFalfa-2a resulted in further decrease after 96 weeks. Mono-therapy with PEG-INFalfa-2a cost N2,395,250 (\$14,089.91) while PEG-INFalfa-2a + ET was N4,182,333 (\$24,601.96).

The treatment of Hepatitis B infection is of significant importance to both individual patients, and the national healthcare system, due to the considerable costs. Considering Hepatitis B infection as a Public Health Emergency will stimulate the relevant policies which can stem the looming epidemic.

Keywords: Hepatitis B; Pegylated-interferon; Outcomes; Costs; Policy

1. Background

Healthcare provision in Nigeria has been associated with significant problems. Key healthcare indices suggest that healthcare delivery in the Nigerian setting is inadequate. For instance, life expectancy at birth is still very low for both sexes. The national maternal mortality ratio as well as the national infant mortality rate are also poor (WHO 2013). Furthermore, access to safe and good quality healthcare is lacking, even at a basic level (Hargreaves 2002).

Additionally, the Nigerian healthcare system has faced considerable challenges because of the increase in its health expenditures. These expenditures may have originated directly from the cost of diagnosis and treatment of the disease or indirectly from loss of productivity and quality of life. Considering the limited resources for delivery of healthcare services, effective healthcare delivery is one of the general concerns of healthcare systems over the world (Bojuwoye 1997). As treatment costs are the major portion of health expenditure in many countries, recognizing and analyzing the direct treatment costs of diseases may provide health care managers with a better understanding of their financing issues and strategies (Akani 2005).

Hepatitis B virus (HBV) is one of the most prevalent blood-borne viruses worldwide, with chronic HBV infection afflicting more than 2 billion people while some 350 million are chronic carriers, harboring the virus in their liver (Forbi et al. 2007). This virus is responsible for 80% of all cases of primary liver cancer, which is one of the leading causes of death in Asia and Africa (Ferlay et al. 2010).

Major clinical consequences of HBV infection include liver failure, cirrhosis, and hepatocellular carcinoma (HCC). These complications lead to more than 1 million deaths each year and make HBV the 10th leading cause of death worldwide (Mahoney 1999; Lee 1997; WHO 1997; WHO 2000). HCC incidence has increased

worldwide, and the disease is now the 5th most frequent cancer, killing 300,000 – 500,000 people each year (Lavanchy 2004) Thus, HBV infection is an important public health problem, especially for developing countries where the endemicity is often significant.

About two billion people are infected with HBV globally with over 620,000 deaths annually (Maiyaki 2014). The prevalence of HBV infection varies markedly in different geographic areas of the world, as well as in different population subgroups (Yu 2000; WHO 2000). Overall, approximately 45% of the global population live in areas of high chronic HBV prevalence (Lavanchy 2004). Nigeria has been classified as an HBV endemic zone, based on global HBV endemicity (Odemuyiwa et al. 2001; Forbi et al. 2007). The World Health Organization (WHO) estimates that about 19 million Nigerians have HBV infection, of which about 20% are chronic carriers and 40% of HBV carriers are likely to die from liver cancer or cirrhosis (Chiejina 2013).

Studies undertaken in Nigeria have corroborated this figure. Indigenous research has shown that close to 20 million Nigerians are infected with Hepatitis B with North Central and North East having the highest prevalence (Obom-Egbulem 2011). Although pregnant women are considered to have a lower risk of Hepatitis B virus infection, rates as high as 11% have been reported among them in Makurdi, North Central region of Nigeria (Yakubu et al. 1998; Mustapha et al. 2004). Similarly, blood donors who have previously been considered fairly healthy persons had prevalence as high as 14.3% (Uneke et al. 2005). Another study showed a total prevalence rate of 8.3% of HBsAg in Ebonyi State located in the South Eastern region of Nigeria. Similar prevalence figures emerged in studies carried out in Zaria (Luka et al. 2008) and Nnewi (Eke et al. 2011), indicating that the disease was fairly widespread geographically (Musa et al. 2015). The implications are that chronic HBV infection and the resulting liver diseases could pose a heavy burden for the Nigerian healthcare system

Although there are small variations, it is clear that prevalence figures of between 10% and 30% in various relevant populations have emerged. These results call for concern as according to WHO's (2009) classification for Hepatitis B virus endemicity, areas with 8.0% prevalence and above are considered endemic. The rising prevalence of HBV therefore presents a peculiar challenge for all relevant stakeholders due to the significant cost implications and the resultant effects on access to care. It has also been identified that viral hepatitis places a heavy burden on the health care system because of the high costs of treatment of liver cancer and failure from cirrhosis (WHO 2000).

A review of the literature indicates that a comprehensive analysis of the financial burden of HBV infection in Nigeria is limited. In view of this, a cost of illness study of HBV infection was conducted prospectively based on treatment of recruited patients following a screening exercise. This evaluation was designed to examine the clinical outcomes of using PEG-IFNalpha- 2a and ET in order to determine the clinical outcomes and economic burden. The policy implications of the aforementioned are also explored.

2. Methods

Following ethics and governance approvals from the National Assembly (NASS) management, a prospective data collection approach was used to collect information from 100 randomly selected patients attending the NASS Medical Centre. The patients who tested positive for HB 'e' surface antigen were recruited for treatment and monitored as out-patients while data collection was carried out during patients' visits. Relevant data were collected through interviews as well as retrieval from the medical records unit of the NASS Medical Centre. The study was carried out between January 2012 and December 2014. Patients were monitored and investigated at intervals on the basis of clinical manifestations; viral load (VL) and liver function test (LFT),

PEG-IFNalpha-2a 180 mcg was administered weekly to the eight selected Patients for 48 weeks. A switch to Emtricitabine + Tenofovir (ET) capsules once daily for 24 weeks was done for 3 patients who exhibited poor response to PEG-IFNalpha-2a. Thereafter, PEG-IFNalpha-2a was administered for another 36 weeks. The unit cost of the drugs was noted. Similarly, the unit cost of laboratory investigations or procedures, clinic visits and other important factors, were noted. Total cost was subsequently determined. The direct medical cost estimated in the treatment of HBV infection included clinic visits (outpatient visits), investigations (laboratory tests and procedures), and drug cost. The study assessed resource utilization based on average private charges in 2012 expressed in Naira and US Dollars (N170:\$1). The use of proxy charges for the estimation of costs was adopted (Drummond et al. 2003) as health care in Nigeria is majorly funded by out of pocket payments (OOP).

3. Results

Figure 1 is a pie chart showing the percentage of HBV positive individuals in the screened population. Treatment of results in figure 2 indicates the patients profile after the 1st phase of treatment with PEG-IFNalpha-2a.

Figure 1: Prevalence of HBV in Screened population.

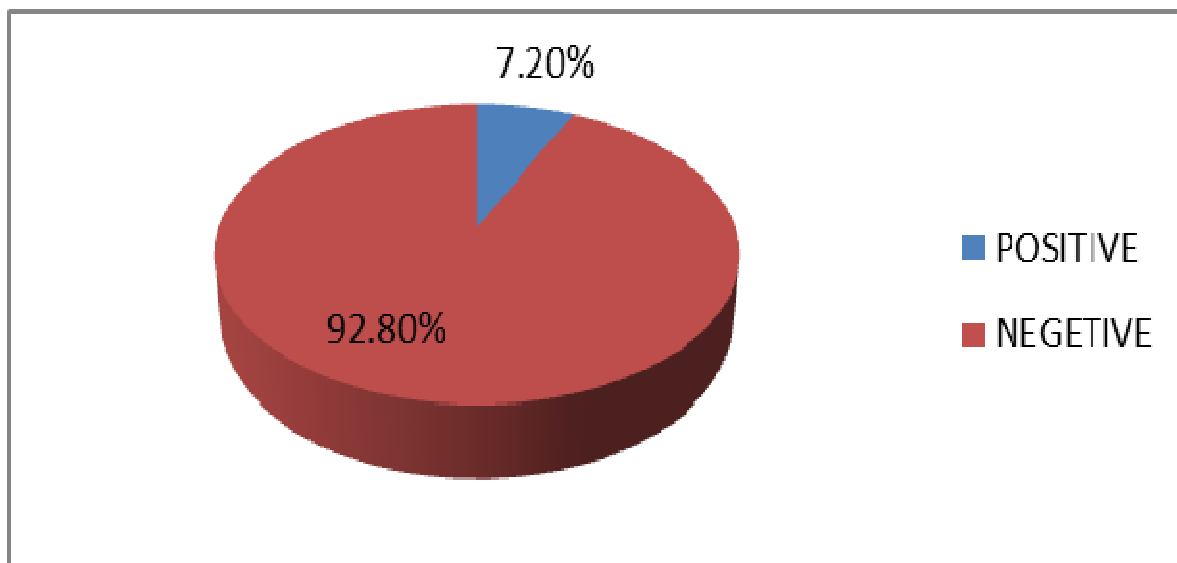
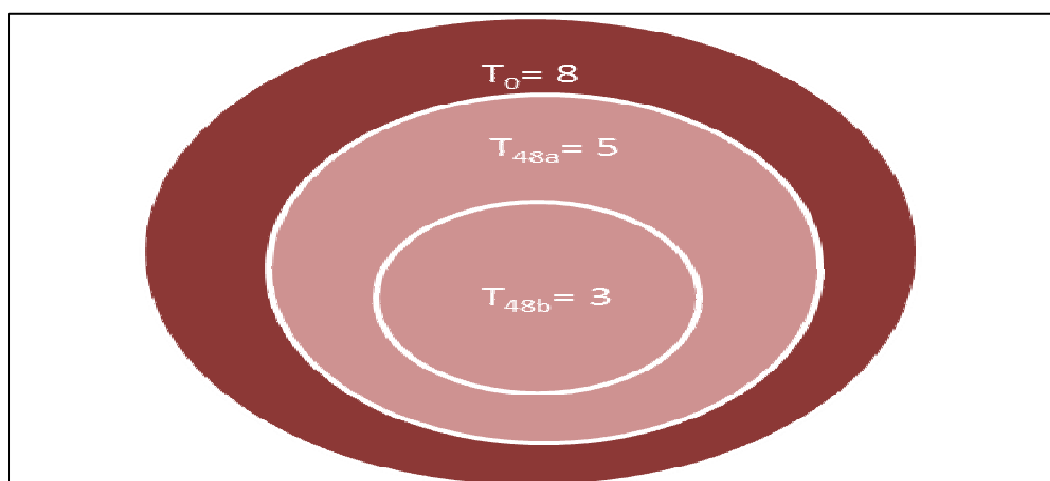


Figure 2: First phase of treatment with PEG-INFalfa-2a and viral load profile



T_0 = 1st phase treatment with PEG-INFalfa-2a in 8 patients for 48 weeks.

T_{48a} = Viral load i.e. undetectable at T48 (62.5% of the patients) – 5 patients

T_{48b} = Viral load rose above 35 million copies/ml after T48 (37.5% of the patients) – 3 patients

Fig 3: Changes in viral load with time (weeks)

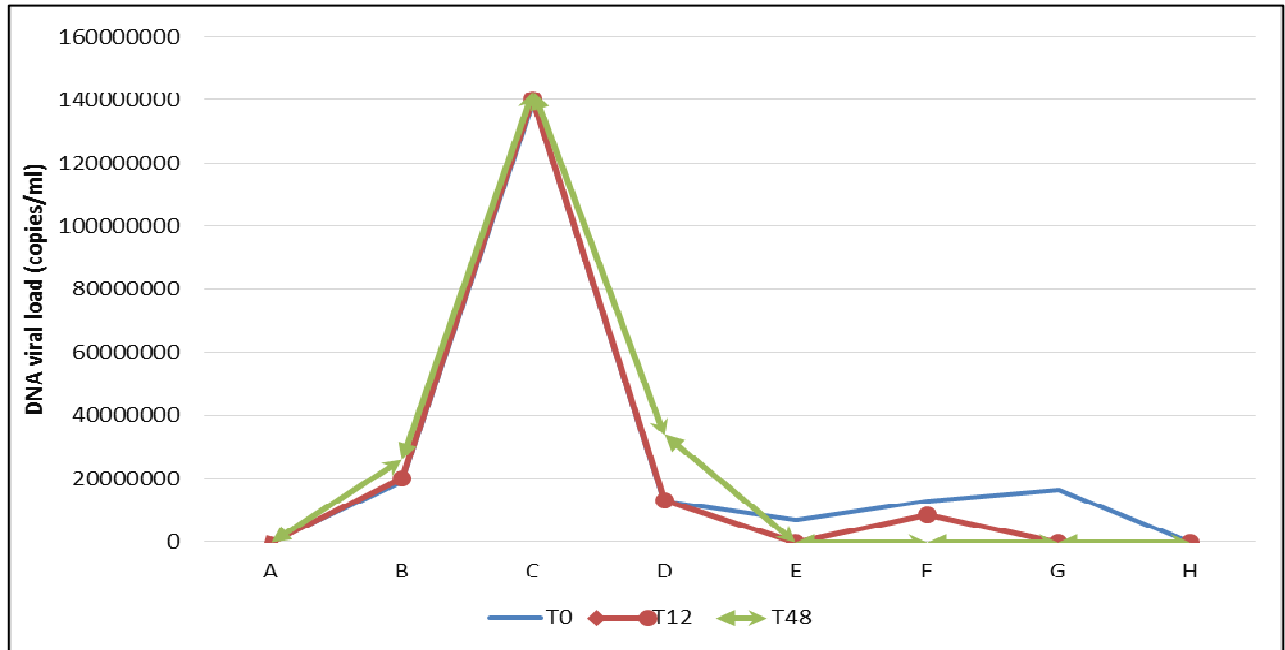


Table 1: Direct Medical and Non-medical Costs

A Therapies

Phase 1

PEG-IFN-2 α , 8 Patients / 48 weeks N17,280,000 (\$101,647)

Phase 2

ET, 3 Patients / 24 weeks N1, 485,000 (\$8,735.29)

PEG-IFN-2 α , 3 Patients/ 36 weeks: N4, 860,000 (\$28,588.24)

B Laboratory Investigations

Case detection

HBsAg test/confirmation 8 Patients (P) N20, 000 (\$117.65)

Viral load (copies/ml)

T0, T24, T48; 8P N1,200, 000 (\$7,058.82)

T72 T96x 3P N 300,000 (\$1,764.71)

Liver Function Tests

T0 T24 T48 X 8 N120, 000 (\$705.88)

T72 T96X 3 N30, 000 (\$176.47)

Average Medical Expenditures per Patient

Phase 1 (5P) N2, 327,500 (\$13, 691.18)

Phase 1+2 (3P) N4, 057,500 (\$23,867.65)

C Direct Non-Medical Cost

Phase 1

Transportation 8 P x (440 visits) at 750/trip	N330,000 (\$1,941.17)
Feeding 3P x 48 weeks (440 visits) @500/meal	N220,000 (\$1,294.12)
Total	N550,000(\$3,235.29)

Phase 2

Transportation 3P (141) @ 750/trip	N105,750 (\$622.06)
Feeding 3P (141) @500/meal	N70,500 (\$414.71)
Total	N171,250 (\$1,007.35)

Average Non- medical expenditures per Patient

Phase 1 (5P)	N67,750 (\$398.52)
Phase 2	N57,083 (\$335.78)
Phase 1+2 (3P)	N124,833 (\$734.31)

Table 2: Summary of Direct Medical and Non-medical Expenditure per patient per batch

Expenditure		Cost N (\$)	
		Batch A	Batch B
Medical	Phase 1	2,327,500 (\$13,691.18)	2,327,500 (\$13,691.18)
	Phase 2	-----	1,730,000 (\$10,176.47)
Non-medical	Phase 1	67,750 (\$398.53)	67,750 (\$398.53)
	Phase 2	-----	57,083 (\$335.78)
	Total	2,395,250 (\$14,089.71)	4,182,333 (\$24,601.96)

4. Discussion

This study aimed at evaluating HBV prevalence and treatment together with the cost implications associated with the disease. It emerged that the prevalence for HbsAg in the sample was 7.2% (See Figure 1). Although at the lower end of the spectrum, this finding reflects the results of earlier studies in Nigeria that reported prevalence rate of 7 - 30% (Yakubu et al. 1998; Mustapha et al. 2004). The VL and the LFT showed high level of derangement as evidenced in Figure 3. These scenarios necessitated commencement of treatment. The first phase of treatment involved the use of only PEG-IFNalpha-2a for duration of 48 weeks.

The European Association for the Study of Liver (EASL 2009) recommends a HBV DNA level of 2000 copies/mL as threshold for initiating therapy. This recommendation applies to patients who are either positive or negative for Hepatitis B e surface antigen (HBeAg) (EASL 2009). The protocol of initial therapy with PEG-IFNalpha-2a in this study was based on the raised DNA VL above the threshold (VL at T0 : 88,100 - 16,850,702 copies/ml) with abnormal Liver Enzymes Level. PEG-IFNalpha-2a monotherapy was used as first line treatment based on findings that the use of PEG-IFNalpha-2a seems to result in the highest rate of off-treatment-sustained-response after a one-year course of therapy (Brunetto et al. 2009). In contrast treatment with nucleoside analogue required a prolonged period for several years before HBsAg loss is observed (Janssen 2009). PEG-IFNalpha-2a works by a two-pronged approach; it stimulates the immune system as well as inhibits virus replication. In a study of a 48-week regimen, after 24 weeks of follow-up the HBeAg sero-conversion rate with PEG-IFNalpha-2a monotherapy was 32%, compared with 27% in those receiving combination therapy with Lamivudine (2',3'-dideoxy-3'-thiacytidine, commonly called 3TC), and 19% in those receiving 3TC monotherapy (Lau 2005). Additionally, PEG-IFNalpha-2a being a pro-drug with indirect antiviral activity confers a line of least tendency for development of drug resistance (Kukka 2014).

After 48 weeks of treatment with PEG-IFNalpha-2a, there was sero-conversion in 62.5% of the patients. Earlier studies have reported sero-conversion rate of 32% and above following the use of PEG-IFNalpha-2a (Flink et al. 2006; Tangkijvanich et al. 2010). Although this study was not designed primarily to determine the sero-conversion rate using different options, it nevertheless agrees with the choice of interferon as rational first line treatment for HBV patients based on clinical outcomes. Ours is a preliminary study that has revealed a sero-conversion of 5 out of the 8 patients treated. This has given us an impetus for designing further studies of a broader population in order to establish statistical significance. The remaining 37.5% (3 Patients) were subsequently placed on ET. The latter group had therapy switch because there was significant increase in their VL from a minimum of 12,716,256 at T0 to a maximum of 35,348,000 at T48 and their ALT (alanine aminotransferase) level was more than twice the normal level in the range of 94-197 IU/mL. After a period of 24 weeks treatment with ET, there was a significant drop in the HBV DNA to a range of 2,527- 3,000copies/mL. The ALT also dropped significantly to a normal range of 19 -30 IU/mL. The patients were then placed on PEG-IFNalpha-2a resulting in a drop in their VL to levels not exceeding 2500 copies/ml after 96 weeks of cumulative treatment.

The direct cost noted in the management of the HBV infection was quite revealing. The total medical cost for the 8 patients (Batch A) summed up to \$14,089.71. The direct medical cost amounted to 97.2% of the total burden while the direct non-medical cost was \$398.53, corresponding to 2.8%.

Previous studies have shown an alarmingly high HBV prevalence among various groups in the Nigerian setting (Ezezbudo et al. 2004; Fakunle et al. 1981; Ukaeje et al. 2005; Yakubu et al. 1998; Abiodun et al. 1986). Recent statistics indicate that not less than 23 million Nigerians are estimated to be infected with the HBV making Nigeria one of the countries with the highest incidence of HBV infection in the world (Ottet al. 2012). The average prevalence of Hepatitis B virus infection in Nigeria is about 13 per cent, with higher prevalence in rural areas than urban areas. HBV is more common and more contagious than HIV, which has an average prevalence rate of 4.5% (Mbaawuaga 2014). The foregoing indicates that attention must be focused on curtailing the spread of HBV in the country.

OOP remains an important source of funding for healthcare in the country, accounting for more than 90% of private expenditures on health. The cost of treatment for HBV infection may be significant for the average Nigerian patient as antiviral drugs and adjunct treatment remain expensive. In assessing poverty, the Nigerian Bureau of Statistics uses several indices including absolute measure; the dollar per day measure; and the subjective poverty measure. The absolute measure puts the country's poverty rate at 99.284 million or 60.9 per cent; the dollar per day measure puts the rate at 61.2 per cent; and the subjective poverty measure puts it at 93.9 per cent (Nigerian Insight 2014). Our study population comprised of low to middle income earners whose annual income is estimated to be N660,000 (\$3,882.35). This figure represents 24% of the estimated total medical cost/patient. What this means is that the income of a middle income earner is inadequate to treat the disease effectively.

The World Health Organization (WHO) estimates that households that spend 40% or more of their non-food expenditure on treatment are most likely to be impoverished (Leighton 1993). Some researchers argue that a cost burden greater than 10% is likely to be catastrophic for the household economy (Prescott 1999; Ranson 2002). Even with health insurance coverage, the direct costs of HBV-related diseases, except acute Hepatitis B, exceeded 40% of household annual income in China, suggesting that HBV-related diseases should be categorized as catastrophic (Ku et al. 2003; Kawabata et al. 2002). This means that in Nigeria, it is likely to force household members to cut their consumption of other basic needs. It could also lead to high levels of debt and impoverishment since payment for health services by the majority of the population is largely OOP. Alternatively, the financial burden may cause patients to refrain from seeking care in an attempt to save cost. The consequences will include increased spread of HBV; individual and national productivity loss; and even higher mortality rate due to complications.

From the evidence, it is clear that Hepatitis B presents a significant challenge for national healthcare in Nigeria. Current treatment protocols and costs impact heavily on the economy, both at an individual, and at a national level. Also, national preventive measures are absent, or at best, uncoordinated. Unfortunately, not much attention has been given to the control of Hepatitis B globally, including in Nigeria where this burden is rapidly increasing. It is unclear what, if any strategies exist for addressing what appears to be a fast approaching National Health Emergency. It is against this backdrop that we argue for the development of a comprehensive strategy to underpin the prevention and treatment of Hepatitis B.

5. Conclusion

Findings from this study have confirmed that PEG-INFalfa-2a is suitable for treatment of Hepatitis B infections in Nigeria. The cost of treatment is however a significant limitation. Stakeholders including pharmaceutical manufacturers, health insurance providers and other healthcare organisations and professionals are enjoined to work out efficient and effective means of making the cost of PEG-INFalfa-2a more affordable. The cost implication in the combined use of PEG-INFalfa-2a and ET occasioned by therapy switch is unacceptably high despite the good clinical outcomes. Further studies can also undertake an exploration of the cost benefit analysis of this combination in contrast to pairs of PEG INFalfa-2a and other ARTs similar to ET.

Insufficient local funding and inadequate awareness for Hepatitis B virus infection are fuelling the disease spread. This has led to millions of Nigerians developing liver cancer/cirrhosis with consequent high medical expenditures and loss of human capital. Improved health insurance coverage with expanded benefit package can help reduce the financial burden of the disease on the most vulnerable sections of the populace. Better engagement and advocacy by national and international development agencies and organisations, can improve funding as well as increase awareness. Additionally, prevention of the disease through efficient public education and the use of vaccines may significantly scale down the prevalence of the infection. It is therefore our opinion that HBV infection be considered a public health issue. This will form the basis for the development of comprehensive and robust policies to help prevent the spread of HBV as well as provide affordable treatment for infected individuals.

Acknowledgement

The research team wishes to express our gratitude to the management of the National Assembly for supporting this project with over 80% of the drug supply as well as free physician consultations. We also acknowledge the role of Pharmacists Bala Ibrahim and Oiza Matthews in the collection of data and manuscript preparation respectively.

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