MODELLING THE IMPACTS OF EFFECTIVE AND INEFFECTIVE TREATMENT TECHNIQUES IN CONTROLLING RELAPSE IN PATIENTS WITH PERSISTENT HBV DISEASE

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Abstract: The effects of treatment strategies in controlling relapse in patients with ongoing HBV disease are analyzed. The reproduction number is obtained from which threshold values for treatment with and without relapse is acquired. The sensitivity analysis of the effective reproduction number uncovers that, transmission rate and the ratio without immunization advocated the disease flare-up. Mathematical experiments were carried out using MATLAB program, the outcome uncovers that patients adopting ineffective treatment systems are inclined to delay in fast reaction to treatment regimens, which thusly slow down the capability of recuperation from the infection. The epidemiological result of the key discoveries is that controlling the illness with an insufficient treatment methodology (self-medicine and visually impaired remedy) ought to be avoided to reduce the outcomes of drug resistance. Running against the norm, people that have embraced effective treatment strategies have shown more prominent possibilities for recuperation from the disease. Likewise, new medications with low obstruction ought to be given, that will assist with limiting the risk of reappearance of the infection because of drug resistance. Thus, a very much planned and satisfactorily carried out effective treatment strategy can significantly lessen the reproduction number, in this manner reducing relapse in patients with constant HBV disease.

Keywords: Treatment, relapse, chronic hepatitis B infection disease, reproduction number

Introduction

In the domain of medicine, the impact of ill-advised treatment, self-medication, or visually impaired remedy are liable for viral persistence in the host genome. In this manner, setting off relapse in patients and subsequently lead to complication and mortality (WHO, 2019; EASL, 2013). For this research, relapse alludes to the reappearance of infection because of drug resistance. It is seen that the people who go through successful treatment tend not to encounter resistance and do recuperate rapidly (CDC 2008, Zoulim, 2009; gish, 2012). Assuming the viral burden increases, it implies that it is resistant to the medications and ought to be altered, however assuming that it fails to reproduce, it implies the medications are effective and the infection is not resistant (Zhang, 2012; Kosinka, 2013).

Notwithstanding, regardless of numerous analysts that have made endeavors to model HBV HBV as seen in (Nwaokolo *et al* 2018, 2020, 2022), none as far as I could possibly know have displayed the effect of effective treatment strategy in controlling relapse in patients with chronic HBV disease. Subsequently, we apply the normalized forward sensitivity index and the fourth order Runge-kutta technique coded by the aid of MATLAB program to simulate the model. Hence, guided by the model of Nwaokolo *et al*. (2020) on the impact immunization and therapy on the control of HBV within the sight of infective immigrants. The current work means to look at; Modelling the impacts of effective and ineffective treatment techniques in controlling relapse in patients with persistent HBV disease. Subsequently, inspired by the work of Nwaokolo *et al.* (2020), the overseeing model equations have the accompanying variables and parameters.

Table 1. Variables and Parameters of the Model

S/N	Parameters	Interpretation
1.	S (t)	Number of Susceptible persons at time t.
2.	E (t)	Number of Exposed persons at time t.
3.	A (t)	Number of Intense infective at time t.
4.	C (t)	Number of Chronic carriers at time t..
5.	V (t)	Number of immunized persons at time t
6.	M (t)	Number of migrated persons at time t.
7.	T (t)	Number of treated persons at time t
8.	R (t)	Number of recuperated persons at time t
9.	δ	Equal per capita birth and demise rate
10.	**II**	The proportion without immunization
11.	γ_1	The rate at which exposed persons become infectious and move to the intensely infected class.

12.	γ_2	The rate at which intensely infected persons move to the chronic carrier class.
13.	γ_3	The rate at which chronic carriers secure immunity and move to the vaccinated class.
14.	β	The transmission coefficient
15.	κ	The irresistibleness of carriers comparative with intense infections.
16.	q	The proportion of intensely infected persons that become chronic disease carriers.
17.	1 - q	The proportion of intensely infected persons that move to the immunity class. .
18.	δ_o	The loss of immunity from the immunized class to susceptible class.
19.	α_0	The ratio of chronic carriers that are treated per unit time.
20.	φ	The rate at which treated persons relapse and continue to the chronic class.
21.	ρ	The proportion of immunized susceptible per unit time.
22.	ξ	Rate of flow from exposed class to migrated class.
23.	α	The flow from migrated class to susceptible class.
24.	μ_1	The transmission rate from migrated class to exposed class.
25.	μ_2	The transmission rate from migrated class to intensely infective class.
26.	η	The proportion of the immunized kids born by carrier mothers.
27.	δ(1 - π)	The babies that are effectively immunized.
28.	δπ(1 – η*C*(t))	Birth transition into the susceptible class.

The governing model equations are as follows (Nwaokolo *et al*. 2020).

$$\frac{dS}{dt} = \delta\pi(1-\eta C) - \delta S - \beta(A+kC)S + \delta_0 V - pS + \alpha M, \quad (3.17)$$

$$\frac{dE}{dt} = \beta(A+kC)S - \delta E + \delta\pi\eta C - \gamma_1 E - \xi E + \mu_1 M, \quad (3.18)$$

$$\frac{dA}{dt} = \gamma_1 E - (\delta+\gamma_2)A + \mu_2 M, \quad (3.19)$$

$$\frac{dC}{dt} = q\gamma_2 A + \varphi T - (\delta+\alpha_0)C\ , \quad (3.20)$$

$$\frac{dT}{dt} = \alpha_0 C - (\delta+\varphi+\gamma_3)T, \quad (3.21)$$

$$\frac{dM}{dt} = \xi E - (\mu_1+\mu_2+\delta+\alpha)M, \quad (3.22)$$

$$\frac{dV}{dt} = \delta(1-\pi) + pS - (\delta+\delta_0)V. \quad (3.23)$$

with

$$S(0) > 0, E(0) \geq 0, A(0) \geq 0, C(0) \geq 0, T(0) \geq 0, M(0) \geq 0, V(0) \geq 0$$

Hence, the laid out reproduction number of the model (3.17-3.23) as contained in Nwaokolo et al (2020) is

$$R_{r^c} = \frac{\left[\beta S^O\left(c + Kq\gamma_2(\delta+\varphi+\gamma_3)\right) + e(\delta+\varphi+\gamma_3)\right](\mu_2\xi+\gamma_1 a) + \xi\mu_1 bc}{dbca} \quad (3.24)$$

Where,

$S^O = \frac{\delta\pi+\delta_0}{\delta+\delta_0+p}, a = (\alpha+\delta+\mu_1+\mu_2), b = (\delta+\gamma_2), c = (\delta+\gamma_3)(\delta+\alpha_0) + \delta\varphi,$

$d = (\delta+\xi+\gamma_1), e = \delta\pi\eta q\gamma_2, f = (\delta+\varphi+\gamma_3), g = (\mu_2\xi+\gamma_1 a)$

Notwithstanding, we are keen on looking at the effect of viable (effective) therapy system in controlling relapse in patients with chronic HBV disease, free of immunization, utilizing the above model.

The importance of the aforementioned is that relapse is the re-emergence of a diseased condition on one that was previously infected. Hence, a relapsed subject does not undergo vaccination; therefore we set vaccinated related parameters in (3.24) to zero ($p = \delta_0 = 0$) to derive the effective reproduction ratios with treatment and relapse given by:

$$R_\varphi = \frac{\left[\beta S_1\left(c + Kq\gamma_2(\delta+\varphi+\gamma_3)\right) + e(\delta+\varphi+\gamma_3)\right](\mu_2\xi+\gamma_1 a) + \xi\mu_1 bc}{dbca} \quad (3.25)$$

where,

$S_1 = \pi, a = (\alpha+\delta+\mu_1+\mu_2), b = (\delta+\gamma_2), c = (\delta+\gamma_3)(\delta+\alpha_0) + \delta\varphi,$

$d = (\delta+\xi+\gamma_1), e = \delta\pi\eta q\gamma_2, f = (\delta+\varphi+\gamma_3), g = (\mu_2\xi+\gamma_1 a)$

Therefore, $R_\varphi < 1$ implies that

$$\beta_{\varphi} < \frac{dbca - (e(\mu_2\xi + \gamma_1 a)(\delta + \varphi + \gamma_3) + \xi\mu_1 bc)}{S_1\left(\left(c + Kq\gamma_2(\delta + \varphi + \gamma_3)\right) + e(\delta + \varphi + \gamma_3)\right)(\mu_2\xi + \gamma_1 a) + \xi\mu_1 bc} \quad (3.26)$$

Also, the effective reproduction number with treatment only $(\varphi = 0)$ becomes

$$R_{\alpha_0} = \frac{[\beta S_1(\delta + \alpha_0 + Kq\gamma_2) + e](\mu_2\xi + \gamma_1 a) + \xi\mu_1 b(\delta + \alpha_0)}{dba(\delta + \alpha_0)} \quad (3.27)$$

Therefore, $R_{\alpha_0} < 1$ implies that

$$\beta_{\alpha_0} < \frac{dba(\delta + \alpha_0) - \left(e(\mu_2\xi + \gamma_1 a)(\delta + \gamma_3) + \xi\mu_1 b(\delta + \alpha_0)\right)}{S_1\left((\delta + \alpha_0 + Kq\gamma_2) + e\right)(\mu_2\xi + \gamma_1 a) + \xi\mu_1 b(\delta + \alpha_0)} \quad (3.28)$$

In this way, successful treatment system (treatment without relapse) assumes a basic role in decreasing the frequency of HBV disease in the populace. Since the chronic carriers change their behaviour which results in a reduction in the spread of HBV infection, it is noted that $R_{\alpha_0} < R_{\varphi}$.

Likewise, the essential reproduction number (without treatment) is given by,

$$R_0 = \frac{[\beta S_1(\delta + Kq\gamma_2) + e](\mu_2\xi + \gamma_1 a) + \xi\mu_1 b\delta}{dba\delta} \quad (3.29)$$

The computation of the various reproductions numbers using MAPLE satisfies the inequality $R_{\alpha_0} < R_{\varphi} < R_0$ However; the presence of relapse posed a threat to HBV control measures if not adequately checked.

Numerical Simulation

Table 3: Parameters Values utilized in Numerical Simulation

Parameters	***Range***	**Value**	**Source**
β		0.8	Khan *et al.*(2016)
δ		0.0143	Khan *et al.*(2016)
γ_1		6 per year	Khan *et al.*(2016)
γ_2		4 per year	Khan *et al.*(2016)
γ_3		0.34	Khan *et al.*(2016)
k		0.1	Khan *et al.*(2016)
π	0-1	0.001	Khan *et al.*(2016)
η		0.7	Khan *et al.*(2016)
μ_1		0.001	Khan *et al.*(2016)
μ_2		0.001	Khan *et al.*(2016)
α	0-1	0.8	Khan *et al.*(2016)
ξ	0-1	0.8	Khan *et al.*(2016)
q	0.005-0.9	0.005	WHO (2002)
φ		0.393	Pan *et al* . (2013)
S_O		0.493	Medley *et al* . (2001)
E_O		0.0035	Medley *et al* . (2001)
A_O		0.0035	Medley *et al* . (2001)
C_O		0.25	Assumed
M_O		0.003	Assumed
α_o		0.8	Assumed

Sensitivity Analysis

We investigate the sensitivity, to determine the significant importance of model parameters liable for disease transmission. The analysis will empower us to figure out parameters that profoundly affect the effective reproduction number and which ought to be focused on by mediation strategies. We calculate the sensitivity indices of the effective reproduction number with relapse R_{φ} to decide if HBV can be eradicated in the populace or not. These indices let us know how indispensable every parameter is to hepatitis B transmission.

Sensitivity analysis is generally used to decide the robustness of model predictions to parameter values since there are normally mistakes in information assortment and assumed parameter values (Chitnis et al., 2008).

To explore which parameters in the model system (3.15) – (3.19) exceptionally affect R_{φ} and ought to be targeted by mediation technique, we apply the

methodology introduced by Chitnis et al. (2008). The normalized forward sensitivity index of a variable to a parameter is a proportion of the relative change in the parameter. At the point when a variable is a differentiable function of the parameter, the sensitivity index may be on the other hand defined using partial derivatives as follows.

Definition 4: The normalized forward sensitivity index of a variable τ that depends differentiable on the index on a parameter p is defined as $r_\tau^\rho = \frac{\partial \rho}{\partial \tau} \times \frac{\tau}{\rho}$

From the formula of effective reproduction, R_φ in condition (3.25), we determine an analytical expression for the sensitivity of R_φ as $r_\tau^{R_\varphi} = \frac{\partial R_\varphi}{\partial \tau} \times \frac{\tau}{R_\varphi}$, where τ signifies the parameter. We compute the sensitive indices of the model system (3.15) – (3.19) for certain parameters involved in R_φ. For instance the sensitivity index of R_φ regarding to β is given by

$r_\beta^{R_\varphi} = \frac{\partial R_\varphi}{\partial \beta} \times \frac{\beta}{R_\varphi}$

Additionally, the sensitivity index of R_φ with respect to α_0 is given by

$r_{\alpha_0}^{R_\varphi} = \frac{\partial R_\varphi}{\partial \alpha_0} \times \frac{\alpha_0}{R_\varphi}$

Moreover, the sensitivity index of $R_{\alpha_0 \varphi}$ with respect to α_0 is given by

$r_{\alpha_0}^{R_{\alpha_0}} = \frac{\partial R_{\alpha_0}}{\partial \alpha_0} \times \frac{\alpha_0}{R_{\alpha_0}}$

Results

In this segment, we present the primary discoveries of the findings under the accompanying sub-headings.

Numerical Results

We start this sub-area by introducing the mathematical results of the above tests.

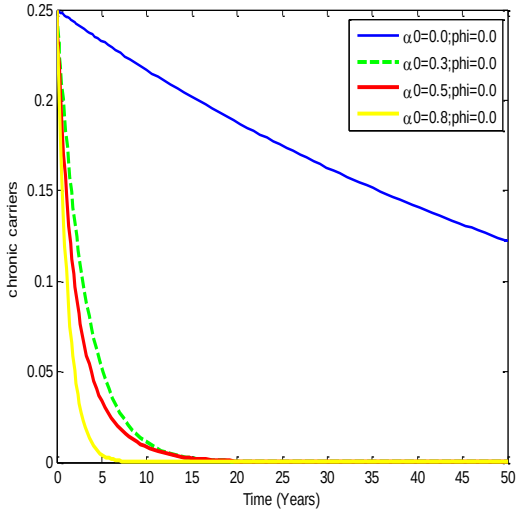

Figure 2: Effect of different treatment strategies on chronic carriers without relapse rate.

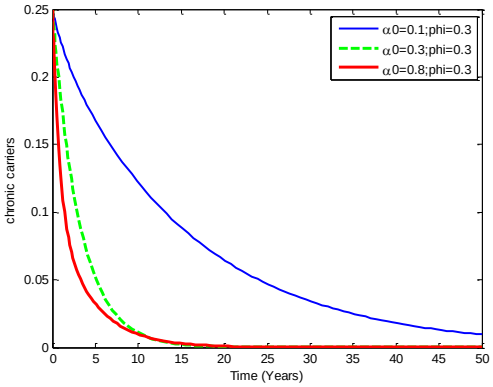

Figure 3: Effect of different treatment strategies on chronic carriers with constant relapse rate.

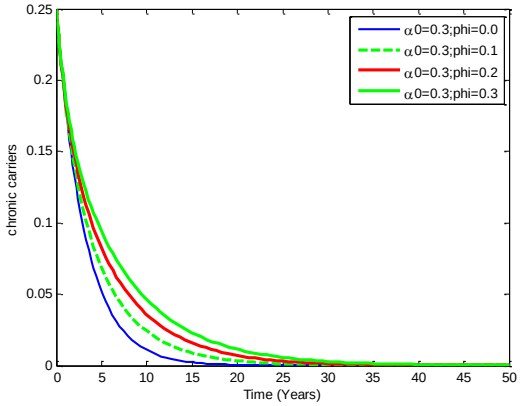

Figure 4: Effect of a treatment strategy on chronic carriers with different relapse rates.

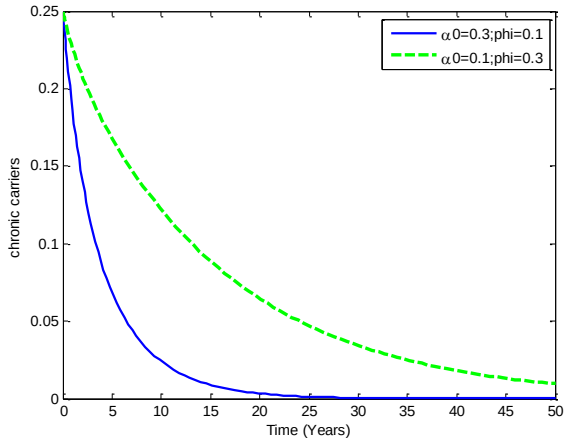

Figure 5: Effect of two different treatment and relapse strategies on chronic carriers.

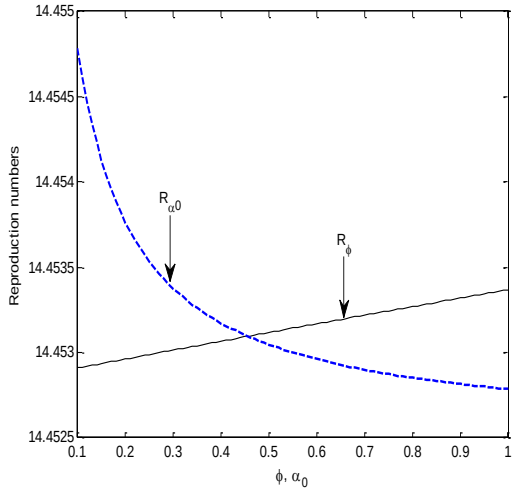

Fig6. The impact of the reproduction numbers (R_φ on φ) and (R_{α_0} on α_0)

We utilize the parameter value displayed in Table 3 to get the numerical values, therefore, the sensitivity index of R_φ and R_{α_0} with respect to β is given by

$r_\beta^{R_\varphi} = r_\beta^{R_{\alpha_0}} = 1$

the sensitivity index of R_φ with respect to α_0 is given by

$r_{\alpha_0}^{R_\varphi} = -0.000008393$

Likewise, the sensitivity index of R_{α_0} with respect to α_0 is given by

$r_{\alpha_0}^{R_{\alpha_0}} = -0.00001532$

The sensitivity indices results of R_φ are given in Table 4 and are arranged from the highest sensitivity value to the lowest value. The indices with positive signs show that the value of R_φ increases when the corresponding parameters are increased and those having negative signs indicate that the value of R_φ decreases when the parameters are increased.

4.3 Sensitivity Results

Table 4: Sensitivity Indices of R_φ with respect to some Parameters

S/N	Parameter	Sensitivity Index	Sign
1	β	1.000000000	+
2	γ_2	0.43385442	−
3	μ_2	0.056317856	+
4	α	0.05641998	−
5	π	1.00000000	+
6	γ_1	0.92384591	+
7	ξ	0.90661118	−
8	μ_1	0.00111063	+
9	q	0.000008586	+
10	α_0	0.000008393	−
11	η	0.0000000007127	+
12	φ	0.000001847	+
13	k	0.000008586	+
14	γ_3	0.000001773	−

Numerical Results

Figure 2 illustrate the dynamical behaviour of chronic carrier with respect to the parameters, α_0 and φ. With no treatment rate, the chronic carriers will persist in the population, implying that the disease fails to be eradicated at that point and begins to decline as the value of effective treatment increases from 0.3 to 0.8. Figure 2 (from 0.3 to 0.8) demonstrates the effectiveness of treatment without relapse in controlling chronic HBV infection. A similar consideration was carried out in figure 3 on chronic carriers who have gone out for treatment and indicates a similar scenario only that the number of treated individuals with an ineffective treatment strategy, who relapse, has a less comparative advantage to those treated individuals without relapse. That is, ineffective treatment strategy increases the time or may not allow the infection to be put under control on time. A clear difference between the above two experiments is given in fig 4 at $\alpha_0 = 0.3$ in which $\varphi = 0 < \varphi = 0.3$.

This inequality shows the significance of effective treatment ($\alpha_0 = 0.3,\ \varphi = 0$) as a essential for reducing relapse in patients with persistent HBV infection and further beats down ineffective treatment (blind prescription, or self-medication) ($\alpha_0 = 0.3,\ \varphi = 0.3$). This result agrees with the work of (T, lai2007, Guo 2018) that adherence to effective anti-HBV therapy prevents relapse and encourages timely cure. The impact of α_0 on patients, who relapse to chronic carrier at different rates, is also given in figure 5. In figure 5, the higher one embraces treatment with less or no relapse at all, the better for chronic infection to be halted. On the other hand, the infection will prove difficult to curtail for those who have gone for ineffective treatment (self-medication). Fig. 6 shows that R_φ increases in the presence of relapse (treatment failure, φ, increases). Therefore, φ increases HBV infection. On the other hand, the

treatment rate α_0 decreases the spread of the disease in the population. Hence, it will be profitable if the causes of treatment failure are checked.

Sensitivity Analysis Result

Table 4 reveals that $\beta, \pi, \varphi, q, \gamma_1$and η increases the value of R_φ when they are increased. This suggests that the HBV disease will grow up in the populace when these parameters values are increased. Running against the norm, $\gamma_{2,}, \alpha_0$ and γ_3 decrease the value of R_φ when they are increased. This suggests that the disease can't grow in the populace when these parameters values are decreasing.

The transmission coefficient, β and the proportion without immunization π are the most, sensitive parameters. Decreasing or increasing the value of β and π leads to the decrease or increase of the value of R_φ with a similar extent since the sensitivity index is equivalent to one. Subsequently, as β and π increases, numerous people become infected, so HBV transmission increases in the population.

Moreover, when treatment rate, α_0 increases then R_{α_0} diminishes, this suggests that numerous persistent chronic carriers move to the removed class after treatment. Consequently, to limit HBV transmission in a populace, this study suggests that treatment ought to be carried out in light of the fact that treatment assists to prevent the spread of infection and its entanglements.

Conclusion

The objective of this paper is to show the effect of therapy in controlling relapse in patients with chronic HBV infection. To this end, we compute the effective reproduction ratios and the incidence function that account for the behaviour of subjects with and without relapse has been introduced. It was demonstrated that effective treatment (Hepatologist prescription) is extremely critical in mitigating and controlling relapse in subjects with chronic HBV infection than the subjects (model) with an ineffective treatment technique. The sensitivity indices of R_φ uncover that, transmission rate and the proportion without vaccination advocated the disease outbreak and could be checked via occurrence of the infection or the number of infected person in the populace. Hence, a well-planned and adequately implemented effective treatment technique can essentially reduce the reproduction number, in this manner reducing relapse in patients with chronic HBV infection. The study can be extended to include the cost-effectiveness of the treatment strategy. In addition, for subsequent research, screening can be incorporated into the work.

References

Adeoye, G. (2010). Twenty Million Nigerians at Risk from Hepatitis B. Retrieved 14/12/2017 from http://www.plurpol.org/joom/index.php/regional-news/64-africa/6245.

Amit, S., and Mansor, M.(2018). Combinatorial Approach in rationale Design of polymetric Nanomedicines for cancer. Journal of Biomedical Application of functionalized Nanomaterials.

Athena, P., Kourtis, M.D., Bulterys, M.D., Dale, J., Hu, M.D. and Denise J.J.(2012). HIV-HBV co-infection- A Global challenge. New England Journal of Medicine.366:1749-1752.

Centers for Disease Control (2008). Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection.

Charan, M.S., Paramita, S.(2016). Health Programs in a Developing Country-Why do we fail? Health system policy press. 3:3 dio:10. 21767/2254-9137. 100046.

Chitnis, N., Hyman, J. M. and Cushing, J. M. (2008). Determining important Parameters in the Spread of Malaria through the Sensitivity Analysis of a Mathematical model. *Bulletin of Mathematical Biology*, 70 (5): 1272-1296.

EASL (2013). European association for the study of liver diseases.

Gish, R., Jia, J. D., Locarnini, S. and Zoulim, F. (2012). Selection of Chronic Hepatitis B Therapy with high Barrier to Resistance. *Journal of Lancet Infectious Diseases*, 12(4): 341–353.

Guo, L., Wang, D., Ouyang, X., Tang, N., Chen, Y. Z., Zhu, H., and Li, X. (2018). Recent Advances in Hepatitis B Virus Reactivation Research. *Biomedical Research International*, 2018: 1- 9.

Hoofnagle, J. H. (2009). Reactivation of hepatitis B. *Journal of Hepatology*. 49(5): 156-165.

Lai, C. L., and Yuen, M. F. (2007). The Natural History and Treatment of Chronic Hepatitis B: A Critical Evaluation of Standard Treatment Criteria and End Points. *Journal of Annals of Internal Medicine*, 147(1): 58-61.

Khan, A. M., Saeed, I., Muhammad, A., and Zahoor, U. H. (2016). Transmission Model of Hepatitis B Virus with the Migration Effect. *Journal of Biomedical Research International*, 2016(2): 1-9.

Kosinska, A. D., Zhang, E., Johrden, L., Liu, J., Seiz, P. L., Zhang, X., Ma, Z., Kemper, T., Fiedler, M. and Glebe, D. (2013). Combination of DNA Prime—Adenovirus boost Immunization with Entecavir elicits Sustained Control of Chronic Hepatitis B in the Woodchuck Model. *Journal of Public library of science pathogens, 9(6): 1371-1391*.

Kumar, M., Chauhan, R., Gupta, N. ET et al (2009). Spontaneous increases in alanine aminotransferase levels in asymptomatic chronic hepatitis B virus-infected patients. Journal of Gastroenterology. 136: 1272-1280.

Medley, G.F., Lindop, N.A., Edmunds, W.J. and Nokes, D.J. (2001). Hepatitis B virus endemicity, heterogeneity, catastrophic dynamics and control. Journal of natural medicine. 7(5): 1-10.

Moore, P. S., and Chang, Y. (2010). Why do viruses cause cancer? Highlights of the first century of human tumour virology. Nature reviews Cancer. 10(12): 878-889.

Nwaokolo, M. A., Kimbir, A. R., Onah, E. S., and Aboiyar, T. (2018): Stability Analysis of the effect of vaccination and treatment on Hepatitis B Virus Transmission with infective migrants. Journal of the Nigerian Association of Mathematical physics. 47(1):353-362

Nwaokolo, M.A., Kimbir, A. R., Onah, E. S. Aboiyar, T. (2020). Global stability analysis of the effect of vaccination and treatment in controlling the spread of HBV with infective immigrants. *Journal of the Nigerian Association of mathematical physics. 54:21-35*.

Nwaokolo, M.A.,Adiku, L. and Nyakubun, G.A. (2022) Numerical Simulation of the Impact of Relapse on Hepatitis B Virus Transmission Dynamics. *FUW Trends in Science and Tecnology Journal*. 7(1): 269-280.

Pan, X., Zhang, K., Yang, X., Liang, J., Sun, H. and Li, X. (2013). Relapse Rate and Associated-Factor of Recurrence after Stopping Nucleosides Therapy with different prolonged Consolidation Therapy in Hepatitis B enveloped Antigen- Positive Chronic Hepatitis B Patients. *Journal of clinical virology*, 8(7): 1-6.

Tseng, T. C., Liu, C. J., Su, J. H. and Kao, J. H. (2012). Young Chronic Hepatitis B Patients with Nucleos(t)ide Analogue-induced Hepatitis B enveloped Antigen Seroconversion Have a Higher Risk of Hepatitis B Virus Reactivation. *Journal of Infectious Disease*, 206(10): 1521-1531.

Vigano, M., Mangia, G. and Lampertico, P. (2014). Hepatitis B enveloped Antigen-Negative Chronic Hepatitis B: Why Do I Treat My Patients with Nucleos(t)ide Analogues? *Journal of* Liver *International*, 34(1): 120–126.

Weinbaum, C. M., Williams, I., Mast, E. E., Wang, S. A., Finelli, L., Wasley, A., Neitzel, S. M. and Ward, J. W. (2008). Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection. *Journal of Morbidity and Mortality Weekly* Report, 57(8): 1-20.

WHO (2009) The growing threats of hepatitis B and C in the Eastern Mediterranean Region; A call for action (56th Edn).

WHO. Hepatitis B. Fact Sheet N°204. http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed 30 Apr 2023.

World Health Organization (2019). Hepatitis B. Retrieved from FactSheet.http:// www.who.int/news room/factsheets/detail/hepatitis-b.(Accessed 30 Apr 2023).

Wu, C. C. H., et al . (2019). Hepatitis B reactivation in patients with previous hepatitis B exposure to immunosuppressants World journal meta- anal. 7(5): 209-217.

Yao, C. C., Hung, C. H., Hu, T. H., Lu, S. N., Wang, J. H., Lee, C. M. and Chen, C. H. (2017). Incidence and Predictors of Hepatitis B Virus Relapse after Cessation of Nucleoside Analogues in Hepatitis B enveloped Antigen-Negative Patients with Hepatitis B Surface Antigen. *Natural Research Journal*, 1839(7): 2045-2322.

Zhang, X., Ma, Z., Liu, H., Liu, J., Meng, Z., Broering, R., Yang, D., Schlaak, J. F., Roggendorf, M. and Lu, M. (2012). Role of Toll-Like Receptor 2 in the Immune Response against Hepadnaviral Infection. *Journal of* Hepatology, 57: 522–528.

World Health Organization (2002), Hepatitis B: World Health Organization Fact Sheet 204.

Zoulim, F. and Locarnini, S. (2009). Hepatitis B Virus Resistance to Nucleos(t)ide Analogues. *Journal of Gastroenterology*, 137(2): 1593– 1608.