

ORIGINAL ARTICLE

AFRICAN JOURNAL OF CLINICAL AND EXPERIMENTAL MICROBIOLOGY
AJCEM/1818

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AFR. J. CLN. EXPER. MICROBIOL 19 (2): 125 -132

MAY 2018 ISBN 1595-689X VOL19 No.2
<http://www.ajol.info/journals/ajcem>

CO-INFECTION OF HEPATITIS B AND C VIRUSES AMONG HUMAN IMMUNODEFICIENCY VIRUS INFECTED CHILDREN IN LAGOS, NIGERIA

RUNNING TITLE: CO-INFECTION OF HBV AND HCV IN HIV POSITIVE CHILDREN

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ABSTRACT

Introduction: The co-infection of Human immunodeficiency virus (HIV), Hepatitis B and C viruses remains a public health problem particularly in resource limited setting like Nigeria. Studies on these co-infections have been done principally among adult and pregnant women with limited information on the pediatric population. The study aims at documenting the burden and the patterns of HIV/HBV, HIV/HCV and HIV/HBV/HCV co-infections in children in Lagos, Nigeria.

Methods: A cross-sectional study carried out at the Virology Research Laboratory, College of Medicine of the University of Lagos between December 2008 and January 2014. A total of 393 confirmed HIV infected children aged between <1 to 15 years were screened from two tertiary health facilities; Lagos State University Teaching Hospital (LASUTH, n=272) and Lagos University Teaching Hospital (LUTH, n=121), Lagos. Plasma samples were screened for markers for HBV (HBsAg, HBeAg, HBeAb, HBcIgM) and HCV (anti-HCV) using a fourth generation enzyme-linked immunosorbent assay (DIA. PRO. Diagnostic Bioprobes Srl., Italy).

Results: Out of the 393 samples analyzed, 40 (10.2%) were sero-positive for dual HIV/HBV co-infection, comprising 21 (52.5%) females and 19 (47.5%) males, while 15 (3.8%) had detectable antibodies to HCV consisting of 7 (46.7%) females and 8 (53.3%) males without any statistical significance. On the overall, two (0.5%) of the participants were seropositive for triple HIV, HBV and HCV co-infections. HIV/HBV co-infection was detected among all the age groups, whereas, HIV/HCV co-infection was not seen among children <1 to 5 years.

Conclusion: This analysis confirmed a high prevalence of HBV, low prevalence of HCV and suggests that chronic hepatitis may be prevalent among our HIV-infected children. Thus, routine screening and early detections are therefore necessary for an appropriate treatment plan for children co-infected with HIV/HBV and or with HCV.

Keywords: Human immunodeficiency virus (HIV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Co-infection and Enzyme-Linked Immunosorbent Assay (ELISA).

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CO-INJECTION DE VIRUS DE L'HÉPATITE B ET C CHEZ LES ENFANTS INFECTÉS PAR LE VIRUS DE L'IMMUNODÉFICIENCE HUMAINE À LAGOS, NIGERIA

TITRE COURANT: LA CO-INFECTION PAR LE VHB ET LE VHC DANS LES ENFANTS SÉROPOSITIFS

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RÉSUMÉ

Introduction: La co-infection du virus de l'immunodéficience humaine (VIH), le virus de l'hépatite B et C reste un problème de santé publique en particulier dans les pays à ressources limitées comme le Nigeria. Des études sur ces co-infections ont été réalisées principalement chez les adultes et les femmes enceintes avec l'information limitée sur la population pédiatrique. L'étude vise à documenter le fardeau et l'évolution du VIH/VHB, VIH/VHC et VIH/VHB/VHC co-infections chez les enfants à Lagos, Nigeria.

Méthodes: Une étude transversale effectuée au Laboratoire de recherche de virologie, Collège de médecine de l'Université de Lagos, entre décembre 2008 et janvier 2014. A confirmé un total de 393 enfants infectés par le VIH âgés de moins de 1 à 15 ans ont été sélectionnés à partir de deux établissements de santé tertiaires ; hôpital d'enseignement de l'Université d'État de Lagos (LASUTH, n =272) et l'Hôpital d'enseignement de l'Université de Lagos (luth, n =121), Lagos. Des échantillons de plasma ont été projetés pour les marqueurs pour le VHB (AGHBS, l'AGHBE, HBeAb, HBcIgM) et du VHC (anti-VHC) à l'aide d'une quatrième génération de dosage immuno-enzymatique (DIA. PRO. Bioprobes Diagnostic Srl., Italie).

Résultats: Sur les 393 échantillons analysés, 40 (10,2 %) étaient séropositifs pour le VIH/VHB co-infection, composée de 21 (52,5 %) et 19 femmes (47,5 %) hommes et 15 (3,8 %) présentaient des anticorps détectables au VHC composé de 7 (46,7 %) et 8 femmes (53,3 %) hommes sans aucune signification statistique. Sur l'ensemble, deux (0,5 %) des participants étaient séropositifs pour le VIH, VHB et VHC co-infections. Le VIH/VHB co-infection n'a été détectée parmi tous les groupes d'âge, tandis que, le VIH/VHC co-infection n'a pas été observé chez les enfants de moins de 1 à 5 ans.

Conclusion: Cette analyse a confirmé une forte prévalence du VHB, une faible prévalence du VHC et suggère que l'hépatite chronique peut être répandu chez nos enfants infectés par le VIH. Ainsi, le dépistage systématique et au début les détections sont donc nécessaires pour un plan de traitement approprié pour les enfants co-infectés par le VIH et le VHB et par le VHC ou.

Mots-clés: virus de l'immunodéficience humaine (VIH), l'hépatite B (VHB), le virus de l'hépatite C (VHC), la co-infection et de dosage immuno-enzymatique (ELISA).

INTRODUCTION

The convergence of Human immunodeficiency virus (HIV), Hepatitis B and C viruses is of great individual clinical significance and a public health challenge at large [1]. While HIV is the causative agent of Acquired Immune Deficiency Syndrome (AIDS), the other two viruses cause Hepatitis, which is a hepatocytic inflammation of the liver [2, 3].

The hallmarks of HIV infection are transmissibility, chronicity and progression to AIDS through gradual

destruction of the immune system, when there is no appropriate intervention [4]. Despite recent declines in HIV/AIDS mortality globally, there is considerable heterogeneity in the levels and patterns of the infection across countries. While many countries have experienced reductions in HIV/AIDS annual new infections and mortality, other countries have had insignificant responses or upsurges in rates of annual new infections [5, 6]. An estimated 60% of new HIV infections in Central and Western Africa was reported from Nigeria in 2015. The country's adult HIV prevalence stands at 3.1% in the report of National

Agency for Control of AIDS (NACA)-2015. The same report gave an estimate of 260,000 children (0 to 14 years) in Nigeria living with HIV as of 2015 [7].

Globally, an estimated 257 million and 71 million people were living with chronic HBV and HCV infection respectively in 2015 [8]. Hence, due to similar or shared routes of transmission, the occurrence of Hepatitis B and C viruses with HIV, albeit as a single or co-infection remains a common public health problem [3, 9]. However perinatal transmission is the most important route of spread to children, due to high rates of infection of these viruses in pregnant women [10, 11]. Although, co-infection with HBV and HCV is a global challenge, the impact is greater on health resource poor settings, particularly Sub-Saharan Africa. This is accentuated by an earlier report of prevalence rates of HBV and HCV of 15% and 7%, respectively among HIV infected people in the region [12].

Varied prevalence rates have been recorded for HBV in Nigeria for children ranging from 4.1% to 44.7% [13], with the country said to have a pooled prevalence of 14% for Hepatitis B virus infection [14]. There is however a dearth of similar data for HCV in the country. Similarly, there is a dearth of combined data for co-infection of HBV and HCV among children with HIV in the country. Studies elsewhere in Africa have shown significant association of HBV and HCV (9.7% and 7% respectively) in HIV infected children [15].

Infections with HBV and or HCV leading to liver hepatitis are leading causes of morbidity and mortality in HIV infected children. As such the WHO recommends that such children should be diagnosed and provided with appropriate and effective treatment for both HIV and the hepatitis [8]. However, this is a challenge in resource limited countries where resources and capacities are inadequate to offer appropriate full laboratory hepatitis viral assays, to evaluate the co-infections of HBV and HCV with HIV. More studies are therefore required to address the burden of the convergence of these viruses in this setting, which informed this study.

MATERIALS AND METHODS

Study Centre: This study was a cross-sectional study carried out at the Virology Research Laboratory (Central Research Laboratory), College of Medicine of the University of Lagos.

Study Population: The study participants were 393 HIV infected children aged between <1 to 15 years confirmed to be HIV positive with Polymerase Chain Reaction (PCR) for children <18 months or Western blot for children ≥18 months born to HIV-positive

mothers attending either the Paediatrics/ Obstetrics and Gynecology Centers of two tertiary health facilities; Lagos State University Teaching Hospital (LASUTH, n=272) and Lagos University Teaching Hospital (LUTH, n=121), Lagos, Nigeria between December 2008 and January 2014. Ethical approval was obtained from both institutional Health Research and Ethics Committee and from the Lagos State Hospital Management Board. Only individuals who consented that their data and samples can be used for research were recruited for the study and they were then identified with unique codes to protect their confidentiality.

The minimum sample size (N) calculated was 162, determined using the equation as described by Naing et al., 2006[16]:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where n= sample size, Z=statistics for a level of 95% confidence interval=1.96, P=prevalence rate. Assumed to be= 12% according to Owolabi et al., 2014 [17] and d= precision (allowable error) =5%=0.05.

Data/Sample Collection and analyses: Socio-demographic data were documented using structured and pretested interviewer administered questionnaire and possible risk factors for HBV/HCV transmission. About 3ml of whole blood samples were collected aseptically into sterile ethylene diamine tetraacetic acid (EDTA) vacutainer bottle, centrifuged within 2 hours of collection to obtain plasma and stored at -70°C for serological assays. All samples were screened for markers for HBV (HBsAg, HBeAg, HBeAb, HBcIgM) and HCV (anti-HCV) using a fourth generation enzyme-linked immunosorbent assay (DIA. PRO. Diagnostic Bioprobes Srl, Italy). All assay protocols and interpretation of results using cut-off values were done according to the manufacturer's instructions.

All quantitative data were entered in the computer Microsoft Excel sheet and analyzed using SPSS version 17 for Windows. Descriptive statistics was computed for all relevant data. Associations between HBV/HCV/HIV infections and the socio-demographic and major risk factors were tested using Chi-square. All significance was accepted at $P < 0.05$.

RESULTS

Three hundred and ninety-three (393) HIV infected children aged <1 to 15 years with mean age of 4.79 ± 3.17 years were enrolled for this study. There were 186 (47.3%) males and 207 (52.7%) females. Out of the 393 samples analyzed, 40 (10.2%) were sero-positive for dual HIV/HBsAg co-infection, comprising 21 (52.5%) females and 19 (47.5%) males, while 15 (3.8%) had detectable antibodies to HCV consisting of 7 (46.7%) females and 8 (53.3%) males without any

statistical significance. On the overall, two (0.5%) of the participants were seropositive for triple HIV, HBsAg and anti-HCV co-infections (Figure 1).

Majority, 185 (47.1%) of the participants were aged between 1 – 5 years, while 107 (27.2%) and 69 (17.6%) were within the age group 6 – 10 and <1 years respectively (Table 1). Based on age group, HIV/HBV co-infection was highest (43.8%) amongst age group 11 – 15 years as compared with 15.9%, 4.3%

and 3.2% amongst of those age groups 6 – 10, <1 and 1 – 5 years respectively. The differences were not statistically significant ($P=0.59$). Co-infection of HIV/HCV was only and predominantly seen in age groups 6 – 10 and 11 – 15 years with prevalence of 46.7% and 53.3% respectively (Table 1). However, 50% each among age groups 6 -10 and 11 - 15 years had triple infection of HIV/HBV/HCV (Table 1).

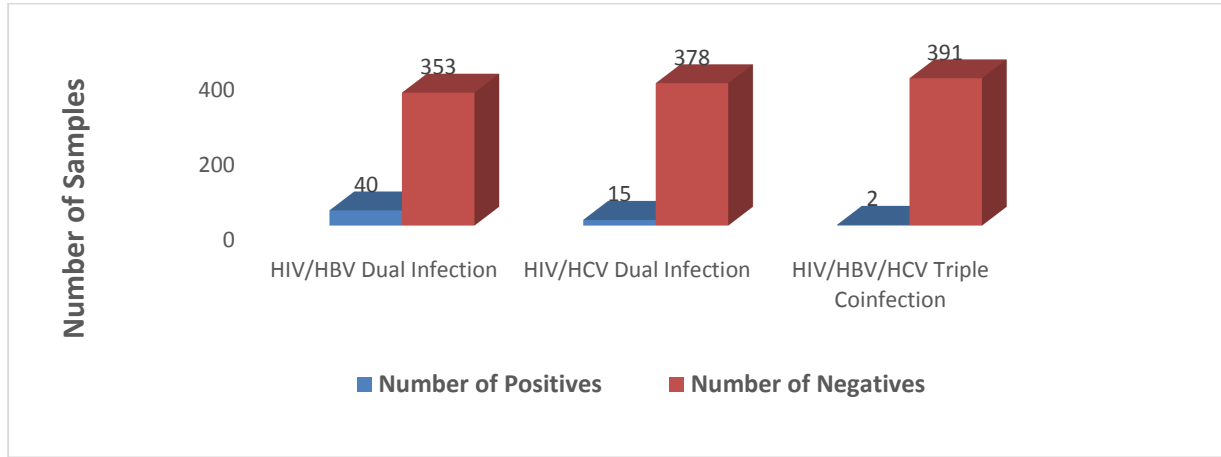


FIGURE 1: CO-INFECTION PATTERN OF HIV WITH HBV AND HCV AMONG PATIENTS IN LAGOS, NIGERIA

TABLE 1: AGE DISTRIBUTION OF HIV CO-INFECTION WITH HBV AND HCV AMONG PATIENTS IN LAGOS, NIGERIA

Age Group	Total (%)	HIV/HBV (%)	HIV/HCV	HIV/HBV/HCV
< 1yr	69 (17.6)	3 (4.3)	0 (0)	0 (0)
1-5yrs	185 (47.1)	6 (3.2)	0 (0)	0(0)
6-10yrs	107 (27.2)	17 (15.9)	7 (46.7)	1 (50)
11-15yrs	32 (8.1)	14 (43.8)	8 (53.3)	1 (50)
Total	393	40	15	2

Analysis of other markers of Hepatitis B virus among the 40 participants that were positive for HBsAg revealed that, 13 (32.5%) and 25 (62.5%) had acute and chronic infections respectively that were not active

based on the combination of markers as shown in table 2. However, 2 (5%) of this participants had chronic infection that is still active based on the combination of markers (Table 2).

TABLE 2: SERO-POSITIVITY OF HBV MARKERS IN PATIENTS AND IMPLICATIONS

Serologic Patterns Observed	Frequency of Occurrence (%)	Interpretation
HBsAg+, HBsAb+, HBeAg-, HBeAb+, HBcAb+	13 (32.5)	Acute Infection (Low or No replicative state)
HBsAg+, HBsAb-, HBeAg-, HBeAb+, HBcAb+	25 (62.5)	Chronic Infection (Low or No replicative state)
HBsAg+, HbsAb-, HbeAg+, HbeAb+, HbcAb+	2 (5.0)	Chronic Infection (ongoing high level replication)
Total	40 (100)	

DISCUSSION

The co-infections of Human immunodeficiency virus (HIV), Hepatitis B and C viruses remain a global

public health challenge on health resource poor settings particularly in Sub-Saharan Africa where the impact is greater. The prevalence rate of dual

HIV/HBV, HIV/HCV and triple HIV/HBV/HCV co-infection in this study was 10.2%, 3.8% and 0.5% respectively. These findings adds to the available data that Hepatitis B virus (HBV) and Hepatitis C virus (HCV) co-infections are important co-morbidities to consider when making management decisions particularly in HIV infected children. Moreso, that the prevalence of HBV or HCV infection and its impact on HIV-infected children has been poorly characterized and studied in our environment.

Varying prevalences had been documented in literature for HBV and HCV co-infections in similar cohort studies on HIV positive children, the prevalence of 10.2% for Hepatitis B surface antigen in this study was higher than the respective 7.7%, 8.4%, 1.2%, 2.6%, 4%, and 4.9% prevalences reported by Sadoh et al. [18] in Benin, Rawizza et al. [19] in Nigeria, Telatela et al. [20] in Tanzania, Toussi et al. [21] in New York, USA, Chakraborty et al. [22] in Kenya, and Zhou et al. [23] in China. Furthermore, the prevalence of 10.2% from our study was lower than the respective 19%, and 12.1% prevalence reported by Ashir et al. [24] in Maiduguri, Nigeria, and Rouet et al. [25] in Ivory Coast also in cohorts of pediatric HIV-infected children. The differences in the prevalence rate of HIV/HBV co-infection in this study and that of others may reflect the differences in the geographical distribution, assay type and sample population.

Although, the prevalence of 3.8% observed for HCV in this study, was higher than the 1.5%, 2.7%, 3.1% prevalences reported by Schuval et al [26] in USA, Rawizza et al [19] in Nigeria and Toussi et al [21] in USA. It is however, lower than the respective 5.2%, 9.6% and 13.8% published by Sadoh et al [18] in Nigeria, Zhou et al [23] in China and by Telatela et al [20] in Tanzania. In the contrary, Rouet et al [25] reported no co-infection of HIV with hepatitis C among a cohort of HIV-infected children in Cote d'Ivoire.

The mean ages of children with HIV/HBV, HIV/HCV co-infections and HIV/HBV/HCV triple infections were not different statistically. Co-infection with hepatitis B was documented in all age groups of children, with those greater than 10 years been more affected. However, no hepatitis C co-infection was detected among children under 5 years of age in this study. This findings was in contrast to a report from Tanzania where children under 5 years of age was found to have a higher incidence of HIV/HCV co-infection [20]. Our findings suggests that there were no vertical transmission of HCV from mother to child as compared to that of HBV since children under 5

years of age were infected with the virus and thus, may reflect differing modes of transmission of HCV which may be peculiar to our environment.

The pattern of the occurrence of the HBV markers from this study revealed that majority (32.5%) and (62.5%) had acute and chronic HBV infections respectively with low or no ongoing replication of the virus. The observed 5% of these children had chronic infection with presently ongoing high level replication of the virus and therefore very important in the transmission cycle of HBV particularly among children population in our environment. It will therefore be appropriate for these small group of children to be provided with suitable and effective treatment for both HIV and hepatitis infections.

CONCLUSION: This study revealed that co-infections of HBV and HCV with HIV among children may further increase the undesirable chances of chronic liver diseases which will consequently reduce the life expectancy of children in our environment. The observed different patterns of co-infection in this study may therefore necessitate the need for full and better understanding of the clinical outcomes and molecular epidemiology of these viruses with a view to alleviating the public health impetus associated with these diseases.

ACKNOWLEDGMENT: The authors would like to acknowledge and thank all patients, students and staffs who contributed to the collection and analysis of samples in the laboratory, especially the Medical Laboratory Scientists of the Virology Research Laboratory, College of Medicine of the University of Lagos.

COMPETING INTERESTS: The authors declare that they have no financial or personal relationship(s) which may have inappropriately influenced them in writing this article.

AUTHORS' CONTRIBUTIONS: S.O.B., O.A.O.B and G.A conceptualized the study and were responsible for the experimental and project design, analysis of data and writing the manuscript. J.A.B, O.B.O, A.O.S and A.A.A made conceptual contributions, performed some of the experimental analysis and assisted in preparing the manuscript. A.K.O made conceptual contributions and assisted in preparing the manuscript, while O.S.A was the laboratory director, team lead of the Virology Research Group and was responsible for the experimental and project design, analysis of data and writing the manuscript. All authors read and approved the manuscript.

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