

Original Research Article

Prevalence and laboratory profile of hepatitis B virus co-infected Nigerian children with human immunodeficiency virus infection.

ABSTRACT

Aims: To determine the prevalence of HBV co-infection in HIV-infected children and compare the baseline laboratory profile of mono-infected and co-infected patients.

Study Design: This was a retrospective cohort study.

Place and Duration of Study: AIDS Prevention Initiative in Nigeria (APIN)-supported HIV clinic at Jos University Teaching Hospital, Jos, Nigeria between January 2008 and December 2012.

Methodology: We reviewed the clinical records of 452 treatment-naïve children aged 2 months to 15 years confirmed to be HIV positive with Polymerase Chain Reaction (PCR) or Western blot enrolled at the clinic within the stated period. Their baseline HBsAg test results, CD4⁺T cell count for children ≥5years or CD4⁺T cell % generated by automated method for children <5years, viral load and alanine transaminase (ALT) were analysed.

Results: Three hundred and ninety-four (87.2%) were mono-infected with HIV while 58 (12.8%) were co-infected with HIV and HBV. The median viral load was 4.6 log copies/mL for mono-infected compared to 4.7 log copies/mL for HIV/HBV ($P = .48$). The median CD4⁺T cell count was 366 cells/μL for mono-infected compared to 332 cells/μL for HIV/HBV ($P = .64$). The median CD4⁺T cell % was 19% for mono-infected compared to 17% for HIV/HBV ($P = .29$). The median ALT level was 23 IU/mL for mono-infected compared to 26 IU/mL for HIV/HBV ($P = .15$).

Conclusion: A high rate of hepatitis B co-infection was observed in HIV-infected children at our centre; however more severe HIV disease and increased liver enzymes were not observed. Early detection is therefore necessary in order to develop an appropriate treatment plan for children co-infected with HIV and HBV.

Keywords: HIV, hepatitis B, co-infection, CD4⁺T, viral load, alanine transaminase, Nigeria.

1. INTRODUCTION

Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) are the two most common chronic viral infections seen in the world.[1,2] With an estimated 260,000 children infected with HIV at the end of 2011, Nigeria accounts for more than 10% of the global paediatric HIV burden. [3] Nigeria is also known to be highly endemic for HBV infection. [4] Co-infection with HBV is common among HIV infected children in sub-Saharan African countries. [5-8] The two viruses share **modes** of transmission and hence co-exist in the same host at significantly high rates. HBV infections acquired in the perinatal period and early childhood are more likely to lead to chronic infection. [9-10] HIV positive individuals, particularly those with suppressed immune systems, are less likely to respond to vaccination against HBV and are more likely to develop chronic disease after being exposed to HBV. [10] As more HIV-infected children are commenced on highly active anti-retroviral therapy (HAART), they will live longer and co-infection with the hepatitis viruses may become a major health care catastrophe in the coming years especially in resource-limited countries.

The effect of HIV infection on progression of HBV infection in adults is well established. [11-12] Co-infection with HIV modifies the natural history of HBV infection, increasing the rate of viral replication, risk of carriage and chronic hepatitis. [11] HBV infection also increases the toxicity to antiretroviral medications. [12] Co-infection with HBV may lead to rapid progression of HIV disease. [7] Previous studies in adults in Nigeria showed that HIV-infected patients with HBV co-

infection had higher HIV RNA loads and more severe immune suppression prior to initiation of HAART compared to HIV mono-infected patients. [13-15]

There is limited information on the effect HBV co-infection has on baseline laboratory profile of HIV-infected children in sub-Saharan African countries. This study therefore aimed to determine the prevalence and laboratory profile of HIV/HBV co-infected children in Jos, Nigeria.

2. MATERIAL AND METHODS

2.1 Background of study area

The study was carried out at AIDS Prevention Initiative in Nigeria (APIN)-supported HIV clinic of Jos University Teaching Hospital, Jos, Plateau State, Nigeria. The programme cares for patients in and outside Plateau state. HIV care, treatment and support services are free for all patients enrolled in the program.

2.2 Study Design

This was a retrospective cohort study.

2.3 Ethical Consideration

Ethical clearance was obtained from the Ethical committee of Jos University Teaching Hospital and the Institution Review Board of Harvard School of Public Health.

2.4 Data Collection

The medical records of all treatment-naïve HIV-positive children enrolled in the Paediatric ART program between January 2008 and December 2012 were reviewed for the study. HIV was confirmed by either deoxyribonucleic acid Polymerase Chain Reaction (DNA PCR) for children <18 months or Western blot for children ≥18 months. The baseline laboratory parameters assessed include HBV, CD4⁺T cell count and CD4⁺T cell percent, viral load, and Alanine

transaminase (ALT). HBV surface antigen (HBsAg) was used to categorize hepatitis status of the patients. HBsAg was determined using enzyme immunoassay (EIA) (Monolisa HBsAg Ultra3; Bio-Rad). HIV RNA levels were measured using Roche COBAS Amplicor HIV-1 monitor test version 1.5 (Roche Diagnostics, GmbH, Mannheim, Germany) with a detection limit of 400 copies/ml. Flow cytometry was used to determine CD4⁺T cell count (Partec, GmbH Munster, Germany) and the CD4⁺T percent determined by automated method.

2.5 Statistical Analysis

The baseline laboratory parameters of HIV mono-infected patients were compared with those that were co-infected with HBV using nonparametric univariate methods; the Kruskal-Wallis test was used for continuous variables. Linear regression analyses were used to determine whether HBV status was associated with baseline CD4⁺T cell counts/percent, viral load, or ALT values. *P* value <0.05 was considered significant. Analysis was done with EpiInfo version 3.5.4.

3. RESULT

Four hundred and fifty-two treatment-naïve children aged 2 months to 5 years were enrolled between January 2008 and December 2012. Males were 254 (56.2%) while females were 198 (43.8%). The mean age for the males was 4.24±2.78 years and that of the females was 5.34±3.55 years (*P* = .06). Three hundred and ninety-four (83.2%) were mono-infected with HIV while 58 (12.8%) were co-infected with HIV and HBV. The characteristics of the patients are shown in Table 1.

Table 1: Characteristics of the patients

Characteristic	Total (%)
Sex	
Males	254 (56.2)

Females	198 (43.8)
Age	
<1year	94 (20.8)
1-5years	227 (50.2)
6-10years	111 (24.6)
11-15years	20 (4.4)
Hepatitis B status	
Negative	394 (87.2)
Positive	58 (12.8)

87

88 Based on age group, 9.6% of those aged <1 year were co-infected with HBV compared to

89 11.9% of those aged 1-5 years, 13.5% of those aged 6-10 years and 35% of those aged 11-15

90 years ($P = .02$) (Table 2). Although more males than females were co-infected with HBV, the

91 differences were not significant (males 13.8%, females 11.6%; $P = .59$).

92 Table 2: HIV/HBV co-infection based on age groups.

Age group	Total (%)	HIV	HIV/HBV	<i>P</i> value
<1 year	94 (20.8)	85	9	
1-5 years	227 (50.8)	200	27	
6-10 years	111 (24.6)	96	15	

11-15 years	20 (4.4)	13	7	.02
-------------	----------	----	---	-----

93

94 The median viral load was 4.6 log copies/mL (range, 3.8-6.8 log copies/mL) for mono-infected
95 compared to 4.7 log copies/mL (range, 3.6-6.1 log copies/mL) for HIV/HBV ($P = .48$).

96 The median CD4⁺T cell count was 366 cells/ μ L (range, 4-2322 cells/ μ L) for mono-infected
97 compared to 332 cells/ μ L (range, 22-1891 cells/ μ L) for HIV/HBV ($P = .64$). The median CD4⁺T
98 cell % was 19% (range, 1-68%) for mono-infected compared to 17% (range, 2-66%) for
99 HIV/HBV ($P = .29$).

100 The median ALT level was 23 IU/mL (range 2-155 IU/mL) for mono-infected compared to 26
101 IU/mL (range, 2-198 IU/mL) for HIV/HBV ($P = .15$). Seventy-eight (17.3%) children had
102 elevated ALT (>41IU/mL in JUTH) but there was no difference in the groups: This comprises of
103 63 (16.8%) of children with HIV alone and 15 (19.2%) of co-infected children ($P = .73$).

104 HBV co-infection was not associated with a reduced CD4⁺T cell count or CD4⁺T cell %, or an
105 elevated viral load or ALT (Tables 3).

106 Table 3: Hepatitis status and median (range) values of different parameters.

Characteristics	HIV alone n= 394	HIV/HBV n= 58	P value
Median (range) viral load (log copies/mL)	4.6 (3.8-6.8)	4.7 (3.6-6.1)	.48
Median (range) CD4 ⁺ T (cells/ μ L)	366 (4-2322)	332 (22-1891)	.64

Median (range) CD4 ⁺			
percent	19 (1-68)	17 (2-66)	.29
Median (range) ALT			
(IU/mL)	23 (2-155)	26 (2-198)	.15

107

108 4. DISCUSSION

109 The prevalence rate of HIV/HBV co-infection in this cohort was 12.8%. The prevalence rate is
 110 higher than the rate of 7.7% in children in Benin [5] and 5.8% in Owerri [16] in Nigeria, 1.2% in
 111 Tanzania [17], and 4.0% in Kenya. [18] However the rate is lower than HBV prevalence rate of
 112 19.6% reported by Angyo [19] in Jos in 1995 before the inclusion of HBV immunization in the
 113 national programme on immunization in 2004, the HIV status of the children were however not
 114 determined. There was no prevalence study in the general population in children in Jos since
 115 implementation of HBV immunization to compare with the present study.

116 The difference in the prevalence rate of HIV/HBV co-infection in this study and those of other
 117 studies may reflect the differences in the geographical distribution and the methodologies as
 118 well as the different sensitivities of tests employed.

119 A significant number of our patients that were co-infected with HBV were found to be
 120 adolescents between the ages of 11–15 years. A similar trend was noticed by Zhou [20] in
 121 China where children older than 11 years were significantly more infected with HBV. Toussi [21]
 122 also found that children who were HIV/HBV co-infected had a higher median age of 17 years
 123 compared to HIV mono-infected children with a median age of 11.4 years in USA. Hepatitis B
 124 vaccine was first introduced as part of the National Program on Immunization in Nigeria in 2004,
 125 and this may partly explain the reason for a higher HBV co-infection among children within 11–
 126 15 years group.

127 No significant difference was observed in the rate of co-infection with HBV between males and
128 females. This is similar to what was reported in Makurdi, Nigeria. [22]

129 We did not observe any significant difference in the median viral load, CD4⁺T cell count and
130 CD4⁺T cell % of mono and co-infected patients. This is similar with what was reported
131 elsewhere in developing countries. [22-24] Toussi [20] however reported that HIV/HBV co-
132 infected children had a lower CD4% and a higher HIV RNA levels than their mono-infected
133 counterparts in USA.

134 In this study, 17.3% of the patients had elevated ALT levels. This is comprised of 16.8% of
135 mono-infected patients and 18.3% of co-infected patients. Although HBV co-infected patients
136 had a slightly higher median ALT level compared to mono-infected patients, the differences
137 were not significant. This is similar to earlier reports in developing countries and China.
138 [20,22,24] In Tanzania [17] elevated ALT value was shown to be associated with HIV/HBV co-
139 infections in the univariate analysis but not in multivariate analysis. However, a report from USA
140 [21] showed that HBV co-infected children were more likely to have mildly elevated
141 transaminase levels (50%), compared to mono-infected group (19%).

142 The World Health Organization [25] recently recommended including tenofovir (TDF) in initial
143 ARV regimens for children ≥ 3 years with HBV co-infection as it offers the potential advantage of
144 reducing the selection of HIV resistance to lamivudine (3TC) that may compromise future
145 options for HBV treatment. Presently in Nigeria, TDF is only recommended for adolescents ≥ 12
146 years of age. [26] With the availability of TDF in the powder form, countries with high prevalence
147 rate of HIV/HBV co-infection like Nigeria should incorporate this recommendation in their
148 guideline on paediatric ART. Harmonizing treatment recommendations with adult regimens
149 could improve children's access to ART. [25] Other benefits of TDF include the ability to
150 combine it with 3TC and efavirenz (EFV) to create a potent once-daily regimen for children as it

will improve adherence [27]. In addition, the fact that HIV resistance to TDF can enhance the antiviral effect of AZT may make TDF a good choice for first-line therapy in terms of sequencing NRTIs from first- to second-line regimens [28-29].

Going forward it will be desirable to do a longitudinal study to determine the impact HBV co-infection has on HIV treatment response and hepatotoxicity to anti-retroviral drugs.

5. CONCLUSION

A high rate of HBV co-infection was observed in HIV-infected children in this study; however more severe HIV disease and increased liver enzyme were not observed. Early detection is therefore necessary in order to develop an appropriate treatment plan for children co-infected with HIV and HBV especially as they grow into adolescence.

ACKNOWLEDGEMENT

This work was funded in part by the US Department of Health and Human Services, Health Resources and Services Administration (U51HA02522) and CDC through APIN (PS 001058). The contents are solely the responsibility of the authors and do not represent the official views of the funding institutions.

REFERENCES

1. WHO Report: 1996: Fighting disease, fostering development. Geneva: World Health Organization. 1996.
2. Lee WM. Hepatitis B virus infection. *N Engl J Med*. 1997; 337: 1733-45.
3. Global HIV/AIDS Response, "Epidemic update and health sector progress towards Universal Access," UNAIDS Progress Report, 2011.

- 173 4. World Health Organization, *Introduction of Hepatitis B into Childhood Immunization*
174 *Services: Management Guidelines, Including Information for Health Workers and*
175 *Parents*, World Health Organization, Geneva, Switzerland, 2001.

- 176 5. Sadoh AE, Sadoh WE, Iduoriyekemwen N J. HIV co-infection with hepatitis B and C
177 viruses among Nigerian children in an antiretroviral treatment programme. SAJCH.
178 2011; 5(1):7-10.

- 179 6. Ogboghodo BC, Aigbirior MR, Bazuaye GN, Ebomoyi MI, Iyave VI. Human
180 immunodeficiency virus-1 co-infection in children in Benin City. African Journal of
181 Biomedical Research. 2009; 12: 1-6.

- 182 7. Telatela SP, Matee MI, Munubhi EK. Seroprevalence of hepatitis B and C viral
183 coinfections among children infected with human immunodeficiency virus attending the
184 paediatric HIV care and treatment center at Muhimbili National Hospital in Dar-es-
185 Salaam, Tanzania. BMC Public Health. 2007; 7: 338-343.

- 186 8. Rouet F, Chaix M, Inwoley A, et al. Frequent occurrence of chronic hepatitis B virus
187 infection among West African HIV type 1 infected children. Clin Infect Dis. 2008; 46: 361-
188 366.

- 189 9. Feld JJ, Ocama P, Ronald A. The liver in HIV in Africa. Antivir Ther. 2005; 10: 953-965.

- 190 10. Thio CL. Hepatitis B in the human immunodeficiency virus-infected patient:
191 epidemiology, natural history, and treatment. *Semin Liver Dis*. 2003; 23: 125-36.

- 192 11. Gilson, RJ, Hawkins, AE, Beecham, MR, Ross E, Waite J, Briggs M, McNally T, Kelly
193 GE, Tedder RS, Weller IV. Interactions between HIV and hepatitis B virus in homosexual
194 men: effects on the natural history of infection. AIDS. 1997; 11: 597-606.

12. Kellerman, SE, Hanson DL, Mcnaghten AD, Fleming PL. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. *J Infect Dis.* 2003; 188: 571-577.
13. Ladep NG, Agaba PA, Agbaji O, Muazu A, Ugoagwu P, Imade G et al. Rates and impact of hepatitis on HIV infection in a large African cohort. *World J Gastroenterol.* 2013; 19(10): 1602–1610.
14. Idoko J, Meloni S, Muazu M, Nimzing L, Badung B, Hawkins C, Sankalé JL, Ekong E, Murphy R, Kanki P, et al. Impact of hepatitis B virus infection on human immunodeficiency virus response to antiretroviral therapy in Nigeria. *Clin Infect Dis.* 2009; 49: 1268–1273.
15. Adewole OO, Anteyi E, Ajuwon Z, Wada I, Elegba F, Ahmed P. Hepatitis B and C virus co-infection in Nigerian patients with HIV infection. *J Infect Dev Ctries* 2009; 3(5):369-375.
16. Nwolisa E, Mbanefo F, Ezeogu J, Amadi P. Prevalence of hepatitis B co-infection amongst HIV-infected children attending a care and treatment centre in Owerri, South-eastern Nigeria. *Pan African Med J.* 2013; 14: 89.
17. Telatela SP, Matee MI, Munubhi EK: Seroprevalence of hepatitis B and C viral co-infections among children infected with human immunodeficiency virus attending the paediatric HIV care and treatment center at Muhimbili National Hospital in Dar-es-Salaam, Tanzania. *BMC Public Health.* 2007; 7:338.
18. R. Chakraborty, G. Rees, D. Bourboulia et al., “Viral coinfections among African children infected with human immunodeficiency virus type 1,” *Clinical Infectious Diseases.* 2003; 36: 922–924.

- 218 19. Angyo AI, Okuonghae HO, Szlachetka R, Yakubu AM. Hepatitis B surface Antigenaemia
219 in Jos. *Nig J Paed.* 1995; 22: 42-6.
- 220 20. Zhou S, Zhao Y, He Y. Hepatitis B and hepatitis C seroprevalence in children receiving
221 antiretroviral therapy for human immunodeficiency virus-1 infection in China. *Journal of*
222 *Acquired Immune Deficiency Syndromes.* 2010; 54: 191–196.
- 223 21. Toussi SS, Abadi J, Rosenberg M, Levanon D: Prevalence of Hepatitis B and C Virus
224 Infections in Children Infected with HIV. *Clin Inf Dis.* 2007; 45:795-798.
- 225 22. Rouet F, Chaix M, Inwoley A. Frequent occurrence of chronic Hepatitis B virus infection
226 among West African HIV type-1 infected children. *Clin Infect Dis.* 2008; 46:361-366.
- 227 23. Anigilaje EA, Olutola A. Prevalence and clinical and immunovirological profile of human
228 immunodeficiency virus-hepatitis B co-infection among children in an antiretroviral
229 therapy programme in Benue State, Nigeria. *ISRN Pediatrics.* 2013; 10: 81-88.
- 230 24. Sadoh AE, Sadoh WE, Iduoriyekemwen NJ. Some laboratory features of HIV infected
231 Nigerian children co-infected with hepatitis B and C. *Annales of Biomedical Sciences.*
232 2012; 11: 29-39.
- 233 25. Consolidated guideline on the use of anti-retroviral drugs for treating and preventing HIV
234 infection. Recommendations for a public health approach. Geneva, World Health
235 Organization. 2013.
- 236 26. Federal Ministry of Health: Nigeria: National Guidelines for Paediatric HIV and AIDS
237 Treatment and Care. 2010.
- 238 27. Use of tenofovir in HIV-infected children and adolescents: a public health perspective –
239 technical update on treatment optimization. Geneva, World Health Organization, 2012.

240 28. Martin A. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-
 241 lamivudine: a randomized, 96-week trial. *Clinical Infectious Diseases*. 2009; 49:1591–
 242 1601.

243 29. Fitzgerald F, Penazzato M, Gibb D. Development of antiretroviral resistance in children
 244 with HIV in low- and middle-income countries. *Journal of Infectious Diseases*. 2013; 207:
 245 S85-92.

246