

Review Article

Prevalence and Burden of Human Immunodeficiency Virus and Hepatitis B Virus Co-infection in Nigeria: A Systematic Review and Meta-Analysis

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Abstract

Background: Studies on HIV/HBV co-infection in Nigeria yielded prevalence ranging between 10% and 70%, giving the widest variation in prevalence of HIV/HBV co-infection from studies emanating from any country all over the world. However, estimation of clinical and public health impacts of HIV/HBV co-infection requires a robust and reliable epidemiological data for an appropriate estimation of the logistical, economic, and humanitarian impact of the two viruses in Nigeria.

Objective: The aim of this review was to estimate the prevalence and burden of HBV infections in HIV-infected patients in Nigeria.

Methods: Estimates were derived from a random effects meta-analysis of observational studies reporting the prevalence of HBV/HIV in Nigeria. The derived estimate for the prevalence of HBV/HIV co-infection was applied to the total HIV-infected populations in Nigeria to give an estimated burden of HBV/HIV co-infection in Nigeria.

Result: Thirty three studies with quality data from seventeen states in Nigeria, up to December 16, 2013, were included. I-squared heterogeneity was 98%. Random effect model (REM) estimate of prevalence among HIV-infected patients from the 33 studies was 15% (95% CI 13-17). The prevalence of HIV/HB co-infection among attendees of HIV clinics was 17% [95% CI 13-20], among pregnant HIV-infected patients were 10% [95% CI 6-15], 12% [95% CI 6-17] among HIV-infected children and among newly discovered HIV-infected voluntary blood donor (VBD) patients 10% [95% CI 6-15]. Meta- regression showed no significant associations between the mean age of the patients, the proportion of female patients, year of the study and prevalence of co-infection. The burden of HBV/HIV co-infection in Nigeria, based on the estimate, was 984 000 C.I. [852 800-1115 200].

Conclusion: In Nigeria, the estimated prevalence of HBV/HIV infection is 15% resulting in a substantial burden for the country.

Keywords: Prevalence; HIV; HBV; Co-infection; Nigeria

Introduction

An estimated 33.2 million people are infected with the human immunodeficiency virus (HIV) worldwide [1]. It was estimated that more than 60% of the infected population are in sub-Saharan Africa [2]. In Nigeria, HIV prevalence among the general population is 4.1% with about 3.1 million people living with HIV and about 300,000 new infections occurring annually [3].

Similarly, infection with hepatitis B virus (HBV) is a serious public health problem in the country [4,5]. Nigeria has remained a hyperendemic area of hepatitis B virus infection, with an estimated 12% of the total population being chronic carriers in spite of the availability of a safe and effective vaccine [6]. In Nigeria, universal childhood vaccination against the HBV started less than fifteen years ago and its coverage has increased over the years.

HIV/HBV co-infection is a growing concern because apart from increasing the toxicity to antiretroviral medications, [7] coinfected patients have higher levels of HBV replication, lower rates of spontaneous resolution of the HBV infection, and higher risk of reactivation of previous infections, and thus, are at an increased risk of developing cirrhosis of the liver [8].

Apart from their ability to integrate within the host genome, a process which is obligatory for the life cycle of HIV but not for HBV [9], HBV and HIV have similar properties such as transmission using a reverse transcriptase enzyme in replication, tendency to develop chronic infections, and an immense capacity of mutation in their genome, causing rapid emergence of mutant strains, some of which are resistant to widely used anti-viral agents [9]. Consequently, knowledge of country-by-country prevalence of HBV/HIV co-infection may impact positively on prevention and treatment strategy of HBV /HIV co-infection in the country of interest.

The impact of co-infection is particularly important in places with widespread use of antiretroviral therapy. As the use of ART increasingly becomes prevalent in certain regions of the world with high HBV endemicity and as long term survival increases, It is likely

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that liver disorder following chronic HBV in HIV-infected population may emerge as a greater public health problem than before [10]. This potential problem was suggested in a meta-analysis that reported on 12382 patients living in Europe which found a significant 36% excess risk of all-cause mortality attributed to the effect of HBV co-infection in HIV patients (pooled effect estimate, 1.36; 95% CI, 1.12-1.64) [11]. Furthermore, establishing a reliable estimate of HIV/HBV burden will facilitate provision of ART regimens that are effective on both HIV and HBV infections such as Tenofovir and either Lamivudine or Emtricitabine ART two drug backbone.

Against this background, a number of studies that were conducted on HIV/HBV co-infection in Nigeria, using HB surface antigen as a marker, yielded prevalence ranging between 10% and 70% giving the widest variation in prevalence of HIV/HBV co-infection from studies emanating from any African country or the world at large.

A systematic review pooling studies conducted on HIV/HBV coinfection in Sub-Saharan Africa reported overall prevalence estimate of 15% [12]. However, while such sub continental values may have their advantages, the country specific prevalence rate may better inform country specific prevention and treatment policies of HIV/HBV infections.

With the use of HAART in HIV-infected individuals in Nigeria with high HBV endemicity, it is likely that liver disease from chronic hepatitis B will emerge as an even greater problem in a foreseeable future. Therefore, it is important to estimate the national HIV/HBV co-infection prevalence in Nigeria with the view to further expand and streamline antiretroviral programs, especially in view of the implications of using HAART agents that also possess anti-HBV activity.

Furthermore, estimation of clinical and public health impacts of HIV/HBV co-infection requires a robust and reliable epidemiological data for a fair estimations of the logistic, economic, and humanitarian impact of HIV/HBV co-infections in Nigeria. Accordingly, it is presumed that this review will go a long way in guiding future policies on prevention and treatment of HIV/HBV co-infection in the country.

The aim of this review was to estimate the prevalence and burden of HBV co-infections in the general and subgroup populations of HIVinfected patients in Nigeria.

Methods

Literature search

An English-language literature search was conducted on PubMed, EMBASE, ISI, African journals online (AJOL) and Endnote databases, existing systematic reviews, specialty journals, several websites and other search engines such as Google. Medical subject heading (MeSH) terms were used in the search for relevant articles before December 16, 2013 using a search criterion combination of the following key words: hepatitis B (with or without hepatitis C), HBV as defined by HBS antigen positivity, HBV-DNA, human immunodeficiency virus, HIV, AIDS and co-infection AND Nigeria. To make our searches more effective, combination of these keywords was also explored. Titles and/or abstracts of the search results were screened to determine the relevance of the studies. Full-texts of selected studies were also reviewed. (Search date 16/12/2013-28/12/2013). When required, we contacted the authors and also manually searched the reference lists of all identified publications and recent systematic reviews. Book chapters, and review articles on the subject were also consulted. Titles and abstracts identified by electronic searches were examined independently by two investigators on-screen, to select potentially relevant studies. All studies that evaluated the point prevalence of hepatitis B in HIV infected patients were considered prima facie relevant.

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The estimate derived from the prevalence of HBV/HIV co-infection was applied to the total HIV-infected populations in Nigeria to give an estimated burden of HBV/HIV co-infection in Nigeria.

Conducting and reporting of this study were in accordance with the guidelines on Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statements [13,14].

Inclusion and exclusion criteria

Studies that reported HBV prevalence data of HIV-infected patients in Nigeria, using at least HB surface antigen detection method, were selected for inclusion. Publications including fewer than 40 HIVinfected individuals or studies that did not include data on patients who were infected with both HBV and HIV were excluded. Studies in which patient selection was based on the presence of liver disease, studies from outside Nigeria and studies without original or with inadequate data were also excluded.

Data extraction

Data were extracted, ascertained and recorded in a standardized form that is used to record relevant items and entered into a database. Information recorded included information on authors, year of publication, state of Nigeria, where the study was conducted, study design, study characteristics, setting, serological test for hepatitis B, age of participants, proportion of female gender, sources of bias, quality measures, absolute numbers of HIV-infected patients, absolute numbers of HIV/ HBV- co-infected patients that were either provided or could be calculated from the available data and any relevant observations or comments. Two of the investigators independently checked the extracted data for accuracy.

Quality assessment

A 12-point scoring system was used to rate the quality of the articles retrieved. Scoring was conducted by two independent investigators using a modification of the Downs and Black checklist [15]. The score was based on 12-point questions (objective of the study clearly described, study design clearly stated, participants representative of the population from which they were recruited, participants accrued during the same time period, modest sample size, management of missing data, age, gender and other characteristics explored/reported, e.g., were confounders reported, was detection method of HBV reported, were potential biases reported, was outcome clearly described?), The assessment also included other items known to be associated with study quality [16]. The studies were classified into three levels that represented their quality. The total score was 12 with a higher score indicating better quality.

Data analysis

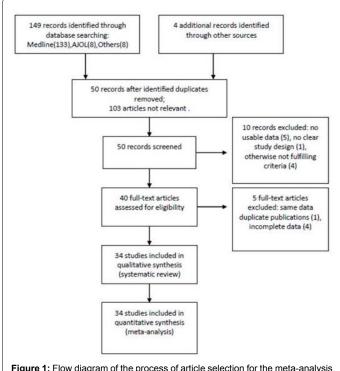
The primary outcome measure was the prevalence of hepatitis B in HIV-infected patients. The standard error of prevalence was determined by binomial probability distribution. The prevalence (P) of HBV/HIV co-infection, which was expressed in percentage with the respective 95% confidence interval (95% CI), was calculated for each study. The logP and the standard error of logP were computed for the respective studies. Meta-analyses were conducted for prevalence estimates. Given the inherent variability among observational studies,

we combined results and obtained meta-analysis estimates using a random effects model (REM) by DerSimonian and Laird for estimate summary and 95% confidence intervals (95% CIs) from included studies [12]. We evaluated statistical heterogeneity by conducting tests of between-study heterogeneity and I squared (I²) statistics with I²>50% denoting substantial heterogeneity, tau squared ('I2) and Gailbrath plot. We performed sensitivity analysis to examine the impact of specific publications on the overall prevalence. Subsequently, restricted scenario or sub-group analyses were performed on data derived from studies with similar characteristics. Publication bias and small study effect were assessed by visual inspection funnel plots and by using Begg's adjusted rank correlation tests and Egger's regression asymmetry test [17,18]. Given the inconsistency and the insensitivity of the tests [19], publication bias was considered to exist only if detected in both tests. We also performed univariate, weighted, least-squares metaregressions to identify study-level characteristics (mean or median age of participants, years of study and proportion of female participants) associated with prevalence. All analyses were carried out using Stata version 12.0 (Stata Corp., College Station, TX, USA).

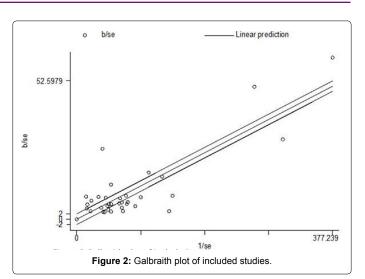
Result

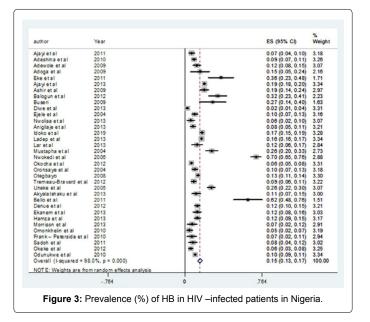
Overview of selected studies and characteristics of participants in studies

A total of 153 citations was identified on electronic search and other sources. On the basis of titles, abstracts, relevance and duplication 103 records were excluded. Thus, a total of 50 articles was screened. After a full-text review, a further 17 articles were excluded. The remaining 33 studies that satisfied the inclusion criteria and were of satisfactory quality were included in the analysis (Figure 1 and Table 1). The Characteristics of the studies and quality assessment scores are presented in Table 1. The studies were conducted in the six geopolitical



and review.





zones (17 states) of Nigeria namely southwest-7, southeast-7, southsouth-6, northwest-2, northeast-3, north central-9 (Table 1). The studies with a point prevalence of HIV/HBV co-infection in study subgroup populations that consisted of the HIV clinic (HC) attendants, children (Chi) voluntary blood donors (VBD), pregnant women (Pre) and one cohort of prison (Pri) inmates were included in the subgroup analysis (Table 1). All of the 33 studies were conducted in urban areas [20-52]. Two [25,29] of the studies were prospective, three [40,41,51] were retrospective, one [22] had retrospective and prospective arms and the remaining studies were cross sectional design. The total number of HIV-infected participants was 53899 in the 33 studies analyzed. Overall, the age of the participants ranged between 0.7 and 84 years.

Findings from the meta-analysis

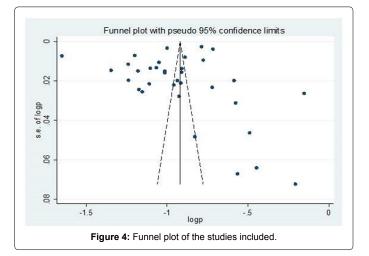
Galbraith plots (Figure 2) showed that there was between studies variation in the pooled studies. Figure 3 showed forest plots of the pooled studies and the overall prevalence. Heterogeneity chi-squared was 1610.84 (d.f.=33) p=0.000, I-squared (variation in ES attributable to heterogeneity) was 98.0% and estimate of between-study variance Tau-squared was 0.0043.

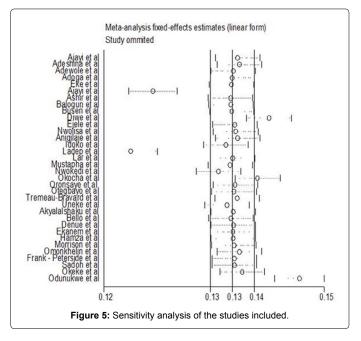
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Author	Geopolitical zone of Nigeria	State of Nigeria	Study population	Study design	Mean/ Median age	Age range	Gender (female)%	Number of HB-HIV co- infection/ Number of HIV patient	Quality Score (A=9-12) (B=5-8) (C=1-4)
Ajayiet al. [22]	SW	Ekiti	HC	С	36.2	16-79	71.1	18/273	А
Adeshina et al. [23]	SW	Оуо	Pre	С	NA	NA	100	64/721	А
Adewole et al. [24]	NC	Abuja	HC	R+P	35.1	20-49	75.0	30/260	А
Adoga et al. [25]	NC	Nasarawa	Pri	С	29.2	15-56	0.0	8/54	А
Eke et al. [26]	SE	Anambra	Pre	С	24.3	14-45	100	20/56	А
Ajayi et al. [27]	NE	Northeast	HC	Р	37.9	15-84	14.7	2044/10645	А
Ashir et al. [28]	NE	Borno	Ch	С	NA	NA	NA	54/284	С
Balogun et al. [29]	SW	Lagos	HC	С	38.0	20-79	68.6	33/102	В
Buseri [30]	SW	Oshun	Ch	С	32.6	18-64	14.9	12/44	В
Diwe et al. [31]	SE	Imo	HC	Р	38.3	NA	69.2	9/404	А
Ejele et al. [32]	SS	Rivers	НС	С	NA	NA	43.9	33/342	В
Nwolisa et al. [33]	SE	Imo	Ch	С	NA	1.5-17	56.1	8/139	В
Anigilaje et al. [34]	NC	Benue	Ch	С	7.53	0.7-15	61.3	31/3954	А
ldoko et al. [35]	NC	Plateau	нс	С	33.0	NA	63.0	262/1564	А
_adep et al. [36]	NC	Plateau	нс	С	4.4	2.6-6	56.6	3638/19408	А
Lar et al. [37]	NC	Plateau	Pre	С	NA	16-40	100	16/135	А
Mustapha et al. [38]	NE	Gombe	VBD	С	35.5	18-65	51.5	53/200	А
Nwokedi et al. [39]	NW	Kano	нс	С	NA	NA	49.3	211/300	В
Okocha et al. [40]	SE	Anambra	м	С	35.0	3-88	10.5	74/1176	В
Oronsaye et al. [41]	SS	Edo	VBD	С	NA	NA	NA	37/383	В
Otegbayo [42]	SW	Оуо	нс	R	34.6	15-70	67.0	229/1779	В
Tremeau-Bravard et al. [43]	NC	Abuja	нс	R	39.0	NA	55.1	38/443	В
Uneke et al. [44]	NC	Plateau	HC	с	28.5	20-40	22.9	127/490	А
Akyalalshaku et al. [45]	NC	Nasarawa	HC	с	NA	20-60	73.0	22/200	В
Bello et al. [46]	SE	Borno	HC	с	NA	20-50	88.9	11/45	С
Denue et al. [47]	SE	Borno	HC	С	34.2	14-81	58.5	70/569	А
Ekanem et al. [48]	SS	Uyo	НС	с	NA	1.5-65	67.4	29/239	В
Hamza et al. [49]	NW	Kano	НС	с	34.4	NA	59.6	54/440	В
Opara-Morrison et al. [50]	SW	Lagos	НС	с	NA	18-60	63.0	7/100	В
Omonkhelin et al. [51]	SS	Edo	НС	R	NA	17-70	65.0	9/200	В
Frank – Petersideet al. [52]	SS	Plateau	Pre	с	NA	NA	100	7/105	В
Sadoh et al. [53]	SS	Edo	Ch	С	6.8	0.8-17	41.3	12/135	А
Okeke et al. [54]	SE	Enugu	Pre	R	36.2	22-43	100	23/401	А
Odunukwe et al. [55]	SW	Lagos	HC	С	NA	NA	59.9	831/8309	В

SW(South West) SS(south South), SE(South East), NC(North Central) NW(North West), NE(North East), HC(HIV clinic), Ch(Children) Pre(Pregnant women), VBD(Voluntary blood donor), Pri (Prison), NA(Data not available), C(Cross sectional study), R(retrospective study).

Table 1: Characteristics of included studies on HBV/HIV coinfection in Nigeria.





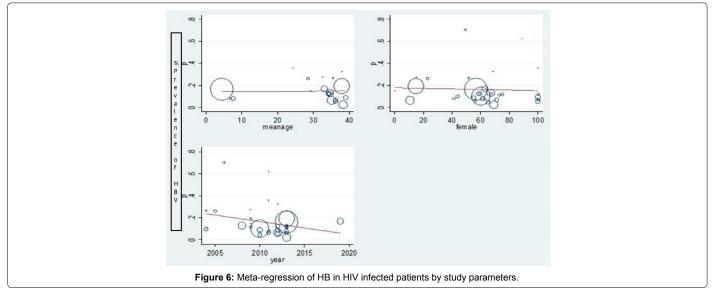
The REM estimate of prevalence among HIV-infected patients from 33 studies was 15% (95% CI 13-17%) (Figure 3). There was a publication bias in Egger's, and Begg's testing (Begg's test, p=0.003; Egger's test, p=0.000). This finding was also evident in the funnel plot shown in Figure 4. On sensitivity analysis, i.e. the weight of individual studies on the pooled summary effect showed that the prevalence estimate was dominated by Ajayi et al. [25], Ladep et al. [54] and Odunukwe [52] studies (Figure 5).

Meta-regression was conducted only on studies reporting Mean/ Median age (19 studies) and the proportion of female gender (31 studies) and year of study. In the analysis, study-specific prevalence estimates showed no significant associations with mean age of the participants and the proportion of female participants: mean/median age of patients in years ranging from 4.4 to 39.0 years had a slope coefficient of 0.00024 (95% CI-0.0037597 to 0.0042334, p=0.902) in 20 studies; proportion of female patients, ranging from 0% to 100%, had a slope coefficient of 0.00027 (95% CI -0.0024 to 0.0019, p=0.801) in 31 studies, and year of the study, ranging from 2000 to 2013 had a slope coefficient of -0.01175 (95% CI-0.02738 to 0.00389, p=0.135) in 31 studies (Figure 6).

Subgroup analysis

In view of the significant heterogeneity recorded in the overall metaanalysis which could be partly explained by different study populations in the composite studies, we performed a subgroup analysis by study population.

The subgroup analysis showed that the prevalence of HIV/HBV co-infection among attendees of HIV clinics was 17% [95% CI 13-20] with heterogeneity statistic of 1331.8 and degree of freedom (df) of 19 (P<0.0001), I² = 98.6 and T² statistic was 0.004. The prevalence of HIV/HBV co-infection among pregnant HIV-infected patients was 10% [95% CI 6-15] with heterogeneity statistic of 25.4 and df of 4 (P<0.0001), I²=84 and T² statistic was 0.002. The prevalence of HIV/HBV co-infection among HIV-infected children (Ch) was 12% [95% CI 6-17] with heterogeneity statistic of 29.5 and df of 4 (P<0.0001), I²=86 and T² statistic was 0.003. The prevalence of HIV/HBV co-infection among HIV-infected voluntary blood donor (VBD) patients was 10% [95% CI 6-15] with heterogeneity statistic of 25.4 and df of 4 (P<0.0001), I²=84 and T² statistic was 0.002 (Figure 6).



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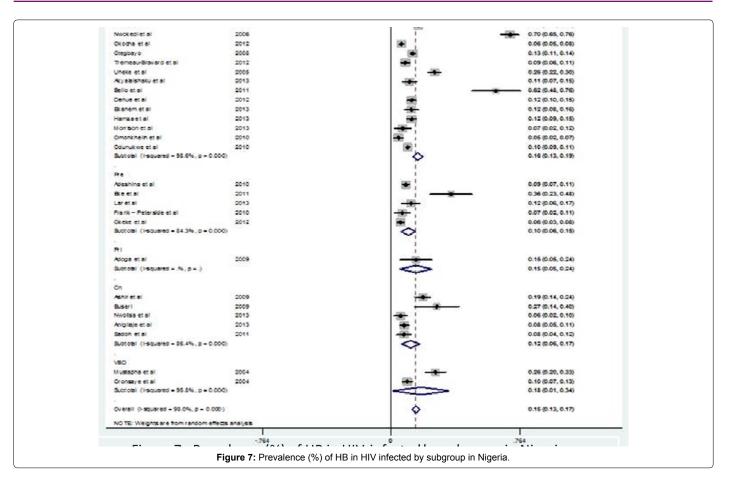


Figure 7 showed the forest plot result when the pooled studies were stratified on the basis of geopolitical region in Nigeria.

The overall pooled prevalence of HBV/HIV co-infection was 15% (95% CI 13-17%). Assuming Nigeria has an estimated population of 160, million people [20] and HIV seroprevalence rate of 4.1% [21], the overall burden based on our estimates would be 984 000 C.I. [852 800-1115 200].

Discussion

To the best of our knowledge, this is the first meta-analysis of hepatitis B HIV co-infection prevalence studies in Nigeria.

In this study, our meta-analysis examined the prevalence of coinfection with HBV/HIV-infected patients in Nigeria by analyzing 33 studies [22-54] that were widely distributed across the six geopolitical zones of the country. The overall analysis showed that a considerable number of HIV-infected patients are co-infected with hepatitis B virus. The overall prevalence of HIV/HBV co-infection was 15%. Barth et al., in a similar study using studies from Sub Saharan Africa, reported prevalence of 15% for the subcontinent [12]. Therefore, our finding further corroborated the sub-Saharan study, the similarity between the findings in the two studies could be attributed to the fact that the aggregate number of participants from studies from Nigeria constituted more than 40% of the overall population of the participants in that particular study. Separate reports from the Malawi, Cote D'Ivoire and Tanzania on hepatitis B prevalence in HIV-infected individuals ranged between 9.0-16.9% [55-57]. In view of the fact that nearly all the studies we have analyzed were cross-sectional studies, the overall estimate found is indicative of the point prevalence of HBV/ $\rm HIV$ co-infection.

In areas, such as Australia, Europe and North America, where HBV endemicity is low, HBV and HIV infection are commonly acquired in adulthood through sexual or percutaneous transmission. In such areas, the prevalence of chronic co infection is about 5-7% among HIVinfected patients [58]. Conversely, in countries with intermediate and high HBV endemicity, such as in sub-Saharan Africa, the main routes of transmission of HBV are either perinatal or in early childhood, and in these regions HBV co-infection rates are 10-20% [59-61]. This HBV/ HIV co-infection prevalence is exemplified by our finding.

Our finding is also a reflection of reports from the other, though individual, studies from different regions of Nigeria, who had observed high prevalence of HBV infection in the general population ranging between 10.3% and 15.1% [44,62].

The HIV epidemic in Nigeria is complex and its prevalence varies widely by region. In some states of the country, the epidemic is more concentrated in certain group and is driven by high-risk behaviors, while other states tend to have more generalized epidemics that are sustained primarily by multiple sexual partnerships in the general population. Since HBV and HIV have similar mode of transmission one would expect a similar trend for HBV infection. In light of this, we conducted a region based analysis of our data, the NW region of the country appeared to have the highest (41%) prevalence of HBV/HIV co-infection. This finding is, however, constrained by the fact that only two studies were conducted in the region and both of them were from the same center and on similar participants, yet yielding a wide

difference in HBV/HIV co-infection prevalence (12% [47] and 70.3% [37]). Otherwise, the other regions had prevalences close to the overall prevalence HBV/HIV co-infection we found in Nigeria.

Unlike in the east and southeast Asia, where perinatal transmission predominates, [63] in Africa most infections are believed to occur in children, with vertical transmission having a less important role [64] and most HBV infections occur in the first 5 years of life [65].

In this study, a lower prevalence of HBV/HIV co-infection was obtained among children (12%) compared to their adult counterpart (16%). In conformity with this finding, two cross-sectional surveys from Ethiopia [66] and Somalia [67] reported a lower prevalence of HBV markers in children than in adults, suggesting either an increase adult infection or a decline in childhood infections over time [68]. This finding is partly a reflection of the high endemicity of HBV in the general population which is sustained possibly by vertical transmission in Nigeria. Nonetheless, the finding of such a high prevalence of HBV/HIV co-infection of 12% in the HIV-infected child population studied partly suggest either poor adherence to vaccination schedules or relatively low vaccination coverage in the country.

Hepatitis B in HIV-infected women in pregnancy is of great concern. HBV/HIV co-infected pregnant women in resource poor setting, like Nigeria, face huge challenges of mother to child transmission. The overall prevalence obtained in our analysis, which is higher than the figures found in the USA and western Europe [69] is largely a reflection of endemicity of HBV infection in Nigeria. The high prevalence of HBV/HIV co-infection in voluntary blood donors in Nigeria further underscores the need for screening for the two viruses in every blood donor.

In the current study, meta-regression of mean age, proportion of the female gender and year of study, which was conducted to explore associations with prevalence failed to confirm significant relationships. Nevertheless, there was a non-significant decreasing trend in prevalence of HBV/HIV co-infection with increasing year of study. This finding may be partly attributed to the impact of hepatitis B immunization in Nigeria.

The figures obtained in this meta-analysis could be considered modest estimates of the various prevalences because the pooled studies did not account for cases of occult HBV infections which are described as the existence of HBV DNA without detectable HBsAg. Antibodies against hepatitis B core antigen (anti-HBc) are often the only serum markers in such patients. Thus, in cases with high risk of hepatitis B where HBsAg is negative, it is necessary to check anti-HBc level to detect HBV infection. None of the studies in this analysis conducted identification of HBV in HIV-infected individuals using this means thereby raising the possibility of underestimation of the prevalence of HBV in HIV-infected patients.

The magnitude of heterogeneity in the current study deserves further mention. There are several possible sources of variability or heterogeneity among the pooled studies including Clinical heterogeneity arising from differences in participant characteristics (e.g., sex, age, baseline disease severity, ethnicity, comorbidities) which can cause statistical heterogeneity and methodological heterogeneity which hinges on aspects of the conduct of the individual study and how they differ from each other.

This study does not, in any way, underestimates the fact that only a large representative national epidemiological study conducted at the same time can give a more reliable overall prevalence of HBV/HIV coinfection in Nigeria. However, in the absence of such a national survey, a meta-analysis of all the observational studies cutting across all the geopolitical zones of Nigeria, provides the best evidence and hence, could be of use in improving the care of HIV/AIDS and HIV/HBV co-infected patients.

Conclusion

In Nigeria, the overall prevalence of HBV/HIV infection is high (15%) resulting in a substantial burden. This finding, which is similar to what obtains in other Sub Sahara Africa countries, has a great implication for management HIV-infected and HIV/HBV co-infected patients in the country. Observation systems seem necessary to monitor infection patterns to target high prevalence regions and high risk groups. Our finding could be a veritable guide for future policies on HBV and HIV treatment and prevention strategies in Nigeria.

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