

# Prevalence of occult hepatitis B among HIV-positive individuals in Africa: A systematic review and meta-analysis

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## Abstract

The prevalence of hepatitis B virus among HIV-seropositive individuals is believed to be high, and yet the disease remains neglected in many areas of the continent. Little is known about occult hepatitis in HIV individuals. This review assessed occult hepatitis B infection and its prevalence in the different regions of the African continent. It also determines its prevalence in the HIV population which is endemic in the region. Studies were searched from the Cochrane, google scholar, PubMed/Medline, and African Journals online. Authors included cross-sectional studies, case controls, and cohorts, from 2010 to January 2021, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Participants, Interventions, Comparisons, Outcomes, and Study design frameworks to develop the search strategy. All studies had participants who were HIV-positive, covering different regions of the continent. Risk ratio was used to measure effect size, and Stata 14 software was used for analysis. Eleven studies met the eligibility criteria, with 2567 participants. Overall prevalence of occult hepatitis B was 11.2%. Regional prevalence was 26.5% for the south, 11% for the north, 9.1% for the east, and 8.5% for the western region. Approximately 10% of HIV-seropositive individuals were co-infected with occult hepatitis B virus. Regionally, the prevalence was highest in the southern region and lowest in the west. The prevalence of occult HBV infection was compared between the southern region and the other regions. It was higher in the south compared to the east (risk ratio = 0.87, 95% confidence interval (0.83–0.91)). It was also higher in the south compared to the north (risk ratio = 0.82, 95% confidence interval (0.79–0.85)), and it was also higher in the south compared to the west (risk ratio = 0.85, 95% confidence interval (0.82–0.87)). Public health measures and interventions are required to raise awareness, increase prevention, and reduce spread of the disease. More evidence-based studies need to be carried out.

## Keywords

Hepatitis B, HIV, occult hepatitis B, prevalence

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## Introduction

Viral hepatitis, ranked the seventh-leading cause of mortality in the world, is also a major cause of morbidity.<sup>1</sup> Hepatitis B virus (HBV) continues to pose a serious threat to public health as it is an endemic in different parts of the world.<sup>2</sup> HBV and HIV frequently co-exist as they share common modes of transmission.<sup>3</sup> At a global level, it is estimated that 3.6% of the world's population is infected with HBV.<sup>4</sup> In sub-Saharan Africa, an endemic area for HBV, the exposure rate is up to 90%.<sup>5</sup> A carrier of the virus is characterized by chronic hepatitis B surface antigenemia (HBsAg). This is more prevalent in developing nations, such as those in sub-Saharan Africa, Asia, and the Pacific region.<sup>6</sup>

The term “occult” hepatitis B infection (OBI) is defined by the presence of HBV DNA in plasma and/or liver tissue of subjects who lack detectable HBsAg.<sup>7</sup> Based on the

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HBV-specific antibody profiles, OBI may be categorized as seropositive OBI—hepatitis B core antibody (anti-HBc) and/or hepatitis B surface antibody (anti-HBs) positive and seronegative OBI—anti-HBc and anti-HBs negative.<sup>8</sup> Identification of anti-HBc alone can also be a predictive marker of occult HBV infection.<sup>2</sup> OBI was observed in 2% of 400 women who were HIV-seropositive and with antibodies to hepatitis B core (HBc) antigen.<sup>9</sup> Occult HBV has been identified in several cohorts of HIV-infected patients.<sup>10,11</sup> Results from the study by Núñez et al.<sup>12</sup> suggested that occult HBV infection is not a frequent phenomenon among both HIV and hepatitis C virus (HCV) co-infected individuals. In a study by de Mendoza et al.,<sup>13</sup> it was found that the prevalence of both chronic HBV (8.5%) and OBI (14%) in HIV patients in Ghana was high. A study by Mbangiwa et al.<sup>4</sup> revealed that the prevalence of chronic HBV in pregnant women was 21% and occult HBV was 6.6%. The prevalence rates in the HIV-positive and HIV-negative participants were not different. In Gabon, a study by Bivigou-Mboumba et al.<sup>5</sup> showed OBI (HBV DNA) in one patient irrespective of the HBV serological marker.

Approximately 20% of HIV-seropositive people in sub-Saharan Africa are also infected with HBV.<sup>14</sup> Both diseases are public health threats in the African continent. Clinically, the relevance of occult HBV infection in patients with HIV and/or HCV co-infection is not clear.<sup>15</sup> In this review, our aim was to understand the prevalence of OBI in Africa and also determine regional prevalences. The results from the review will show the burden of the disease in Africa allowing stakeholders to use it as a guide for making informed decisions.

## Methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used.<sup>16–18</sup> We included studies that reported OBI in HIV participants in Africa. Diagnosis of OBI was laboratory-based in all studies.

## Search methods

Electronic databases such as Cochrane, PubMed/Medline, Google Scholar, and African Journals OnLine (AJOL) were searched so as to identify relevant studies. Occult hepatitis B, hepatitis B, HIV, and Africa were the keywords used. For PubMed, Medical subject's headings (MeSH)<sup>19</sup> terms were used that were driven from our research question. Boolean operators were also used between the search terms.

## Search strategy

The MeSH terms included “HIV” [Text word] OR “AIDS” [MeSH terms] OR “immune-compromised” [MeSH] AND

“hepatitis B virus” [Text word] OR Hepatitis [MeSH] OR “Occult hepatitis B” [MeSH terms] OR “occult infection” [MeSH] AND Africa [text word] OR “Sub-Saharan Africa” AND “incidence” [Text word] OR “incidence” [MeSH] OR “epidemiology” [MeSH] OR “epidemiology” [Subheading]

## Eligibility criteria

Eligibility was formulated by PICOS (Participants, Interventions, Comparisons, Outcomes, Study design):<sup>20</sup>

- Population: HIV-positive individuals;
- Intervention: testing HBV-DNA in HIV-seropositive participants;
- Comparison: the development of OBI or not in participants;
- Outcome: positive HBV-DNA test;
- Study design: cross-sectional and cohorts from 2005 to 2021.

## Study selection

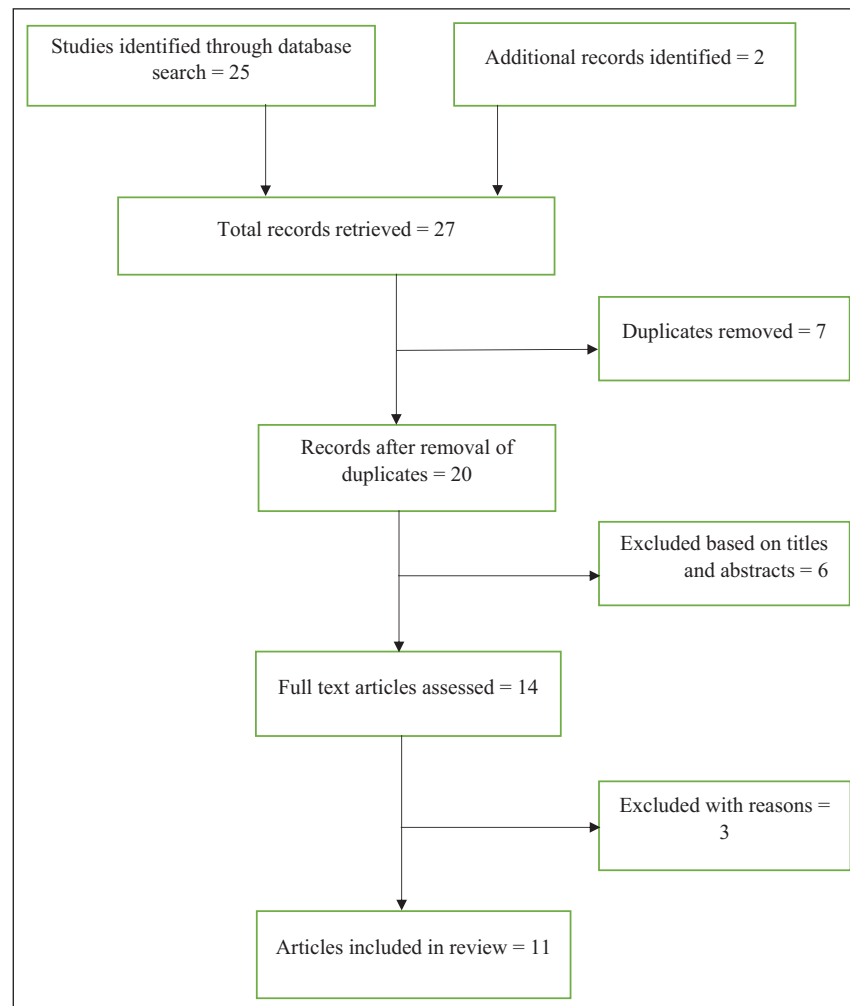
Published articles in English based on the eligibility criteria were selected. The articles were imported from electronic databases into Mendeley reference manager. Screening for titles, abstracts, and full texts was done by two authors independently. Discrepancies in the findings between the authors were resolved by discussion. Quality of studies and risk of bias assessments were done. The Mendeley reference manager was used to remove duplicate studies.

## Data extraction

Data extraction was done by all authors. Any disagreements were resolved by discussion among the authors. A form for data extraction was designed in MS Excel that was used to extract data from the studies. Data extracted included author names and the publication year of the article, country, design of the study, total number of HIV participants, and OBI and HIV co-infection.

## Quality assessment

Assessment of quality of the studies was done using the Newcastle-Ottawa scale.<sup>21</sup> The scale has the following characteristics: standardized methods of diagnosis confirmation, large enough sample size, multicenter study, appropriate statistical methods that report outcomes, accounting for confounders (demographics, socioeconomic status, previous treatment history),<sup>22</sup> and clear methodology for the selection of participants. Additional sources for retrieving outcomes and participant information, treatment duration, missing data at final analysis, and proof of ethical review of the study were also considered.<sup>22</sup>



**Figure 1.** A PRISMA flow diagram of the retrieval process for the searched studies.

### Statistical analysis

Stata version 14 was used for the meta-analysis.<sup>23</sup> Heterogeneity was calculated using chi-square and  $I^2$ , with a 95% confidence interval (CI). All of our results were binary outcomes, and the Mantel–Haenszel random-effects method was used in our analysis, with risk ratio (RR) as our effect estimate.

### Results

Figure 1 above shows the study search steps highlighting how the studies were retrieved. Total studies identified = 27, and studies included in the final review = 11. All the studies reported OBI in HIV-positive participants. There was a total of 2283 participants in all the studies. Studies were conducted across different regions in Africa. We divided the regions as follows: South (Botswana, South Africa), East (Kenya, Ethiopia), North (Egypt, Sudan), and West (Cameroon, Nigeria, Ivory Coast, Ghana) (Table 1).

Table 1 characteristically summarizes the reviewed studies. Participants aged 18 years and above were included. Overall, the prevalence of occult hepatitis B was 12.4% (319 of 2567 total participants). Regionally, the prevalence in the South was 27.7%, East 9.1%, North 11%, and West 8.5% (Figure 2).

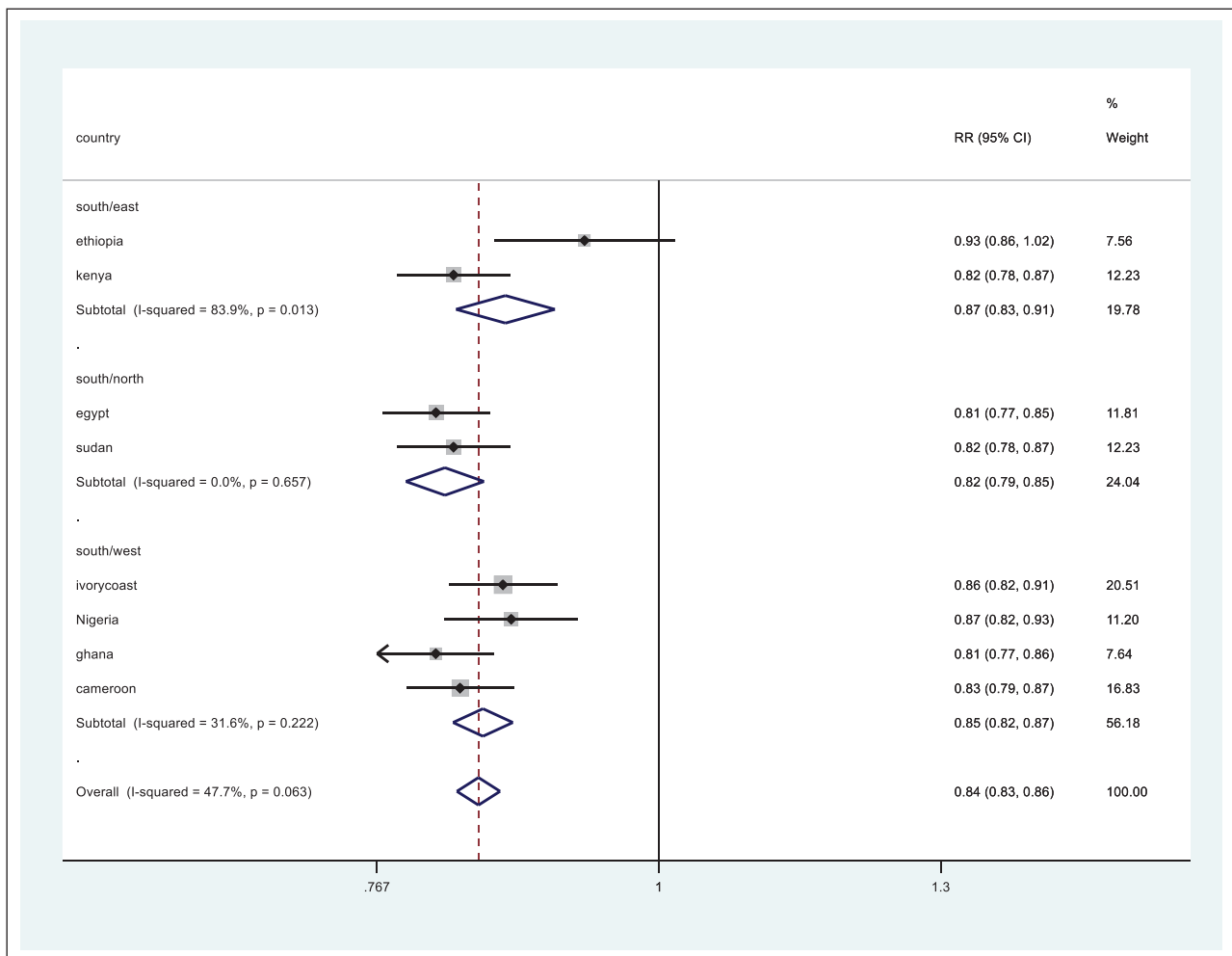
### Discussion

The main focus of this review was to determine the prevalence of OBI in HIV-positive individuals. To the awareness of the authors, this is the first meta-analysis on OBI and HIV co-infection in the African setting. There was a generally high prevalence of OBI and HIV co-infection of 12%. Notably, there was a higher prevalence in the southern region. Heterogeneity was substantial in the studies. This could be attributed to the different study settings and the anti-retroviral therapy (ART) status of the individuals. Two studies, one by Mudawi et al.<sup>24</sup> and the other by N'Dri-Yoman et al.,<sup>27</sup> had HIV-positive treatment-naïve participants.

**Table 1.** Characteristics of the studies that were included.

Study author and publication year	Study country	Study design	HIV-positive individuals in the study	OBI and HIV co-infection
Mudawi et al. (2014) <sup>24</sup>	Sudan	Cross-sectional	358	54
Abdelaziz et al. (2019) <sup>25</sup>	Egypt	Cross-sectional	197	7
Attiku et al. (2021) <sup>26</sup>	Ghana	Longitudinal purposive	113	4
N'Dri-Yoman et al. (2010) <sup>27</sup>	Ivory Coast	Cross-sectional	495	51
Opaleye et al. (2014) <sup>28</sup>	Nigeria	Retrospective analysis	188	21
Patel et al. (2020) <sup>29</sup>	Ethiopia	Cross-sectional	115	22
Salyani et al. 2021 <sup>30</sup>	Kenya	Cross-sectional	208	11
Gachara et al. (2017) <sup>31</sup>	Cameroon	Cross-sectional retrospective	337	20
Ryan et al. (2021) <sup>32</sup>	Botswana	Retrospective analysis	272	72
Ayana et al. (2020) <sup>33</sup>	Ethiopia	Cohort	117	7
Mphahlele et al. (2006) <sup>34</sup>	South Africa	Case control	167	50

OBI: occult hepatitis B infection.

**Figure 2.** Comparison of OBI in the southern and other regions (eastern, northern, and western regions).

A cohort study from Italy by Tramuto et al.<sup>7</sup> investigated how impactful occult HBV infection can be in HIV-infected individuals in Sicily and found the overall prevalence of

5.9% (95% CI: 3.8%–8.7%). Another cohort by Filippini et al.<sup>35</sup> revealed a 20% prevalence of OBI in HIV-positive and HBsAg-negative patients, who were not on antiretroviral

**Table 2.** Summary of risk of bias in each study using the Newcastle-Ottawa quality assessment scale.

	Standardized methods confirming OBI	Large enough sample size	Multicenter study	Appropriate statistical methods that report outcomes	Accounting for confounders	Clear methodology for the selection of participants	Representativeness of infected population
Mudawi et al. (2014) <sup>24</sup>	Green	Green	Red	Green	Green	Green	Green
Abdelaziz et al. (2019) <sup>25</sup>	Green	Green	Red	Green	Green	Green	Green
Attiku et al. 2021 <sup>26</sup>	Green	Green	Red	Green	Green	Green	Green
N'Dri-Yoman et al. (2010) <sup>27</sup>	Green	Green	Red	Green	Green	Green	Green
Opaleye et al. (2014) <sup>28</sup>	Green	Green	Red	Green	Green	Green	Green
Patel et al. (2020) <sup>29</sup>	Green	Green	Red	Green	Green	Green	Green
Salyani et al. 2021 <sup>30</sup>	Green	Green	Red	Green	Green	Green	Green
Gachara et al. (2017) <sup>31</sup>	Green	Green	Red	Green	Green	Green	Green
Ryan et al. (2021) <sup>32</sup>	Green	Green	Red	Green	Green	Green	Green
Ayana et al. (2020) <sup>33</sup>	Green	Green	Red	Green	Green	Green	Green
Mphahlele et al. (2006) <sup>34</sup>	Green	Green	Red	Green	Green	Green	Green

OBI: occult hepatitis B infection.

Green cells indicate low risk of bias. Red cells indicate high risk of bias. Blank cells indicate unknown risk.

therapy. Hepatic flare was more frequently seen in patients with occult HBV infection than in those without.<sup>35</sup> A retrospective analysis was performed on laboratory data in India and indicated that HIV-infected patients are at a higher risk of HBV co-infection in their set-up, as illustrated by the high prevalence of HBsAg (7.28%) in HIV-positive patients in comparison with HIV-negative patients (1.4%).<sup>3</sup> The study also showed a very high persistence of HBV genome (overall 37.5%) even in those patients who are HBsAg-negative.<sup>3</sup> In a study by Azadmanesh et al.,<sup>36</sup> the HBV-DNA was found in 13.6% of Iranian HIV-positive patients with isolated anti-HBc. There are several explanations for the persistence of HBV-DNA with the absence of HBsAg.<sup>36</sup> These reasons could be presence of HBV-DNA at a low copy number, genetic variations in the S gene and the presence of immune complexes in which HBsAg may be hidden.<sup>36</sup> A study by de Mendoza et al.<sup>13</sup> revealed a 14.2% prevalence of OBI in the general population in Ghana. Soriano et al.<sup>37</sup> found that OBI was negligible in the HIV population.

There is lack of a clear description of the clinical impact of occult HBV in HIV-seropositive patients in Africa.<sup>38</sup> There was an increase in liver complications measured by elevated liver transaminases in HIV-seropositive patients who were co-infected with occult HBV in Italy.<sup>38</sup> Another study found the cause of hepatocellular carcinoma to be linked to OBI.<sup>15</sup> Tsui et al. revealed that OBI was more likely to reduce the CD4 cell count to <200 cells/mm<sup>3</sup>, without elevated aminotransferase levels being associated with detectable HBV-DNA.<sup>9</sup> OBI has also had public health implications, especially in terms of blood donations and transfusions. A study in Spain in seronegative participants deduced that 0.003% of blood donors were found with OBI, the majority being immigrants.<sup>39</sup>

In most African settings and HIV clinics, testing for HBV or HCV is not done. It is also not part of the recommendations of most country guidelines. So, our only hope is that people are initiated on ARTs early enough, to benefit from the early antiretroviral (ARV) treatments. With these results, recommendations on screening and testing for HBV and HBV-DNA is necessary. In countries like the United States and Canada, it is part of the comprehensive care in HIV clinics to screen for OBI, and their co-infection rates are low.<sup>40</sup> Recommendations on immunization of HIV and hepatitis-negative persons, as a priority group.<sup>40</sup> Vaccination and molecular OBI diagnostics may not be feasible due to financial reasons and other logistical reasons. So, we strongly recommend screening of the HIV patients.

Some study limitations were the fact that we failed to find enough studies to represent some of the regions. The southern, eastern, and northern regions were represented by two studies. Regardless, the available studies are well sourced and discussed.

## Conclusion

Approximately 12% of HIV-seropositive patients have OBI. Screening for OBI is necessary as the review reports high rates of disease in Africa. Without screening, OBI may cause transmission of HBV as many settings test for HBsAg only. Clinical significance and implications of OBI need to be further examined, as it is a potential threat.

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### Author's contributions

V.D.K. and S.S.S. were responsible for study design. V.D.K., S.S.S., and S.G. were responsible for literature search. V.D.K. and S.G. were responsible for methodology, data analysis, and synthesis. V.D.K., S.S.S., and S.G. prepared the article.

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