

Evolutionary insights of hepatitis B virus genotypes among seropositive-drug-experienced HIV patients in Nigerian tertiary health Centre

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Abstract

Background: Co-infection with the Hepatitis B virus (HBV) in HIV-positive patients poses a considerable public health challenge in sub-Saharan Africa. The natural history, response to treatment, and development of liver disease are all significantly influenced by the distribution of HBV genotypes. On the other hand, little is known about the distribution of HBV genotypes among HIV-positive individuals in North Central Nigeria.

Aim: This study focused on identifying and characterizing the distribution of circulating HBV genotypes among HIV-positive, antiretroviral-experienced patients attending Federal Medical Centre, Keffi, Nasarawa State, providing evolutionary insights into HBV diversity in this population.

Methods: This cross-sectional study involved HIV-positive adults on antiretroviral therapy (ART) who tested positive for hepatitis B surface antigen (HBsAg). Plasma samples were subjected to HBV DNA extraction and genotype-specific PCR amplification using standard protocols. Genotype identification was based on amplification product size comparison and confirmed with genotype-specific primers and genotype frequencies were calculated. Demographic and clinical data were collected and analyzed for associations with genotype distribution.

Results: Out of the 289 HBsAg-positive HIV patients enrolled, 37 (12.8%) were successfully genotyped. Genotype E was the most prevalent with 0.91 frequency, followed by Genotype D and B with 0.83 frequency and genotype B with 0.74 frequency. No significant association was observed between genotype and gender, age group, or ART duration ($p > 0.05$).

Conclusion: In line with regional patterns, this study shows that HBV Genotype E is more common among HIV-positive people in North Central Nigeria. These results highlight the significance of using genotype screening in HBV management, especially in co-infected populations, to monitor disease progression and optimize treatment.

Keywords: Hepatitis B Virus; Genotype; HIV; Antiretroviral Therapy; Nigeria; Co-Infection

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1. Introduction

A major global public health concern is still hepatitis B virus (HBV) infection, especially in sub-Saharan Africa, where it commonly coexists with HIV. The most common cause of hepatitis worldwide are viruses (viral hepatitis) (1). Other causes include consumption of heavy alcohol, certain medication, toxins, other infections and autoimmune diseases. HBV and HIV co-infection poses a number of complicated clinical issues, such as increased liver disease progression, altered immunological responses, and difficulties managing antiretroviral therapy (ART), thereby causing severe morbidity including cirrhosis and hepatocellular carcinoma (HCC) due to intra-hepatic apoptosis and mortality particularly among HIV-infected individuals (2). Similarly, the presence of HBsAg in the blood is the specific serologic marker for HBV infection and there are several sensitive enzyme immunoassays (EIA) that have improved the detection of HBV (3). However, it was recognized that there may be individuals with acute and chronic hepatitis B infection and asymptomatic patients where HBsAg levels may be too low to detect with EIAs (4). Over time, the chronic hepatitis may progress to scarring of the liver, liver failure, or liver cancer (5). The introduction of antiretroviral therapy (ART) has significantly decreased HIV/AIDS-related morbidity and mortality, however, deaths resulting from non-AIDS-related illnesses have been on the increase (6). Thus, the global prevalence of HBV among PLHIV is 7.6 % or 2.7 million people. Respectively (7). Co-infection of HIV with viral hepatitis B occurs due to similar mode of transmission (Ferreira, 2016), posing big public health issues hence, knowledge on HBV and HCV status of PLHIV is vital for their effective management (8).

Nigeria is one of the nations where both infections are highly prevalent. HIV is surveyed and controlled through a well-coordinated support program; however, free HBV laboratory testing and treatment are not provided side-by-side HIV testing and treatment due to lack of resources, and this might have negative effect on the efficacy of the regimens used to manage them (9). With the introduction of highly active retroviral therapy (HAART), more people are living longer. However, this gain is being threatened by the emerging challenges posed by co-morbidity with other viral infections like HBV and knowing the genetic traits of circulating HBV strains is essential for developing clinical and public health interventions (10).

The evolution of HBV is driven by this high mutation rate which leads to a high degree of genetic heterogeneity with a resultant ten genotypes (A–J), that have distinct geographical distribution (11). The specific HBV genotype may provide clues regarding the possible routes of transmission in certain geographical areas, serving as an epidemiological tool for following routes of transmission and clustering of the virus (12). Genotype E is the most common in West Africa, while reports of A, B, and D have also been made (13). Variation in genotype can affect the responsiveness to antiviral treatment, the risk of chronicity, and the severity of the disease (14). Notwithstanding these consequences, there is still a dearth of molecular information on HBV genotypes in Nigerian HIV-positive populations.

This study aimed to characterize the HBV genotypes circulating among ART-experienced HIV-positive individuals at a tertiary health facility in Keffi, North Central Nigeria, providing insights that could improve co-infection management and policy development.

2. Methodology

2.1. Study Area

Keffi and the surrounding area in Nasarawa State, Nigeria, served as the study location for this investigation. Keffi is roughly 128 kilometers from Lafia, the capital of Nasarawa State, and 68 kilometers from Abuja, the Federal Capital Territory. It is 850 meters above sea level and lies between the equator's Latitude 8°05'N and Longitude 7°08' E (15). In July 2000, Federal Medical Centre Keffi (formerly known as General Hospital, Keffi) was founded. Among other things, they provide laboratory services, public health initiatives, administrative services, social and welfare services, and medical consulting in many discipline (16).

2.2. Study Design and Population

This cross-sectional study was conducted at the Federal Medical Centre (FMC) Keffi, Nasarawa State, from. Seropositive drug experienced HIV patients attending Federal Medical Centre Keffi, Nasarawa State, Nigeria who agreed to participate in the study. The participants were persons of both sexes and between the ages of 18-65 years.

2.3. Sample Size

Leslie kish formula was used to calculate the sample size. 289 participants were sampled for the study

2.4. Inclusion Criteria

Seropositive drug experienced HIV patients between the ages of 18-65 attending clinic at Federal Medical Centre, Keffi, Nasarawa State.

2.5. Exclusion Criteria

Seropositive drug naïve HIV patients who decline consent and those who don't attend clinic at Federal Medical Centre, Keffi, Nasarawa State.

2.6. Ethical Approval

The Ethical Review Board of the Federal Medical Centre Keffi, Nasarawa State, Nigeria, gave its approval to this study (Ref No: FMC/KF/HREC/372/19). For every participant, written informed consent was obtained.

2.7. Data Collection Tools

Structured Questionnaire was used as the quantitative data collection tool for this study to get sociodemographic information for each participant. The questionnaire was adopted and carefully designed to align with the study's objectives, covering key areas.

2.8. Sample Collection

Blood samples were collected from consenting study participants accessing healthcare at the ART clinic of Federal Medical Center, Keffi. The venipuncture method of Julius and Schiff (2007) was employed to aseptically collect blood samples from each of the 289 participants. Using a new and sterile vacutainer needle for each patient, five ml (5ml) of blood sample was collected into a properly labeled plain/EDTA plastic pressure or vacutainer bottle and centrifuged at 3000rpm for 15 minutes to obtain the serum respectively. The resultant sera were harvested into labelled cryovials and stored at -200C, ready for use.

2.9. Sample Processing and Storage

Samples collected were stored at -20°C in an icebox and transported immediately from the heart-to-heart center of FMC keffi to the immunology laboratory of Federal Medical Centre Keffi, Nasarawa State, Nigeria.

2.10. Method of Screening for HBsAg (HBV Serologic Markers)

All the blood samples collected were screened for HBV using the HBsAg rapid test kit (ACON, USA) following the manufacturer's instructions. It is a kit for rapid immunochromatographic assay for the qualitative detection of HBV infection markers such as HBsAg, HBsAb, HBeAg, HBeAb and HBcAb in serum

2.11. Genotype Based Techniques

Molecular techniques have become an efficient tool for Hepatitis and HIV detection. HBsAg-positive serum samples from seropositive HIV patients attending clinic in Federal Medical Centre were used. All serum samples were stored at -20 °C until use. HBV DNA was extracted from serum using QIAamp DNA Mini kit (Qiagen, Valencia, CA) and QIAamp MinElute Virus Spin Kit (Qiagen), according to the manufacturer's instruction. Briefly, 200 µl of serum was used for DNA extraction and 50 µl of elution buffer was used for elution while strictly adhering to standard laboratory practices.

2.12. Polymerase Chain Reaction

Two-round PCR was performed to amplify S region of HBV DNA (17). The sequences of the primers used in this study are shown in Table I. Under identical circumstances and primer concentrations, 50 µl of reaction mix was utilized in the first round, and 5 µl of the first-round product was used in the second. In order to do phylogenetic study of HBV (18), the PCR products was purified, and sequenced using cycle sequencing, and the results examined. For the PCR, HBV DNA was isolated and ready. The 50µl reaction mix used for the first round of PCR contained primers, Taq polymerase, MgCl₂, KCl, 2-mercaptoethanol, extracted DNA, Tris-HCl buffer, dNTPs, and primers. The PCR thermocycler was set up to denature at 94°C for the first time, then denature at 94°C for 45 cycles, anneal at 60°C, and extend at 72°C. At 72°C, the last extension step was carried out. Examined. After the nested PCR, the PCR products were purified using a QIA quick PCR Purification kit. The purified products were then sequenced using the BigDye Terminator Cycle Sequencing kit and an ABI 310 Genetic Analyzer. The resulting nucleotide sequences were aligned using the CLUSTAL W program and then analyzed phylogenetically using the MEGA program. The analysis included a 404 bp fragment of the HBV S gene

analyzed using Kimura's 2-parameter algorithm and the neighbor-joining method. 1000 bootstrap replicates were performed to assess the reliability (19).

Table 1 Primers Used for PCR and Sequencing of HBV DNA

| Virus | Region | Name | Round | Sequence (5–3) | Position | size bp |
|-------|--------|-------------|-------|----------------------------|----------|---------|
| HBV | s | S_out_upper | I | CAGAGTCTAGACTCGTGGTGGACTT | 242–266 | 467 |
| | | S_out_lower | | CCTACGAACCACTGAACAAATGGCAC | 708–683 | |
| | | S_in_upper | II | TCTAGACTCGTGGTGGACTTCTCTCA | 247–272 | 454 |
| | | S_in_lower | | CCACTGAACAAATGGCACTAGTAA | 700–677 | |

2.13. Molecular Characterization of HBV

A genotyping system based on polymerase chain reaction (PCR) using type-specific primers was used for the determination of genotype A through J of hepatitis B virus (20).

2.14. Hepatitis B Virus DNA Extraction

The AccuPrep genomic DNA extraction kit (Bioneer Corporation, Daejeon, South Korea) was used for DNA extraction from serum according to the manufacturer's instructions. Proteinase K was prepared by dissolving 25mg of the proteinase K in 1.25ml of nuclease free water and mixed thoroughly. For the lysis buffer, 25mg of the buffer was dissolved in 25ml of distilled water and mixed properly. Washing buffers 1 (W1) and 2 (W2) were prepared by adding 30ml and 80ml absolute ethanol to the concentrated form of W1 and W2 provided respectively. The elution buffer (EL) was prepared by dissolving 10mg of Tris-chloride (pH 8.5) in 30ml distilled water.

2.15. DNA Extraction Procedure

For each sample, using an Eppendorf micropipette, 200µl of serum was transferred into a labelled 1.5ml centrifuge tube. Then 20µl and 200µl of already prepared proteinase K and binding buffer were added and mixed immediately with a Vortex mixer. The tubes were incubated for 10 minutes at 60°C (to activate the enzyme) (21). One hundred µl of isopropanol (C 3H 7OH) was added and mixed again with a Vortex mixer. The formed lysate was transferred into the upper reservoir of the binding column (fit in a 2ml tube) and centrifuged at 8,000rpm for 60seconds. The liquid under the tube was discarded and 500µl of washing buffer 2 was added. The content of the tube was centrifuged for 60 seconds at 8,000rpm to completely remove ethanol.

The binding column tube was transferred into a new 1.5ml centrifuge tube and 200 µl of elution buffer was added. The tube was kept at room temperature for 1 minute (until the elution buffer was completely absorbed into the glass fibre of the binding column tube) and the content was centrifuged at 8,000rpm for 1minutes to finally elute the DNA which settled at the bottom of the tube.

2.16. PCR Products Purification

The PCR products of HBV S region was purified using QIA quick PCR Purification kit (Qiagen), sequenced with corresponding primers using BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems) and ABI 310 Genetic Analyzer (Applied Biosystems) (22).

2.17. Data Analysis

The information obtained from the questionnaire and the laboratory tests were analysed using statistical package for social sciences (SPSS) version 21.0. statistical software (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were presented in tables, figures, graphs and charts.

Pearson Chi-square test was used to establish association between prevalence and different risk factors considered in the study. A P- value of < 0.05 was accepted as significant.

3. Result

3.1. Data Presentation

Sociodemographic Characteristics among 289 Seropositive HIV Patient accessing care at Federal Medical Centre, Keffi, Nigeria, that were screened for HBV is shown in Table 4.1.

3.2. Data Analysis

A total of 289 seropositive HIV positive drug experienced adults were successfully enrolled into the study after a well written informed consent was obtained (figure 1), comprising of 109(37.9%) male and 180(62.3%) females. The overall mean age of each gender was 32.9 years (18-50years). Majority are urban dwellers 189(65.4%), single 100(34.9%) and employed 192(66.4%) as seen in table 2. The overall prevalence of HIV-HBV was 12.8 (37/289). In table 3, the baseline characteristics among the 289 cohort was outlined and stratify by gender of the 22 confirmed female with mean age 20 vs 35, $p=0.002$. of the 37 confirmed HBsAg, 22 (12.2%) were females while 15(13.8) were male. Also, test for HBeAg positive was carried out as an indication for viral active replication. Out of the 37 HBsAg seropositivity, 25 (13.9%) were positive for HBeAg-female while 10(9.0%) of male were positive for HBeAg.

3.3. Genotyping

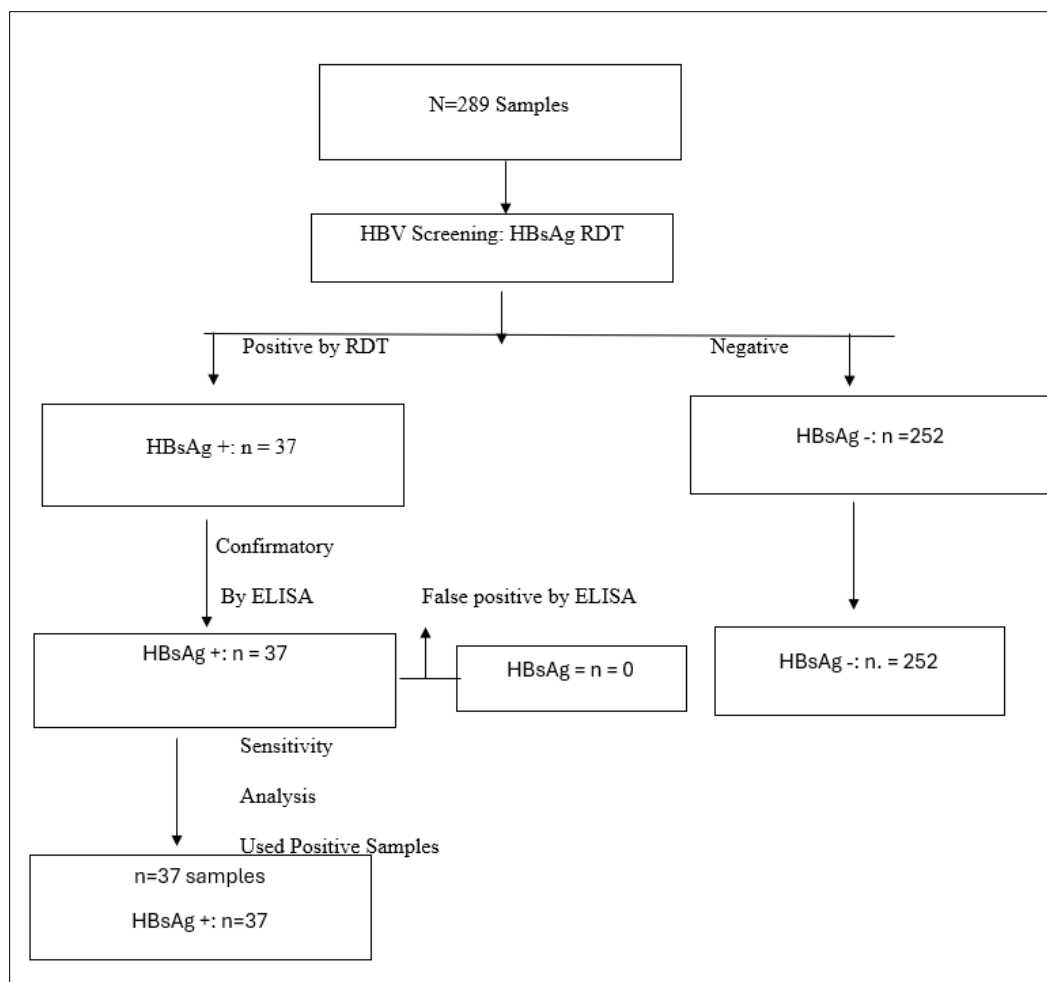


Figure 1 Viral algorithm for Hepatitis B Surface antigen (HBsAg) from Seropositive HIV infected Samples n=289

Of the 289 HBsAg-positive patients, HBV DNA was detected and genotyped in 37 individuals, yielding a genotyping success rate of 12.8%. Genotype E was the most prevalent, identified in 91% (frequency = 0.91) of cases. Genotype D and B was detected in 83% (frequency = 0.83) and Genotype A in 74% (frequency = 0.74), with several samples showing possible mixed genotypes or overlapping amplification as seen in Figure 2. Analysis of demographic variables revealed no significant association between HBV genotype and gender, age group, or ART duration ($p > 0.05$).

Table 2 Sociodemographic Characteristics of 289 Seropositive HIV Patient accessing care at Federal Medical Center, Keffi. North Central Nigeria

| Characteristics | Total number examined (n =289) | HBV-HIV Seropositivity n=37 |
|---------------------------|-----------------------------------|--------------------------------|
| | | Positive n (%) |
| Age (years) | | |
| 18 – 30 | 140 | 20 (14.3) |
| 31 – 40 | 60 | 10 (16.7) |
| 40 – 50 | 46 | 5 (10.9) |
| >50 | 43 | 2 (4.6) |
| Gender | | |
| Male | 109 | 15 (13.8) |
| Female | 180 | 22 (12.2) |
| Marital Status | | |
| Married | 90 | 10 (11.1) |
| Single | 100 | 15 (15) |
| Widow/Divorced | 99 | 12 (12.1) |
| Residency | | |
| Urban | 189 | 30 (15.9) |
| Rural | 100 | 7 |
| Employability | | |
| Employed | 192 | 12 (6.25) |
| Unemployed | 87 | 25 (25.7) |
| Level of Education | | |
| Primary | 60 | 12 (20) |
| Secondary | 90 | 5 (5.6) |
| Tertiary | 49 | 10 (20.4) |
| No formal Education | 90 | 10 (11.1) |

Table 3 Baseline Characteristics of HBV marker in relation to gender among Sero-positive 289 HIV infected adult accessing care at Federal Medical Center, Keffi. North Central Nigeria

| Viral Infection type | Baseline characteristic | | P-value |
|----------------------|-------------------------|------------|---------|
| | Female n=180 | Male n=109 | |
| HBsAg | | | |
| Positive | 22(12.2) | 15(13.8) | 0.002 |
| Negative | 158(87.7) | 94(86.2) | |
| HBeAg | | | |
| Positive | 22(12.2) | 10(9.17) | 0.456 |
| Negative | 158(87.7) | 94(86.2) | |

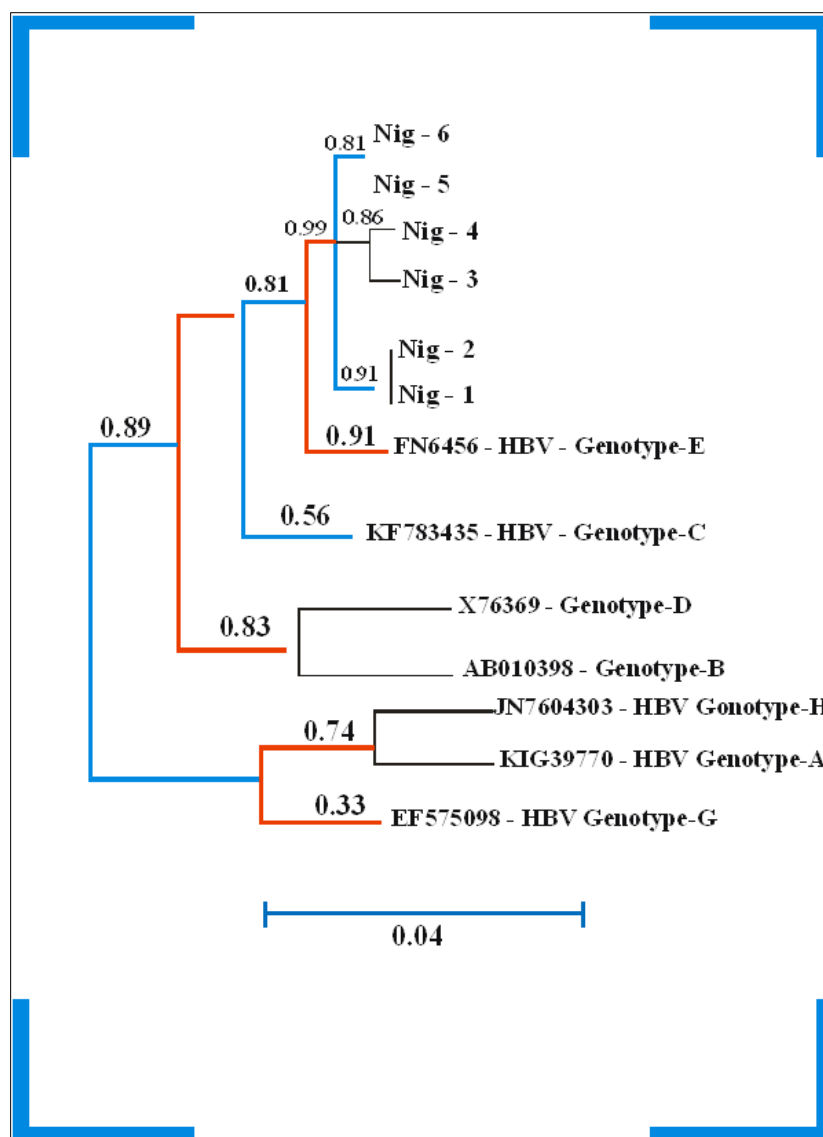


Figure 2 Genotypic Characteristics of Hepatitis B Virus Isolates Among Seropositive-Drug-Experienced HIV Patients at the Federal Medical Centre, Keffi, Nasarawa State, Nigeria

4. Discussion

In Sub-Saharan Africa, HBV co-infection with HIV is a major global health burden, with two third of the population being infected. Chronic cases of Hepatitis B have been observed in HIV patients with severe immune suppression and persistent HBV (Surface antigen) > 6 months in HIV patients is higher. Several serological patterns of HBV emerged in HIV patients because of increased risk of exposure and immunosuppression (23). During ART regimen uptake in HIV patient, several clinical manifestations have been observed in individual co-infected with HBV. Leading to increase to liver toxicity related to ART (24). This interplay has upheld the significance of timely screening of one virus on the presence of the other (25). Significantly, HBV infection have been linked to wide range of clinical manifestation in HIV infected individual who are drug experienced with increase impaired immune response and ART related liver toxicity. Therefore, it determined the prevalence and impact of HBV coinfection on drug experienced HIV infected adults in North central Nigeria immunological and virological outcomes (26).

With the introduction of ART program in the management of HIV infection, morbidity and mortality rate has declined, but that could be complicated because of other opportunistic infections co-infection with viral Hepatitis B in Sub-Saharan Africa where resources are constraint and access to viral load estimation is difficult. This viral co-infection in HIV infected individuals has been associated with increased immune suppression and increase elevated liver enzymes and ART related liver toxicity (27).

Of the 289 seropositive HIV positive drugs experienced adults who enrolled into this study, Majority of the respondents were young people within the age group of 18-30 years, urban dwellers and predominantly singles, as shown in Table 2. This result is similar to the study conducted in Lagos (28) but in contrast with a previous study in Nasarawa State (29) which recorded highest prevalence among patients aged >40 years, rural dwellers and among the married but however shows some similarities in terms of gender and levels of education. The reason for the variation may be attributed to increased risky sexual behaviour and intravenous drug users among that age group (30). More Infections among urban dwellers could be due to increased rural-urban migration of people, while gender differences could be due to the anatomy and physiology of female reproductive organs which expose them to acquire these hepatitis viruses more easily (31). It also reveals overall prevalence rate of HIV-HBV infection at, 12.8%. A similar study carried out in Nigeria reveals the Seroprevalence of Hepatitis B Viruses among 200 Human Immunodeficiency Virus Infected Patients Accessing Healthcare in Federal Medical Centre, Keffi, Nigeria as: HBV infection 12.5% (32).

Results from this study is in agreement with a systematic review and meta-analysis study on viral hepatitis B infection in HIV patients, with higher prevalence rate reported in West-African countries (7). This study in Table 3, which is consistent with a study in Ghana that showed a higher HBsAg of 12 (6.7%) (33). A study in South Africa showed HBeAg prevalence among HBsAg positive women was 9.48%, with higher rates among HIV infected women (11.29%) compared to HIV-uninfected women (7.34%, $p = 0.7931$) (34), HBeAg status across both developed and developing countries.

This study supports the previous data on genotype distribution throughout West Africa (35) by confirming that HBV Genotype E is more common among HIV-positive people in North Central Nigeria as seen in figure 2. Although less common, the existence of genotypes D and B raises the possibility of either genetic variety or circulation patterns impacted by migration in the studied area.

The lack of significant association between genotype and patient characteristics may reflect the homogeneity of the study population or the limited sample size. However, the findings underscore the importance of including HBV genotyping in the clinical management of co-infected patients to better anticipate disease progression and treatment responses.

Limitations of this study include the relatively small number of genotyped samples. Nevertheless, the results provide valuable baseline data for further investigation.

5. Conclusion

HBV Genotype E is the most common among HIV-positive, ART-experienced patients at FMC Keffi. These findings support regional surveillance trends and highlight the need for broader molecular studies and the integration of genotype screening into HBV management protocols in Nigeria.

Recommendations

Routine HBV genotyping should be integrated into HIV care programs in Nigeria to guide treatment and monitor disease progression. Further multi-centre, longitudinal studies are recommended to elucidate genotype-related clinical outcomes and viral evolution.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declared that there is no conflict of interest

Statement of ethical approval

This study received ethical approval from the Federal Medical Centre, Keffi's Health Research Ethics Committee in accordance with national and international guidelines governing biomedical research involving human subjects (Reference No: FMC/KF/HREC/372/19). All participants gave written informed consent before enrollment, after being

fully informed about the study's purpose, procedures, risks, and benefits; all personal and clinical data were kept confidential; all study procedures were carried out in accordance with the Declaration of Helsinki's ethical principles and adhered to the standards set by the institutional and national research ethics regulations.

Statement of informed consent

Every participant received complete information about the study's goals, methods, possible dangers, and advantages. Prior to enrolment, each participant provided written informed consent in compliance with ethical standards for research involving human subjects.

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Authors contributions

- Awayimbo Ruth Jaggu * (First and Corresponding Author): Conceptualization, Methodology, Formal Analysis, Data Curation, Writing – Original Draft, Supervision, Project Administration. Ruth led the design of the study, managed the research process, performed data analysis, and drafted the original manuscript.
- Adamu Ishaku Akyala: Writing, reviewing, editing, and supervision. Akyala contributed to the manuscript's intellectual content revision, evaluated the methodology and findings, exercised critical oversight and ensuring adherence to standard protocols.
- Akolo Yohanna Jaggu: Resources, Data Curation, and Investigation. Jaggu contributed in writing, organizing the study materials, supported field research, and ensuring proper collection/handling of data.
- Samuel Chukwuemeka Obasi: Data analysis, software, and visualization. Abdullahi was in charge of data analysis software and the creation of figures, tables as well as drawing the recommendation.
- Victor Aboh took part in ensuring proper sample processing, writing and improving the paper in addition to contributing to the literature review.
- Islamiyyat Olatinwo: Managing Projects, Ethics and Compliance. Throughout the research process, Olatinwo assisted in organizing administrative logistics, and making sure ethical standards were fulfilled.

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