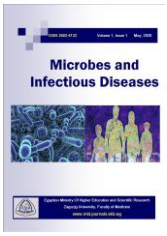
Microbes and Infectious Diseases 2024; 5(2): 479-488



Microbes and Infectious Diseases

Journal homepage: https://mid.journals.ekb.eg/

Original article

# Drug resistance in HIV's interaction with reverse transcriptase and integrase strand transfer inhibitors among Nigerians attending a military hospital

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**ARTICLE INFO**

*Article history:*
Received 27 January 2024
Received in revised form 25 February 2024
Accepted 8 March 2024

**Keywords:**
Drug resistance
HIV
Antiretroviral therapy
Unsuppression

**ABSTRACT**

**Background:** Human Immunodeficiency Virus (HIV) is a complex and dynamic virus that interacts with various cellular components and pathways, leading to the development of antiretroviral therapy (ART) resistance. One of the key factors contributing to ART resistance is the toxicity and inflammatory response associated with the virus's interaction with reverse transcriptase and integrase strand transfer inhibitors. The study aimed to assess circulating strains of HIV in relation to drug resistance among clients on tenofovir lamivudine dolutegravir (TLD) attending Nigerian Navy Hospital (NNH) Warri. **Methods**: This was a cross-sectional study in which 120 HIV seropositive subjects, aged 18-65 were recruited through simple random sampling, and data was collected via semi-structured interviews. Five milliliters of venous blood were collected from each participant and plasma separation was done by centrifugation. Immuno-chromatographic Lateral Flow Assay and real-time PCR assay were employed for HIV strain typing and viral load estimation, respectively. Statistical analysis was conducted using Epi-info Statistical Software version 7.2, with significance set at $p < 0.05$. **Results**: The mean age of participants was 38.4±11.1 years and 68(56.7%) were females. Majority of the participants 41(34.2%) belonged to age group 41-50 years and 57(47.5%) were married. Most of the participants 107 (89.1%) had HIV-1 and 11(9.2%) had HIV-2 while only 2(1.7%) were having co-infection with HIV 1 and 2. Viral load was undetected in 48(40%) of the subjects and 64(53.3%) had suppressed viral load (≤1000 copies/ml) while 8(6.7%) had unsuppressed viral load (>1000 copies/ml). All subjects with unsuppressed viral load had HIV-1 with a mean age of 39.6±13.1 years and 4(50%) were male. **Conclusion**: Our study highlights the prevalence of unsuppressed viral load in HIV-1-infected individuals on TLD at NNH Warri. Addressing drug resistance concerns remains crucial for effective antiretroviral therapy management. Clients with unsuppression were recommended for enhanced adherence counseling to diagnose treatment failure.

DOI: 10.21608/MID.2024.265823.1775

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## Introduction

The relentless battle against Human Immunodeficiency Virus (HIV) remains a global health priority, characterized by ongoing research endeavors to enhance the efficacy of antiretroviral therapy (ART) [1]. As HIV continuously evolves, understanding the dynamics of drug resistance becomes pivotal in the quest for sustainable treatment outcomes [2]. The emergence of drug resistance in the context of HIV treatment presents a significant challenge in the management of the infection, particularly in the Nigerian population attending a military hospital. The use of reverse transcriptase inhibitors (RTIs) and integrase strand transfer inhibitors (INSTIs) has been a cornerstone of antiretroviral therapy (ART) for HIV seropositive clients. However, the development of resistance to these drugs has raised concerns about their long-term efficacy and the need for alternative treatment strategies [3].

In sub-Saharan Africa, including Nigeria, the burden of non-nucleoside reverse transcriptase inhibitor (NNRTI) HIV drug resistance has been high, particularly among individuals receiving ART [4]. Additionally, limited emergence of resistance to INSTIs has been reported in ART-experienced individuals in Northeast Nigeria, highlighting the evolving landscape of drug resistance in this population [5]. These findings underscore the importance of understanding the specific resistance patterns and their implications for the management of HIV in the Nigerian context. Nigeria, like many other countries, faces the dual challenge of combating the HIV epidemic and managing the complexities associated with antiretroviral treatment [6].

Furthermore, the genetic diversity of HIV-1 in Nigeria has been shown to impact the emergence of drug-resistant variants, potentially influencing treatment outcomes and the effectiveness of different drug classes, including RTIs and INSTIs [7]. This genetic diversity, coupled with the prevalence of specific resistance mutations, necessitates a comprehensive assessment of the resistance patterns and their clinical implications for individuals receiving HIV treatment in this setting. In response to the threat of drug resistance, many low- and middle-income countries, including Nigeria, are transitioning away from NNRTIs and implementing policies to address the emergence of resistance mutations. Thus, highlighting the urgent need for tailored approaches to HIV treatment and the importance of ongoing surveillance of resistance patterns [3].

This study seeks to provide a comprehensive analysis of the resistance pattern associated with RTIs and INSTIs among Nigerians attending a military hospital. By synthesizing the latest research findings and clinical data, this analysis seeks to inform evidence-based strategies for optimizing HIV treatment and mitigating the impact of drug resistance in this specific patient population. Our study delves into the intricate interplay between HIV and antiretroviral agents, with a specific focus on the role of RT and INSTIs, among a cohort of Nigerians receiving care at a military hospital. Military hospitals, as key healthcare institutions, play a crucial role in providing care to a diverse population, including military/paramilitary personnel and their families as well as civilians in host communities. Investigating drug resistance patterns among Nigerians attending a military hospital provides valuable insights into the specific dynamics within the locality. The study aimed to assess circulating strains of HIV in relation to drug resistance among clients on Tenofovir Lamivudine Dolutegravir (TLD) attending Nigerian Navy Hospital (NNH) Warri.

## Methods

The study was a cross-sectional study and a meticulously chosen cohort of 120 participants, comprising HIV seropositive individuals under care at the NNH Warri. The NNH Warri is a military healthcare facility in Uvwie Local Government Area of Delta State. It provides healthcare for military (Nigerian Navy, Nigerian Army, and Nigerian Airforce) and paramilitary personnel, their families, as well as the civilian populace as part of its corporate social responsibility. The NNH Warri is also a Ministry of Defence Health Implementation Program (MODHIP) site for the United States Department of Defence program on HIV/AIDS in Delta State, Nigeria.

Inclusion criteria encompassed consenting adult male and female Nigerians aged between 18 and 65 years. Patients with other major chronic co-morbidities such as diabetes mellitus, chronic obstruction pulmonary disease, and cancer were excluded from the study. Employing a stringent selection process, simple random sampling ensured the representation of diverse demographic elements within the study. Ethical approval for this study was

obtained from the Ministry of Defence Research and Ethics Review Committee (NHREC/MOD-HREC/15/02/23C). Administrative approval was also obtained from the management of NNH Warri before the study commenced. Data collection involved the use of a semi-structured interviewer-administered questionnaire, allowing for a nuanced exploration of the participants' clinical, demographic, and behavioral attributes.

Five milliliters (5ml) of whole blood samples were aseptically collected by venipuncture and dispensed into a sodium ethylene di-amine tetra acetic acid specimen bottle. Blood sample collection was done by Medical Laboratory Scientists and Medical Laboratory Technicians using sterile disposable vaccutainer needles from subjects recruited. Blood samples were centrifuged in a bench centrifuge at 4,000 revolutions per minute for 3-5 minutes to obtain plasma. Separated plasma samples were stored at $-20^0$C pending laboratory analysis.

HIV strain typing was done by qualitative immuno-chromatographic Lateral flow assay while viral load estimation was performed through real-time PCR assays by Cobas 8800 analyzer at the Defence Reference Laboratory in Abuja. Samples for viral load estimation were aseptically shipped to the testing laboratory. The immuno-chromatographic lateral flow assay kit used for strain typing has a coloured control band in the control region which appears at the end of test procedure regardless of test result. The control band indicates that the colloidal gold conjugate is functional. The PCR assay on the other hand includes HIV-1/HIV-2 control kits. Nucleic Acid from patient samples were added to armored RNA internal control molecules (which served as the sample preparation and amplification/detection process control). In addition, the test utilizes three external controls: two positive controls and a negative control which are incorporated in the assay procedure for each run. For each batch of assay, one normal plasma negative control and two positive controls were processed alongside.

Data analysis was done using Epi-info Statistical Software version 7.2. This underscored the study's credibility, with results deemed significant at a p-value below 0.05. This meticulous approach, from subject selection to data analysis, enhances the reliability and relevance of the study's outcomes, providing valuable insights into the HIV dynamics within the specific demographic under investigation.

**Results**

The mean age of participants was 38.4 ± 11.1 years and 68 (56.7%) were females. Majority of the participants 41(34.2%) belonged to age group 41-50 years and 57(47.5%) were married. Seventy-nine (65.8%) were from monogamous families, 67 (55.8%) had secondary education and the majority of them were traders as shown in **table (1).**

Results of HIV strain typing show that most of the participants 107 (89.1%) had HIV-1 and 11(9.2%) had HIV-2 while only 2(1.7%) had co-infection with HIV 1 and 2 as shown in **figure (1).** This distribution provides a baseline understanding of the prevalence of different HIV Serotypes among the study population.

**Figure 2** shows viral load was undetected in 48(40%) of the subjects and 64(53.3%) had suppressed viral load (≤1000 copies/ml) while 8(6.7%) had unsuppressed viral load (>1000 copies/ml). All subjects with unsuppressed viral load had HIV-1 strain and their mean age was 39.6 ± 13.1 years while 4(50%) were male. Four (50%) of them were married in monogamous family settings and 5(62.5%) of them were traders as shown in **table (2).**

**Table 1.** Demographic characteristics of HIV seropositive subjects for HIV serotyping at Nigerian Navy Hospital Warri.

| Variables | Frequency (n = 120) | Percentage (%) | HIV serotype | | |
|---|---|---|---|---|---|
| | | | 1 | 2 | 1 & 2 |
| **Age Group (years)** | | | | | |
| ≤20 | 8 | 6.7 | 5 | 3 | - |
| 21-30 | 22 | 18.3 | 21 | 1 | - |
| 31-40 | 38 | 31.6 | 35 | 2 | 1 |
| 41-50 | 41 | 34.2 | 36 | 4 | 1 |
| 51-60 | 6 | 5.0 | 5 | 1 | - |
| >60 | 5 | 4.2 | 5 | - | - |
| Mean ± SD | 38.4 ± 11.1 | | | | |
| **Gender** | | | | | |
| Male | 52 | 43.3 | 45 | 7 | - |
| Female | 68 | 56.7 | 62 | 4 | 2 |
| **Marital Status** | | | | | |
| Single | 44 | 36.6 | 38 | 2 | 1 |
| Married | 57 | 47.5 | 52 | 4 | 1 |
| Co-habiting | 1 | 0.8 | 1 | 1 | - |
| Widowed | 6 | 5.0 | 5 | - | - |
| Divorced/separated | 6 | 5.0 | 5 | 1 | - |
| Missing | 6 | 5.0 | 1 | - | - |
| **Type of family** | | | | | |
| Monogamy | 79 | 65.8 | 71 | 6 | 2 |
| Polygamy | 37 | 30.8 | 33 | 4 | - |
| Missing | 4 | 3.3 | 2 | 1 | - |
| **Ethnic Group** | | | | | |
| Hausa/Fulani | 14 | 11.6 | 14 | - | - |
| Yoruba | 19 | 15.8 | 17 | 1 | 1 |
| Igbo | 22 | 18.3 | 20 | 2 | - |
| Others | 61 | 50.8 | 53 | 7 | 1 |
| Missing | 4 | 3.3 | 3 | 1 | - |
| **Religion** | | | | | |
| Christianity | 96 | 80.0 | 85 | 10 | 1 |
| Islam | 18 | 15.0 | 16 | 1 | 1 |
| Traditional | 4 | 3.3 | 4 | - | - |
| Missing | 2 | 1.7 | 2 | - | - |
| **Educational Level** | | | | | |
| Primary | 12 | 10.0 | 10 | 2 | - |
| Secondary | 67 | 55.8 | 58 | 6 | 2 |
| Tertiary | 27 | 22.5 | 25 | 2 | - |
| Postgraduate | 3 | 2.5 | 1 | 2 | - |
| None | 1 | 0.8 | 1 | - | - |
| Missing | 10 | 8.3 | 10 | - | - |
| **Occupation** | | | | | |
| Student | 17 | 14.2 | 13 | 4 | - |
| Civil servant | 18 | 15.0 | 17 | 1 | - |
| Farmer | 1 | 0.8 | 1 | - | - |
| Business/Trader | 61 | 50.8 | 54 | 5 | 2 |
| Unemployed | 6 | 5.0 | 6 | - | - |
| Retired | 12 | 10.0 | 11 | 1 | - |
| Missing | 5 | 4.2 | 5 | - | - |

**Table 2.** Demographic characteristics of HIV seropositive subjects with viral load unsuppression at Nigerian Navy Hospital Warri.

| Variables | Frequency (n = 8) | Percentage (%) |
|---|---|---|
| **Age Group (years)** | | |
| ≤20 | - | - |
| 21-30 | 1 | 12.5 |
| 31-40 | 4 | 50.0 |
| 41-50 | 1 | 12.5 |
| 51-60 | 1 | 12.5 |
| >60 | 1 | 12.5 |
| Mean ± SD | 36.9 ± 13.1 | |
| | | |
| **Gender** | | |
| Male | 4 | 50.0 |
| Female | 4 | 50.0 |
| **Marital Status** | | |
| Single | 4 | 50.0 |
| Married | 4 | 50.0 |
| Co-habiting | - | - |
| Widowed | - | - |
| Divorced/separated | - | - |
| Missing | - | - |
| | | |
| **Type of family** | | |
| Monogamy | 4 | 50.0 |
| Polygamy | 3 | 37.5 |
| Missing | 1 | 12.5 |
| **Ethnic Group** | | |
| Hausa/Fulani | 1 | 12.5 |
| Yoruba | 2 | 25.0 |
| Igbo | 5 | 62.5 |
| Others | - | - |
| Missing | - | - |
| **Religion** | | |
| Christianity | 7 | 87.5 |
| Islam | 1 | 12.5 |
| Traditional | - | - |
| Missing | - | - |
| **Educational Level** | | |
| Primary | 2 | 25.0 |
| Secondary | 4 | 50.0 |
| Tertiary | 2 | 22.5 |
| Postgraduate | - | - |
| None | - | - |
| Missing | - | - |
| **Occupation** | | |
| Student | 1 | 12.5 |
| Civil servant | 1 | 12.5 |
| Farmer | - | - |
| Business/Trader | 5 | 62.5 |
| Unemployed | 1 | 12.5 |

**Figure 1.** Chart showing circulating strains of HIV among study participants at NNH Warri.

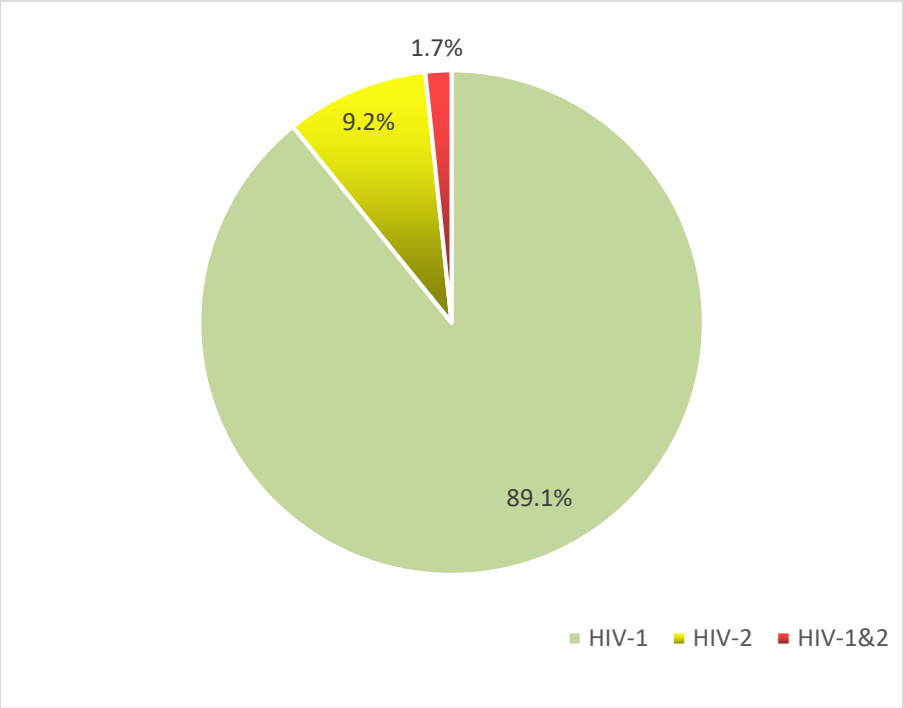
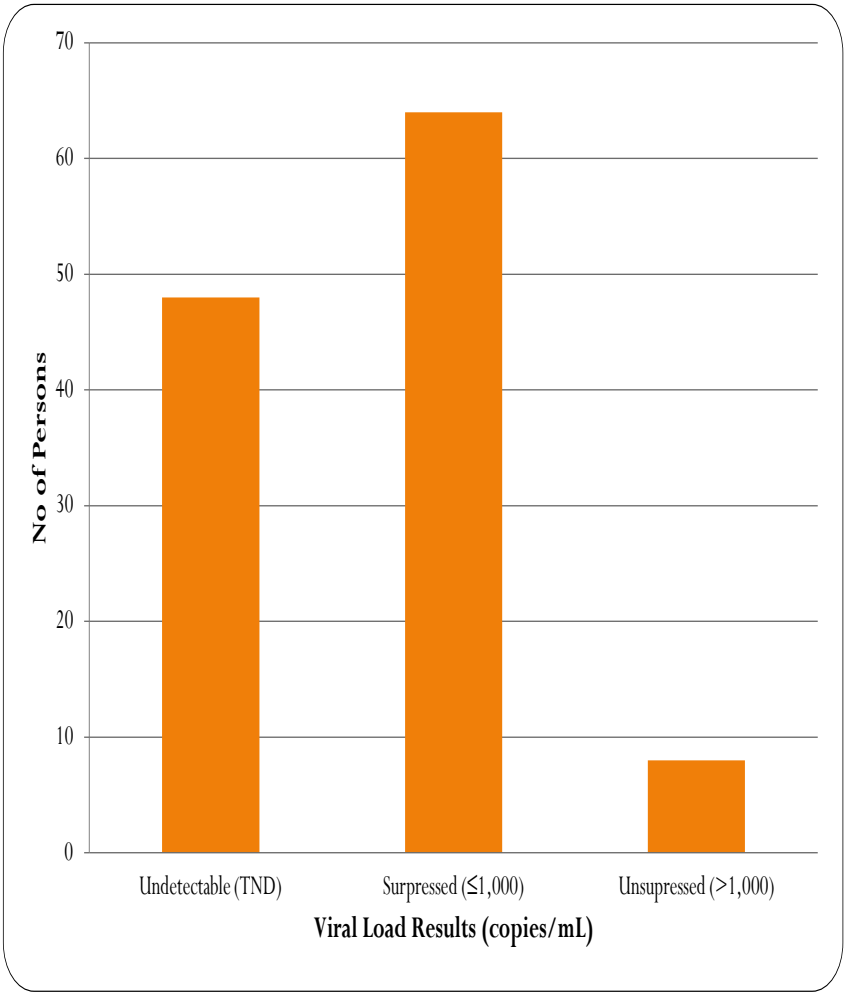



**Figure 2.** Chart showing viral load results among study participants at NNH Warri.



**Discussion**

This study provides valuable insights into the demographic and virological characteristics of the study population. The high prevalence of HIV-1 compared to HIV-2 and the presence of co-infection with both strains highlight the importance of understanding the local HIV strain distribution for effective management and treatment. The distribution of viral load levels among the participants is also significant, as it reflects the effectiveness of antiretroviral therapy and the potential for HIV transmission within the population.

Our findings are consistent with existing research on HIV strain distribution and viral load levels in similar populations. For example, a study on HIV strain variability in London, UK, revealed a diverse HIV-1 subtype distribution, emphasizing the need for comprehensive strain typing to understand local epidemics [8]. Additionally, a report on HIV-2 diagnoses in the United States highlighted the low prevalence of HIV-2 and the importance of accurate laboratory testing for differentiating HIV-1 and HIV-2 infections [9].

The finding of both HIV-1 and HIV-2 co-infection among the study population is significant and has implications for HIV management and treatment. The prevalence of HIV-1 and HIV-2 co-infection varies across different regions and populations. For example, a study conducted in Zimbabwe found that 4% of HIV-1-positive and 99% of HIV-2-positive women were co-infected [10]. Similarly, a study in Cameroon reported a prevalence of 1.6% co-infection among voluntary counseling and testing subjects [11]. These findings highlight the importance of differentiating between HIV-1 and HIV-2 infections, as co-infection may have implications for disease progression, treatment response, and the development of antiretroviral resistance.

HIV-2 is known to be less easily transmitted than HIV-1, and individuals with HIV-2 infection often have lower viral loads compared to those with HIV-1 infectionc[12]. Findings from our study are consistent with this observation as all the participants with unsuppressed viral load had HIV-1 strain. This difference in viral load has been associated with variations in pathogenicity and disease progression between HIV-1 and HIV-2 infections [13]. Additionally, the prevalence of HIV-2 has been declining in some countries, such as Guinea, while HIV-1 prevalence has been increasing, suggesting dynamic changes in the epidemiology of HIV-2 infection [14]. Findings from our study are equally similar to this observation.

The co-infection of HIV-1 and HIV-2 presents unique challenges for HIV management, including the need for modified antiretroviral therapy and the potential for antiretroviral resistance [11]. Understanding the characteristics and disease outcomes of individuals with HIV-1 and HIV-2 co-infection is essential for tailoring effective interventions and treatment strategies. Further research, such as the IeDEA-West Africa HIV-2 Cohort Study, is ongoing to address the specific challenges and implications of HIV-2 infection within the West African context [15].

The finding of HIV-1 and HIV-2 co-infection among the study population underscores the importance of differentiating between HIV-1 and HIV-2 infections for effective HIV management. The unique characteristics of HIV-2 infection, including lower transmission efficiency and viral load, have implications for disease progression, treatment response, and the development of antiretroviral resistance [14]. Ongoing research and collaborative efforts are essential for addressing the specific challenges and implications of HIV-2 infection within the West African context and for tailoring effective interventions and treatment strategies.

The results from our study also raise important questions for future research and clinical practice. For instance, the factors contributing to the high prevalence of HIV-1 and the relatively lower prevalence of HIV-2 in the study population could be further investigated. Moreover, the characteristics of individuals with unsuppressed viral loads, such as age, gender, and marital status, warrant additional attention to tailor interventions for this subgroup.

Furthermore, the results of the study provide a comprehensive understanding of the demographic and virological profile of the study population. It sheds light on the prevalence of different HIV strains and the distribution of viral load levels among subjects on TLD as ART. These findings have implications for local HIV management and highlight the need for tailored interventions to address the specific characteristics of the population, particularly those with unsuppressed viral loads [16]. The results also underscore the importance of ongoing research and

surveillance to inform evidence-based HIV prevention and treatment strategies.

**Conclusion**

The study accentuates the significance of continuous research and surveillance, shaping evidence-based HIV prevention and treatment strategies tailored to the specific characteristics of the population. Our findings align with global research on HIV strain diversity, emphasizing the need for comprehensive strain typing in diverse populations [17]. The study prompts crucial questions for future research, such as exploring factors contributing to the prevalence differences between HIV-1 and HIV-2 and understanding the characteristics of individuals with unsuppressed viral loads. The study provides valuable insights into the demographic and virological profile of the study population, providing valuable insights for local HIV management. The implications of the study highlight the necessity for tailored interventions, especially for individuals with unsuppressed viral loads [18].

Our findings reinforce the ongoing importance of research and surveillance, emphasizing evidence-based strategies for HIV prevention and treatment in this specific patient population [19]. The study illuminates critical aspects of HIV dynamics, drug resistance, and treatment outcomes among Nigerians attending a military hospital. The prevalence of HIV-1 and the distribution of viral load levels underscore the importance of understanding local strain variations for effective management. The findings align with global research on HIV strain diversity, emphasizing the need for comprehensive strain typing in diverse populations.

The study's emphasis on tailored interventions and the need for comprehensive strain typing aligns with global research on HIV strain diversity. It also highlighted the significance of ongoing research and surveillance to inform evidence-based HIV prevention and treatment strategies tailored to the specific characteristics of the population. The findings provide a foundation for future research and clinical practice, emphasizing the necessity of understanding local HIV strain variations and the characteristics of individuals with unsuppressed viral loads for effective HIV management in this specific patient population. The study's comprehensive analysis enhances our understanding of the demographic and virological profile of the study population, providing valuable insights for local HIV management.

Clients with unsuppressed viral loads are recommended for enhanced adherence counseling to address treatment failure. Although about 20 percent of Nigerian clients with viral unsuppression are due to drug-resistant HIV infection, Enhanced Adherence Counseling (EAC) has been identified as the Gold Standard for managing such cases [20]. EAC is a strategy to enhance adherence to ART and improve viral load suppression among HIV-positive clients [21]. The World Health Organization (WHO) recommends intensive adherence counseling for individuals with unsuppressed viral loads to address non-adherence to ART and improve treatment outcomes [22].

Previous studies have highlighted the effectiveness of EAC in achieving viral load suppression, with a focus on addressing barriers to adherence and promoting behavior change [23, 24]. Phone-based enhanced adherence counseling has also been found to be effective in improving viral suppression among key populations with unsuppressed viral loads [25]. The implementation of structured enhanced adherence counseling has been identified as a key strategy to address poor adherence and reduce the risk of unsuppressed viral loads. Additionally, it is recommended that clients with unsuppressed viral loads undergo a thorough clinical examination to identify the underlying causes of treatment failure.

**Conflict of interest**

Non declared.

**Funding**

Non declared.

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