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HIV/*Plasmodium falciparum* Coinfection among HIV-1 Infected Individuals in Uyo, Nigeria

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Abstract: Human immunodeficiency virus (HIV) and Malaria are two main global public health threats that dent development in low and middle-income countries. This study evaluated the HIV/*Plasmodium falciparum* coinfection among HIV-1 infected individuals in Uyo, Nigeria. A total of 176 from HIV-infected individuals participated in this study. The age range of the 176 HIV-1 positive individuals who participated in the study was 6-72 years (average age = 40.0 years). Plasma samples were analyzed for HIV and Malaria using ELISA. The CD4 count was enumerated using the Partec CyFlow® Counter. Plasma viral loads (PVL) were determined using the Abbott Real-Time HIV-1 assay. Results showed that 21.0% of the subjects fell within age range 36-40 years, closely followed by 31-35 years (19.0%) and 41-45 years (17.0%). Females were more in proportion (61.9%) than males (38.1%) with ratio of 2.3:1. Majority were married (60.2%), 32.4% were singles and 7.4% were divorced/widows/widowers. Majority had tertiary education (49.5%), secondary (35.2%), primary (13.6%) and no formal education (1.7%). In terms of occupation, traders were more in proportion (31.3%) while farmers were the least (2.3%) among others. Clinical characteristics of HIV-infected individuals revealed that the CD4 (cells/µl) count ranged from 7 – 1217cells/µl (average = 431.6 cells/µl). Plasma viral loads (PVL) ranged from TND to 18191806 copies/mL (average = 237,030.1 copies/mL). Results also showed an overall prevalence of HIV/*Plasmodium falciparum* coinfection to be 6.3%. Higher coinfection rates were obtained in ages <25 years (28.6%), males (8.5%), singles (12.3%), primary education (8.3%), business owners (33.3%), CD4 cell count 200-349 cells/µl (9.4%) and in those with PVL >5000 copies/mL (13.6%). This study confirmed the presence of HIV/*Plasmodium falciparum* coinfection in Uyo, Nigeria. Among all the variables studied, only age (P = 0.04) and plasma viral loads (P=0.01) were statistically associated with HIV/*Plasmodium falciparum* coinfection. Our findings highlight the need for a well-structured approach to the management of HIV/*Plasmodium falciparum* coinfection. In spite of the prevalence of 6.3% obtained in this study, there is still the need for intensified awareness of HIV and Malaria prevention.

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Introduction

HIV/AIDS in particular has the potential to impact negatively on the socioeconomic development of individual societies because of the associated high adult mortality in some countries, especially in sub-Saharan Africa (Vitoria et al., 2009). Despite the progress made in the response to HIV/AIDS during the last decade, the HIV pandemic remains one of the most serious challenges to global health and probably will continue to be one of the leading causes of death and disability in the world for the next decades (Vitoria et al., 2009). Since the initial description of HIV as the causative agent of AIDS, more than 60 million people have been infected with the virus, and more than 25 million people have died (Cohen et al., 2008; Vitoria et al., 2009).

Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected female Anopheles mosquitoes. It is preventable and curable (WHO, 2020). According to the World Malaria Report 2019, *Plasmodium falciparum* accounted for 99.7% of estimated malaria cases in the African Region in 2018 (WHO, 2020). Malaria is endemic in 109 countries and continues to cause between 189 and 327 million clinical episodes of illness each year (231 million in 2017 and 228 million in 2018), with at least 881,000 associated deaths (416,00 in 2017 and 405,000 in 2018) (Vitoria

et al., 2009; WHO, 2020). Around 60% of the global malaria burden and more than 93% of malaria cases and 94.0% malaria deaths occur in sub-Saharan Africa, where malaria is the leading cause of morbidity and mortality in children younger than 5 years and pregnant women (Vitoria et al., 2009; WHO, 2020). According to WHO (2020), 6 countries accounted for more than half of all malaria cases worldwide: Nigeria (25%), the Democratic Republic of the Congo (12%), Uganda (5%), and Côte d'Ivoire, Mozambique and Niger (4% each) in 2018 (WHO, 2020). Furthermore, malaria consumes around one fourth of household incomes in most African endemic countries, reducing access to preventive interventions and lifesaving services (WHO, 2007).

Human immunodeficiency virus (HIV)-1 infection has an important impact on malaria (Chavale et al., 2012). The 2 pathogens interact synergistically in human hosts (Orlov et al., 2012; Naing et al., 2016). HIV-1 and *Plasmodium falciparum* coinfected individuals (HIV/*Pf*) present with a high degree of anaemia, enhanced parasitaemia and decreased $CD4^+$ T cell counts, which increase the risk of developing severe malaria. In addition, infection with either Pf or HIV-1 alone causes extensive immune activation (Chavale et al., 2012).

Plasmodium falciparum infection with HIV-1 causes progressive cellular immunosuppression, and any resulting impairment in the immune response to malaria might be associated with failure to prevent infection or to suppress parasitemia and clinical disease (Good and Doolan, 1999; Whiteworth, 2006). However, laboratory-based studies have found that although some components of the human immune response to *Plasmodium falciparum* are modified by HIV-1, others are unaffected (Wabwire-Mangen et al., 1989; Migot et al., 1996; Moore et al., 2000; Whitworth, 2006). On the other hand, *P falciparum* has been shown to stimulate HIV-1 replication through the production of cytokines (interleukin-6 and tumor necrosis factor-alpha) by activated lymphocytes (Xiao et al., 1998; Froebel et al., 2004). *P falciparum* also increases the potential reservoir for HIV in the placenta by increasing the number of $CCR5^+$ macrophages (Tkachuk et al., 2001).

As leading causes of morbidity and mortality, malaria and human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) are two of the most important diseases in Africa (Idemyor et al. 2007). *Plasmodium falciparum*-associated HIV-1 (*Pf*/HIV) infection has been described in many sub-Saharan Africa countries and data from these countries account for most of the available clinical data regarding this co-infection (Chalwe et al. 2009, Davenport et al. 2010, Kiyingi et al. 2010, Mills et al. 2010, Serna-Bolea et al. 2010, Naniche et al. 2011).

HIV coinfection has its impact on disease presentation, with an increased risk of complicated and severe malaria and death (Chirenda et al., 2000; Grimwade et al., 2004; Cohen et al., 2005). A relevant issue in malaria-endemic regions is the identification of HIV/AIDS patients among suspected cases of acute malaria (Mills et al. 2010, Serna-Bolea et al. 2010). Furthermore, HIV-1 infection is a risk factor for receiving an incorrect diagnosis of malaria (Berg et al. 2008).

Few studies addressing the compromised immunological state have been reported for malaria/HIV-AIDS coinfection (Naniche et al. 2011; Chavale et al., 2012), thus, surveillance health programs should invest considerable effort to minimise the misdiagnosis of febrile diseases. Consequently, the present study aimed at determining the prevalence of HIV/ *Plasmodium falciparum* coinfection in HIV-1 infected individuals in Uyo, Akwa Ibom State, Nigeria.

2. Materials And Methods

2.1. Study Areas

The study was conducted at the University of Uyo Teaching Hospital (UUTH), Akwa Ibom State, Nigeria. Akwa Ibom state which is made up of 31 LGA's lies between latitudes 4^o 32'N and 5^o 33'N, and longitudes 7^o 25'E and 8^o 25'E.

2.2. Study Design

A cross-sectional study in the University of Uyo Teaching Hospital (UUTH) in Uyo Akwa Ibom State, Nigeria was carried out. Approval for the study was gotten from the ethical committees of UUTH. Demographic data and other needed information were collected in a labelled questionnaire form.

2.3. Study population

The study population was HIV-infected individuals attending University of Uyo Teaching Hospital (UUTH), Uyo, Akwa Ibom State, Nigeria. At most, 176 HIV-1 infected individuals were selected and enrolled for the study (Table 1).

2.4. Serological analysis of HIV

All the 176 plasma samples were re-tested using Determine^{TM} and Stat-pak HIV-1/2 rapid strips to detect HIV-1/2 antibodies (serial algorithm); samples positive to at least, one of the rapid tests were re-tested using 4^{th} generation ELISA (Genscreen Ultra HIV Ag-Ab, Bio-Rad, In-vitro Diagnostics, Raymond Poincare', France). All seropositive samples were subjected to P^{24} antigen detection by ELISA following the manufacturer's specifications.

2.5. Serological analysis of Malaria

Plasma samples were analyzed for the presence of Malaria *Plasmodium falciparum* using the ELISA

kit manufactured by DIA. PRO Diagnostic Bioprobes Srl Via G. Carducci nº 27 20099 Sesto San Giovanni (Milano) – Italy, according to manufacturer's specifications.

2.5. CD4 T Cell Count Enumeration

EDTA-treated blood samples were used for CD4 T cell count using Partec CyFlow® Counter (Partec GmbH, Munster, Germany) and was done as stipulated by the manufacturer.

2.6. HIV-1 Viral Load Testing (Abbott Real-Time Assay)

Plasma viral load (PVL) was analyzed using Abbott Real-Time HIV assay US Protocol.

3. Results

3.1. General characteristics of the subjects

The age range of the subjects was 6-72 years (average age = 40.0 years). Majority of the subjects fell within age range 36-40 years (21.0%), closely followed by 31-35 years (19.0%) and 41-45 years (17.0%). Females were more in proportion (61.9%) than males (38.1%) with ratio of 2.3:1. Majority were married (60.2%), 32.4% were singles and 7.4% were divorced/widows/widowers. Majority had tertiary education (49.5%), secondary (35.2%), primary (13.6%) and no formal education (1.7%). In terms of occupation, traders were more in proportion (31.3%) while farmers were the least (2.3%) among others. Clinical characteristics of HIV-infected individuals revealed that the CD4 (cells/µl) count ranged from 7 – 1217cells/µl (average = 431.6 cells/µl). Plasma viral loads (PVL) ranged from TND to 18191806 copies/mL (average = 237,030.1 copies/mL) (Table 1).

3.2. Overall prevalence of HIV/*Plasmodium falciparum* coinfection

Results showed an overall prevalence of HIV/*Plasmodium falciparum* coinfection to be 6.3% (Table 1).

3.3. Age-specific HIV/*Plasmodium falciparum* coinfection

The age-specific HIV/*Plasmodium falciparum* coinfection was highest in ages <25 years (28.6%) and lowest in 41-45 years with zero prevalence, however, these differences were statistically associated (P = 0.04) as shown in Table 1.

3.4. Sex-specific HIV/*Plasmodium falciparum* coinfection

The sex-specific HIV/*Plasmodium falciparum* coinfection was higher in males (8.5%) than in females (6.4%). This difference was statistically associated (P = 0.90) (Table 1).

3.5. Marital Status-specific HIV/*Plasmodium falciparum* coinfection

The marital status-specific HIV/*Plasmodium falciparum* coinfection was highest in singles (12.3%), followed by divorced/widow/widower (7.7%) while the married (2.8%) recorded the least. This difference was not significant (P=0.06) (Table 1).

3.6. Educational Status-specific HIV/*Plasmodium falciparum* coinfection

The educational status-specific HIV/*Plasmodium falciparum* coinfection was higher in subjects with primary (8.3%) and tertiary (8.0%) education compared to those with secondary (3.2%) and no formal education (0.0%). This difference was not significant (P=0.61) (Table 1).

3.7. Occupational-specific HIV/*Plasmodium falciparum* coinfection

The occupational-specific HIV/*Plasmodium falciparum* coinfection was highest among business owners (33.3%), followed by students (16.7%), civil servants (7.7%), teachers (6.7%) and traders (5.5%). While other occupations recorded zero HIV/*Plasmodium falciparum* coinfection rates. No significant difference (P=0.14) exist between occupation and HIV/*Plasmodium falciparum* coinfection (Table 1).

3.8. CD4 counts-specific HIV/*Plasmodium falciparum* coinfection

The CD4 counts-specific HIV/*Plasmodium falciparum* coinfection was highest among subjects with CD4 cell count 200-349 cells/µl (9.4%), followed by 350-499 cells/µl (8.1%) and <200 cells/µl (4.4%) and the least prevalence occurred in those with >500 cells/µl (3.3%) (Table 1). This difference was not significant (P = 0.52).

3.9. Plasma Viral Load (PVL)-specific HIV/*Plasmodium falciparum* coinfection

The PVL-specific HIV/*Plasmodium falciparum* coinfection was higher among subjects with PVL >5000 copies/mL (13.6%) compared to those with PVL <40 copies/mL (3.0%) and 40-5000 copies/mL (0.0%) (Table 1). This difference was highly significant (P = 0.01).

4. Discussion

There is evidence that HIV/*Plasmodium falciparum* coinfection enhances the spread of both HIV-1 and *Plasmodium falciparum* malaria infection and may also influence the severity of the clinical manifestations of these diseases. Indeed, HIV infection has been considered an important risk factor for severe *Plasmodium falciparum* malaria (Grimwade et al. 2004, Chalwe et al. 2009; Chavale et al., 2012).

The present study showed that HIV/*P. falciparum* coinfections was 6.3%. As shown in previous studies, the prevalence of HIV in malaria cases was higher ranging from 16.0–27.0% than that of the malaria in HIV-infected patients which ranged from 15.0–23.0% (Naing et al., 2016). HIV infection could impair immune responses to malaria parasites, leading to a decreased ability to control parasitemia

(Cohen et al., 2005; Naing et al., 2016), whereas malaria infection can modulate HIV progression (Ned et al., 2005; Naing et al., 2016) and HIV RNA replication (Ismaili et al., 2003; Ned et al., 2008; Naing et al., 2016).

The 6.3% HIV/*P. falciparum* coinfection rate reported in the present study is lower than the 10.3% reported in Akure, Ondo State, Nigeria (Dada *et al*., 2016). But it is higher than 0.0% reported in Port Harcourt (Okonko *et al*., 2018); the 4.55% reported in another study in Akure, Nigeria (Olusi and Abe, 2014), 2.24% reported in Bamenda Cameroon (Njunda et al., 2012).

Table 1: **Socio-demographical and Clinical Characteristics of HIV-1/*Plasmodium falciparum* coinfected Individuals in Uyo, Nigeria**

Variables	No. Tested (%)	Malaria (%)	Chi-square Analysis
Age groups (Years)			
≤25	14(8.0)	4(28.6)	P = 0.04 (Significant)
26-30	16(9.1)	1(6.3)	
31-35	33(19.0)	1(3.0)	
36-40	37(21.0)	1(2.7)	
41-45	30(17.0)	0(0.0)	
46-50	16(9.1)	1(6.3)	
51-55	13(7.4)	1(7.7)	
56-60	10(5.7)	1(10.0)	
≥61	7(4.0)	19(14.3)	
Sex			
Males	47(38.1)	4(8.5)	P = 0.90 (Not significant)
Females	109(61.9)	7(6.4)	
Marital Status			
Married	106(60.2)	3(2.8)	P=0.06 (Not significant)
Singles	57(32.4)	7(12.3)	
Divorced/Widowed	13(7.4)	1(7.7)	
Educational Status			
Non-Formal	3(1.7)	0(0.0)	P=0.61 (Not significant)
Primary	24(13.6)	2(8.3)	
Secondary	62(35.2)	2(3.2)	
Tertiary	87(49.5)	7(8.0)	
Occupation			
Trading	55(31.3)	3(5.5)	P=0.14 (Not significant)
Teaching	15(8.5)	1(6.7)	
Civil Servant	26(14.8)	2(7.7)	
Public Servant	10(5.7)	0(0.0)	
Business	6(3.4)	2(33.3)	
Artisans	12(6.8)	0(0.0)	
Driving	10(5.7)	0(0.0)	
Retired	10(5.7)	0(0.0)	
Farming	4(2.3)	0(0.0)	
Student	18(10.2)	3(16.7)	
Unemployed	10(5.7)	0(0.0)	
CD4 counts (cells/µl)			
< 200	26(14.8)	1(4.0)	P = 0.52 (Not significant)
200-349	53(30.1)	5(9.4)	
350-499	37(21.0)	3(8.1)	
≥500	60(24.1)	2(3.3)	
Viral load (copies/mL)			
< 40	74(40.0)	2(3.0)	P = 0.01 (Significant)
40 – 5000	36(20.5)	0(0.0)	
5001 & above	66(37.5)	9(13.6)	
Total	**176(100.0)**	**11(6.3)**	

Higher HIV/*P. falciparum* coinfection was observed among age groups ≤25 years (28.6%) than in other age-groups. This is slightly different from a study where higher HIV/*P. falciparum* coinfection was observed in ages of 20-49 (Dada *et al*., 2016).

Gender has been highlighted as an important risk factor in the frequency of both malaria and HIV disease with women being 50% more likely to contract malaria than men (Jenkins *et al*., 2015). Higher HIV/*P. falciparum* coinfection was observed among males (5.1%) than in females (3.9%). The study showed a significant difference ($P<0.05$) between sex and HIV/*P. falciparum* coinfections. This deviated from the finding in Akure, Ondo State, Nigeria where the frequency was higher in females than males (Dada *et al*., 2016). It also deviated from that of Njunda *et al*. (2012) who reported higher rates in females than males in Bamenda, Cameroon.

In the present study, higher HIV/*P. falciparum* coinfection was observed in singles (12.3%) than in divorced/widow/widower (7.7%) than in the married individuals (2.8%).

The present study revealed a higher HIV/*P. falciparum* coinfection was observed among individuals who had primary education than other educational status. This is contrary to other previous studies which have shown frequency of coinfection to be higher among those with no formal education (Bhattacharya *et al*., 2011).

From the results obtained in the present study, the occupational-specific HIV/*P. falciparum* coinfection was highest among business owners (33.3%), followed by students (16.7%), civil servants (7.7%), teachers (6.7%) and traders (5.5%). While other occupations recorded zero HIV/*P. falciparum* coinfection rates. No significant difference (P=0.14) exist between occupation and HIV/*P. falciparum* coinfection.

It was observed in this study that CD4 counts-specific HIV/*P. falciparum* coinfection was insignificantly higher among subjects with CD4 cell count 200-349 cells/µl compared to other CD4 categories. Increased Plasmodium parasitaemia is most likely related to the impairment of parasite control caused by HIV-1-related immunosuppression (Whitworth et al. 2000, Patnaik et al. 2005; Chavale et al., 2012). Patients with low $CD4^+$ T cell counts of less than 350 cells/mm^3 are more likely to exhibit complications arising malaria (Cohen et al. 2005, Mouala et al. 2009; Chavale et al., 2012). Moreover, HIV-1 infection is associated with an increased prevalence of anaemia in *P. falciparum* malaria (Otieno et al. 2006, Davenport et al. 2010; Chavale et al., 2012).

Malaria can also affect HIV-1 infection (Chavale et al., 2012). HIV/AIDS patients with malaria can exhibit a transitory reduction in the number of $CD4^+$ T cells, which may be partially reversible after successful antimalarial therapy (Van Geertruyden et al. 2006a; Chavale et al., 2012). A causal relationship between malarial episodes and a decline in $CD4^+$ T cell counts in HIV-1 patients remains to be established (Mermim et al. 2006; Chavale et al., 2012). The preference of HIV-1 for infecting activated memory $CD4^+$ T lymphocytes can increase cell death (Grossman et al. 2002; Chavale et al., 2012). Consequently, it is possible that, in coinfected patients, *P. falciparum* coinfection-specific T-cell clones are depleted by HIV-1 during each malaria episode (Whitworth and Hewitt 2005, Mermim et al. 2006; Chavale et al., 2012).

Viral replication is a well-known factor that contributes to lymphocyte activation and is considered a predictor parameter for HIV plasma Viral Load (PVL) (Benito et al. 2004). In this present study, PVL-specific HIV/*P. falciparum* coinfection was significantly higher among subjects with PVL >5000 copies/mL (13.6%) compared to others. In HIV-1/AIDS, it is well established that the PVL is directly associated with $CD8^+$ T cell activation (Benito et al. 2004; Chavale et al., 2012). However, the mechanism by which the association of these two pathogens can impact the immunopathogenesis of HIV/*P. falciparum* coinfection remains under discussion (Chavale et al., 2012). Acute malaria elevates the HIV PVL, which in turn can enhance the risk for HIV transmission (Kublin et al. 2005; Chavale et al., 2012). In addition, Plasmodium antigens lead to strong cellular activation (Worku et al. 1997) which may facilitate *de novo* HIV-1 infection and replication (Froebel et al. 2004; Chavale et al., 2012).

Therefore, these factors (CD4 counts and plasma viral loads) can decrease the immune response to both HIV and *P. falciparum* and contribute to HIV disease progression (Chavale et al., 2012).

5. Conclusion

This study confirmed the presence of HIV/*Plasmodium falciparum* coinfection in Uyo, Nigeria. Our findings highlight the need for a well-structured approach to the management of HIV/*P. falciparum* coinfection. In spite of the prevalence of 6.3% obtained in this study, there is still the need for intensified awareness of HIV and Malaria prevention.

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