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

1Ejike Immaculate Ugochi, 1Kparobo Marian Orhuesie, 2Innocent-Adiele Hope Chioma, 1Okonko Iheanyi Omezuruike

1Virus Research Unit, Department of Microbiology, University of Port Harcourt, Port Harcourt, Nigeria;

2.Department of Applied Microbiology, Ebonyi State University, Abakaliki, Nigeria

E-mail: iheanyi.okonko@uniport.edu.ng; Tel: +2348035380891

**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-Ti*m*e 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.

[Ejike Immaculate Ugochi, Kparobo Marian Orhuesie, Innocent-Adiele Hope Chioma, Okonko Iheanyi Omezuruike

. **HIV/*Plasmodium falciparum* Coinfection among HIV-1 Infected Individuals in Uyo, Nigeria.** *N Y Sci J* 2020;13(6):1-8]. ISSN 1554-0200 (print); ISSN 2375-723X (online). <http://www.sciencepub.net/newyork>. 1. doi:[10.7537/marsnys130620.01](http://www.dx.doi.org/10.7537/marsnys130620.01).

**Keywords:** HIV, Coinfections, Malaria, Nigeria

**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 4o 32’N and 5o 33’N, and longitudes 7o 25’E and 8o 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 DetermineTM 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 4th generation ELISA (Genscreen Ultra HIV Ag-Ab, Bio-Rad, In-vitro Diagnostics, Raymond Poincare’, France). All seropositive samples were subjected to P24 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/mm3 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.

**Acknowledgements**

The authors wish to thank the administrations of University of Uyo Teaching Hospital (UUTH), Uyo, Akwa-Ibom State, Nigeria for the ethical approval and all the individuals who participated in this study. Our immense gratitude also goes to Dr. Emeka Michael, University of Uyo Teaching Hospital, Uyo, Mr. Inyang Shedrack at the CD4 Unit, University of Uyo Teaching Hospital, Uyo, Mrs. Onasochi Shedrack at the Viral Load Unit, University of Uyo Teaching Hospital, Uyo and Mrs Tochi Ifeoma Cookey at the Virus Research Unit, Department of Microbiology, University of Port Harcourt, Port Harcourt, Nigeria.

**References**

1. Benito JM, Lopez M, Lozano S, Martinez P, Gonzalez-Lahoz J, Soriano V 2004. CD38 expression on CD8+ T lymphocytes as a marker of residual virus replication in chronically HIV-infected patients receiving antiretroviral therapy. *AIDS Res Hum Retroviruses 20*: 227-233.
2. Berg A, Patel S, Langeland N, Blomberg B 2008. *Falciparum* malaria and HIV-1 in hospitalized adults in Maputo, Mozambique: does HIV-infection obscure the malaria diagnosis? *Malar J 7*: 252.
3. Bhattacharya, M. K., Naik, T. N., Ghosh, M., Jana, S., and Dutta, P. (2011). Pulmonary tuberculosis among HIV seropositives attending a counseling center in Kolkata. *Indian Journal of Public Health*, *55*(4), 329.
4. Chalwe V, Van Geertruyden JP, Mukwamataba D, Menten J, Kamalamba J, Mulenga M, D'Alessandro U 2009. Increased risk for severe malaria in HIV-1-infected adults, Zambia. *Emerg Infect Dis 15*: 749.
5. Chavale, H., Santos-Oliveira, J.R., Da-Cruz, A. M. and Enosse, S. (2012). Enhanced T cell activation in *Plasmodium falciparum* malaria-infected human immunodeficiency virus-1 patients from Mozambique. Mem. Inst. Oswaldo Cruz, vol.107 no.8. http://dx.doi.org/10.1590/S0074-02762012000800004.
6. Chirenda J, Siziya S, Tshimanga M. Association of HIV infection with the development of severe and complicated malaria cases at a rural hospital in Zimbabwe. Cent Afr J Med 2000; 46:5-9.
7. Cohen, C., Karstaedt, A., Frean, J., Thomas, J., Govender, N., Prentice, E., and Crewe-Brown, H. (2005). Increased prevalence of severe malaria in HIV-infected adults in South Africa. *Clinical Infectious Diseases*, *41*(11), 1631-1637.
8. Cohen MS, Hellmann N, Levy JA et al. 2008. The spread, treatment, and prevention of HIV-1: evolution of a global pandemic. *J Clin Invest*; 118:1244–1254.
9. Dada, E. O., Okebugwu, Q. C., and Ibukunoluwa, M. R. (2016). Co-Infection of Human Immuno-Deficiency Virus (HIV) with Malaria in Gbalegi, Idanre and State Hospital, Akure, Ondo State, Nigeria. *HIV Current Research*, *1*(111), 2.
10. Davenport GC, Ouma C, Hittner JB, Were T, Ouma Y, Ong'echa JM, Perkins DJ 2010. Hematological predictors of increased severe anemia in Kenyan children coinfected with *Plasmodium falciparum* and HIV-1. *Am J Hematol 85*: 227-233.
11. Froebel K, Howard W, Schafer JR, Howie F, Whitworth J, Kaleebu P, Brown AL, Riley E 2004. Activation by malaria antigens renders mononuclear cells susceptible to HIV infection and re-activates replication of endogenous HIV in cells from HIV-infected adults. *Parasite Immunol 26*: 213-217.
12. Good MF, Doolan DL. Immune effector mechanisms in malaria. Curr Opin Immunol 1999; 11:412-9.
13. Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. 2004. HIV infection as a cofactor for severe *falciparum* malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS 18*: 547-554.
14. Grossman Z, Meier-Schellersheim M, Sousa AE, Victorino RM, Paul WE 2002. CD4+ T-cell depletion in HIV infection: are we closer to understanding the cause? *Nat Med 8*: 319-323.
15. Idemyor V 2007. Human immunodeficiency virus (HIV) and malaria interaction in sub-Saharan Africa: the collision of two Titans. *HIV Clin Trials 8*: 246-253.
16. Ismaili J, van der Sande M, Holland MJ, et al. Plasmodium falciparum infection of the placenta affects new-born immune responses. Clin Exp Immunol 2003; 133:414–421.
17. Jenkins R, Omollo R, Ongecha, M, Sifuna, P, Othieno C, Ongeri L, Kingora, J, Ogutu B (2015) Prevalence of malaria parasites in adults and its determinants in malaria endemic area of Kisumu county, Kenya. *Malaria Journal,* 14: 263.
18. Kiyingi HS, Egwang TG, Nannyonga M 2010. Prolonged elevation of viral loads in HIV-1-infected children in a region of intense malaria transmission in Northern Uganda: a prospective cohort study. *Pan Afr Med J 7*: 11.
19. Kublin JG, Patnaik P, Jere CS, Miller WC, Hoffman IF, Chimbiya N, Pendame R, Taylor TE, Molyneux ME 2005. Effect of *Plasmodium falciparum* malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. *Lancet 365*: 233-240.
20. Mermin J, Lule JR, Ekwaru JP 2006. Association between malaria and CD4 cell count decline among persons with HIV. *J Acquir Immune Defic Syndr 41*: 129-130.
21. Migot F, Ouedraogo JB, Diallo J, Zampan H, Dubois B, Scott-Finnigan T, Sanou PT, Deloron P. Selected P. falciparum specific immune responses are maintained in AIDS adults in Burkina Faso. Parasite Immunol 1996; 18:333-9.
22. Mills LA, Kagaayi J, Nakigozi G, Galiwango RM, Ouma J, Shott JP, Ssempijja V, Gray RH, Wawer MJ, Serwadda D, Quinn TC, Reynolds SJ 2010. Utility of a point-of-care malaria rapid diagnostic test for excluding malaria as the cause of fever among HIV-positive adults in rural Rakai, Uganda. *Am J Trop Med Hyg 82*: 145-147.
23. Moore JM, Ayisi J, Nahlen BL, Misore A, Lal AA, Udhayakumar V. Immunity to placental malaria. II. Placental antigen-specific cytokine responses are impaired in human immunodeficiency virus-infected women. J Infect Dis 2000; 182:960-4.
24. Mouala C, Guiguet M, Houzé S, Damond F, Pialoux G, Viget N, Costagliola D, Le Bras J, Matheron S, FHDH-ANRS CO4 Clinical Epidemiology Group 2009. Impact of HIV infection on severity of imported malaria is restricted to patients with CD4 cell counts < 350 cells/microl. *AIDS 23*: 1997-2004.
25. Naing C, Sandhu NK, Wai VN. The Effect of Malaria and HIV Co-Infection on Anemia: A Meta-Analysis. Medicine. 2016 Apr; 95(14):e3205. DOI: 10.1097/MD.0000000000003205.
26. Naniche D, Letang E, Nhampossa T, David C, Menendez C, Alonso P 2011. Alterations in T cell subsets in human immunodeficiency virus-infected adults with co-infections in southern Mozambique. *Am J Trop Med Hyg 85*: 776-781.
27. Ned RM, Moore JM, Chaisavaneeyakorn S, Udhayakumar V: Modulation of immune responses during HIV-malaria co-infection in pregnancy. Trends Parasit. 2005, 21: 284-291.
28. Ned RM, Price AE, Crawford SB, et al. Effect of placental malaria and HIV infection on the antibody responses to Plasmodium falciparum in infants. J Infect Dis 2008; 198:1609–1619.
29. Njunda, L. A., Kamga, H. L. F., Nsagha, D. S., Assob, J. C. N., and Kwenti, T. E. (2012). Low malaria prevalence in HIV-positive patients in Bamenda, Cameroon. *Journal of Microbiology Research*, *2*(3), 56-59.
30. Olusi, T. A., and Abe, A. F. (2014). Co-infection of HIV and malaria parasites in pregnant women attending major ante-natal health facilities in Akure, Ondo State, Nigeria. *Journal of Parasitology and Vector Biology*, *6*(9), 124-130.
31. Orlov M, Vaida F, Finney OC, et al. P. falciparum enhances HIV replication in an experimental malaria challenge system. PLoS One 2012; 7:e39000.
32. Otieno RO, Ouma C, Ong'echa JM, Keller CC, Were T, Waindi EN, Michaels MG, Day RD, Vulule JM, Perkins DJ 2006. Increased severe anemia in HIV-1-exposed and HIV-1-positive infants and children during acute malaria. *AIDS 20*: 275-280.
33. Patnaik P, Jere CS, Miller WC, Hoffman IF, Wirima J, Pendame R, Meshnick SR, Taylor TE, Molyneux ME, Kublin JG 2005. Effects of HIV-1 serostatus, HIV-1 RNA concentration and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. *J Infect Dis 192*: 984-991.
34. Serna-Bolea C, Muñoz J, Almeida JM, Nhacolo A, Letang E, Nhampossa T, Ferreira E, Alonso P, Naniche D 2010. High prevalence of symptomatic acute HIV infection in an outpatient ward in southern Mozambique: identification and follow-up. *AIDS 24*: 603-608.
35. Tkachuk AN, Moormann AM, Poore JA, Rochford RA, Chensue SW, Mwapasa V, Meshnick SR. Malaria enhances expression of CC chemokine receptor 5 on placental macrophages. J Infect Dis 2001; 183:967-72.
36. Van Geertruyden JP, Mulenga M, Kasongo W, Polman K, Colebunders R, Kestens L, D'Alessandro U 2006a. CD4 T-cell count and HIV-1 infection in adults with uncomplicated malaria. *J Acquir Immune Defic Syndr 43*: 363-367.
37. Vitoria, M., Granich, R., Gilks, C. F., Gunneberg, C., Hosseini, M., Were, W., and De Cock, K. M. (2009). The Global Fight against HIV/AIDS, Tuberculosis, and Malaria Current Status and Future Perspectives. *American Journal of Clinical Pathology*, *131*(6), 844-848.
38. Wabwire-Mangen F, Shiff CJ, Vlahov D, Kline R, Serwadda D, Sewankambo NK, Mugerwa RD, Quinn TC. Immunological effects of HIV-1 infection on the humoral response to malaria in an African population. Am J Trop Med Hyg 1989; 41:504-11.
39. Whitworth J, Morgan D, Quigley M, Smith A, Mayanja B, Eotu H, Omoding N, Okongo M, Malamba S, Ojwiya A. 2000. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet 356*: 1051-1056.
40. Whitworth JA, Hewitt KA 2005. Effect of malaria on HIV-1 progression and transmission. *Lancet 365*: 196-197.
41. Whitworth, J. (2006). Malaria and HIV. In: HIV InSite Knowledge Base Chapter. http://hivinsite.ucsf.edu/InSite?page=kb-05-04-04. Accessed February 21, 2020.
42. World Health Organization (2007). *2006 Year in Review*. Geneva, Switzerland: World Health Organization; 2007. WHO document WHO/DGO/2007.
43. World Health Organization (2020). Malaria Key Facts. https://www.who.int/news-room/fact-sheets/detail/malaria. Accessed February 7, 2020
44. World Health Organization (2019). World malaria report 2019. https://www.who.int/malaria/publications/world-malaria-report-2019/en/. Accessed February 7, 2020.
45. Worku S, Björkman A, Troye-Blomberg M, Jemaneh L, Färnert A, Christensson B 1997. Lymphocyte activation and subset redistribution in the peripheral blood in acute malaria illness: distinct gammadelta+ T cell patterns in *Plasmodium falciparum* and *P. vivax* infections. *Clin Exp Immunol 108*: 34-41.
46. Xiao, L., Rudolph, D. L., Owen, S. M., Spira, T. J., and Lal, R. B. (1998). Adaptation to promiscuous usage of CC and CXC-chemokine coreceptors in vivo correlates with HIV-1 disease progression. *AIDS*, *12*(13): F137-F143.

5/16/2020