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Impact of antiretroviral therapy on immunity and malaria among febrile HIV-infected children seen in a tertiary hospital in Sokoto, Nigeria

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ABSTRACT

Background: Coexistence of malaria with HIV in Sub-Saharan African and its attendant high morbidity and mortality could be a threat that can reverse the gains of ART in HIV-infected children. **Aim:** This study aims to determine the impact of ART on immunity and malaria among febrile HIV-infected children seen in UDUTH, Sokoto, Nigeria. **Materials and Methods:** A cross-sectional study was conducted among HIV-infected children presenting with fever at the Paediatric ART and other Paediatric Outpatient Clinics in the hospital between May and October 2016. Blood film for malaria parasite, packed cell volume, random blood sugar, retroviral test and $CD4^+$Tcell count were done for the participants. Data were analyzed using the IBM SPSS version 23.0 computer statistical software package. A p-value ≤ 0.05 was considered as significant. **Results**: A total of 100 febrile HIV-infected children on ART, and 40 febrile newly diagnosed HIV-infected children not on ART were recruited. The prevalence of malaria among the febrile HIV-infected children on ART was 60% (60/100) compared to 100% (40/40) among those not on ART (χ^2=25.6, p < 0.001). Among the 60 HIV-infected children on ART who had malaria, 12(20.0%) had severe malaria compared to 34 (85.0%) among the 40 that were not on ART (χ^2=25.6, p < 0.001). The mean $CD4^+$T cells count was 403 ± 168cells/µl among the HIV infected children on ART compared with 194 ± 67cells/µl in the treatment naïve patients, and the difference was statistically significant (p < 0.001). Although, the $CD4^+$T-lymphocyte level correlates negatively with malaria parasite density among the HIV-infected children, it was not statistically significant (r = -0.082, p = 0.33). **Conclusion**: ART boosted immunity and reduced malaria prevalence and severity in febrile HIV-infected children. Efforts should be intensified towards early diagnosis and prompt commencement of ART in HIV-infected children.

Keywords: HIV infection, ART, impact, immunity, malaria, children

INTRODUCTION

Human Immunodeficiency Virus (HIV) is an infection of global health importance.[1]Before the introduction of antiretroviral therapy in the mid-1990s, HIV infection in human was considered a death penalty because people with HIV infection rapidly progressed to AIDS in just a few years. In 2017, more than half of the global population living with HIV were receiving antiretroviral treatment including 52% of HIV-infected children aged 0–14 years.[1] Hence, AIDS-related deaths reduced by more than 51% since the peak in 2004. Today ART has converted HIV, a once fatal infection, to a chronic stable infection. Therefore, HIV-infected persons can live nearly as long as someone who is non-HIV infected. The World Health Organization (WHO) had looked into ways of sustaining this great achievement of ART and identified the need to focus on other preventable and treatable infections that may add to the morbidity and mortality of HIV-infected persons, hence the consideration of malaria in this study.

Malaria is also an infection of global health importance that affects about 200 million people worldwide annually and causes about 584,000 deaths each year.[2] More than 90% of malaria cases and death occur in sub-Saharan Africa and remain a major cause of childhood mortality. Nigeria which currently ranks top among the African nations plagued by HIV/AIDS has the highest burden of malaria in the WHO sub-Saharan Africa region.[3,4] It is feared that the coexistence of Malaria with HIV in the sub-Saharan African countries including Nigeria and its

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attendant high morbidity and mortality could be a threat that can reverse the gains of ART in HIV-infected children.

Studies in sub-Saharan Africa have reported increased risk of malaria parasitaemia and clinical malaria in HIV-infected populations compared to HIV-negative groups.[5-7] In Nigeria, high prevalence of malaria in HIV-infected population has been documented in a few studies.[8,9] However, most of these studies were carried out among adult populations who were not on antiretroviral treatment.[5-9] It is suspected that ART which is able to prevent destruction of $CD4^+$Tcell to boost immunity and prolong the life of HIV-infected patients may also offer some protection against malaria and the severe form of malaria in HIV-infected children who are on ART as compared to HIV-infected children who are not on ART. This study was conducted to assess the impact of ART on immunity, malaria prevalence and severity among febrile HIV- infected children with the hope that the findings would provide additional evidence on the need to intensify efforts towards timely ART uptake among HIV-infected children.

MATERIALS AND METHODS

Study Design, Population and Area

A cross-sectional study was conducted among febrile HIV-infected children, aged 3-months to 15-years from May to October 2016**.** The study population comprised known HIV-infected children presenting with fever at the Paediatric ART clinic and newly diagnosed HIV – infected children during visit to the Paediatric Out-Patient Department (POPD), Emergency Paediatric Unit (EPU) or Paediatric Medical Ward (PMW) of Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto, Nigeria. Children that were aged 3 months to 15 years, with confirmed HIV infection (i.e., HIV positive), and axillary temperature ≥ 37.5^{0}C or complaint of fever, whose parents or caregiver gave informed written consent (and assent in children aged 7 years and above[13]) were considered eligible for enrollment into the study; while those with prior anti-malaria treatment (< 2 weeks) before presentation, those known to have background chronic illnesses like sickle cell anaemia, malignancy, allergic disorders, severe malnutrition (not due to HIV infection), and those with obvious clinical features of alternative causes of fever other than malaria were excluded.

Sample Size Estimation and Sampling Technique

A sample size of 140 was estimated using the statistical formula for calculating the sample size for cross-sectional studies,[10] based on a 9.1% prevalence of malaria among HIV-infected children in a previous study in Nigeria[11], a precision level of 5%, and an anticipated 90% response rate. All known HIV-infected children presenting with fever at the Paediatric ART clinic and all febrile children attending the EPU, POPD or PMW that were found to be reactive to retroviral screening during the study period, and met the eligibility criteria were recruited consecutively until the sample size was met.

Data Collection and Analysis

A proforma was used to obtain information on the socio-demographic characteristics (age, sex, educational and employment status of parents), and their clinical parameters (HIV status, ART treatment, clinical features of severe malaria, recent treatment of malaria and other symptoms that may present with fever e.g. urinary symptoms, respiratory tract infection), and the results of the laboratory tests (including blood film for malaria parasite, packed cell volume, random blood sugar, HIV serology test, HIV DNA PCR for confirmation of HIV infection, $CD4^+$T cell count) which were also done according to standard procedures.[16-19] The socioeconomic class of the parents was determined using Oyedeji's classification.[15] Data analysis was done using the IBM SPSS version 23.0 computer statistical software package. Comparison of arithmetic means was done using Student t-test, while comparison of proportions was done using Chi-square test, and Fisher's exact test where applicable, and the results were presented using frequency distribution tables. A p-value ≤ 0.05 was considered as significant.

Operational definition of terms

Severe *P. falciparum* malaria was defined using the WHO criteria[12] as a person with P. falciparum asexual parasitemia and one of the following clinical features: impaired consciousness or coma (i.e., a Blantyre coma score < 3 in children), prostration, failure to feed, multiple convulsions, acidotic breathing, circulatory collapse, clinical jaundice with evidence of other vital organ dysfunction, hemoglobinuria, abnormal spontaneous bleeding, and/or pulmonary edema. The laboratory findings can include: hypoglycemia (blood glucose < 2.2mmol/l or < 40mg/dl), metabolic acidosis (plasma bicarbonate < 15 mmol/l), severe normocytic anemia (Hb < 5g/dl or Haematocrit of < 15% in children), hemoglobinuria, hyperparasitemia (> 5% / 250,000 per µl), and renal impairment (serum creatinine > 265µmol/l).

Ethical Consideration

Ethical approval was obtained from UDUTH`s Health Research and Ethics Committee

(UDUTH/HREC/2015/No.341) while informed written consent was obtained from the parents or caregivers. In addition, assent was obtained from children aged 7 years and above.[13] Participants recruited were assigned identification numbers (ID) and the details were kept confidential by the investigator. The content of the consent form was read and interpreted in a language that the parent/caregiver understood. The consent form provided information on the importance of the study, the blood tests to be done, and need for anti-malarial treatment. Children with uncomplicated or severe malaria were treated according to the current WHO guidelines on treatment of malaria.[20,21]

RESULTS

Socio-demographic characteristics of participants

A total of 140 febrile HIV-infected children of which 71 (50.7%) were males and 69 (49.3%) were females. One hundred (71.4%) of the 140 participants were on ART, while 40 (28.6%) were newly diagnosed HIV- infected children who were not on ART (Figure I). The mean age of the HIV–infected children that were on ART was 6.00 ± 4.10 years while the mean age of the HIV-infected children that were not on ART was 4.20 ± 3.90 years, and there was no significant difference between the mean ages of the participants in the two treatment categories (t= 0.11, p= 0.315) [Table1]. Twelve (12.0%) of the 100 HIV-infected children that were on ART were in the upper socioeconomic class while none of the HIV-infected children that were not on ART was in the upper socioeconomic class and the difference in distribution of participants by socioeconomic class was statistical significant (χ^2 = 6.030, p = 0.049) [Table1].

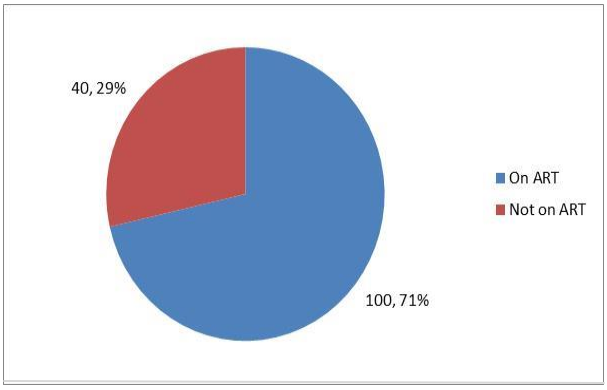

Figure 1: Distribution of participants by type of treatment

Prevalence of malaria among participants

Malaria parasite was demonstrated in 60 (60.0%) of the 100 febrile HIV-infected children that were on ART as compared to all the 40 (100%) febrile HIV-infected children that were not on ART (χ^2 = 25.6, p < 0.001) [Figure 2]. The prevalence of malaria among the HIV-infected children on ART was found to be significantly associated with age (χ^2 = 11.848, p = 0.003) [Table 2].

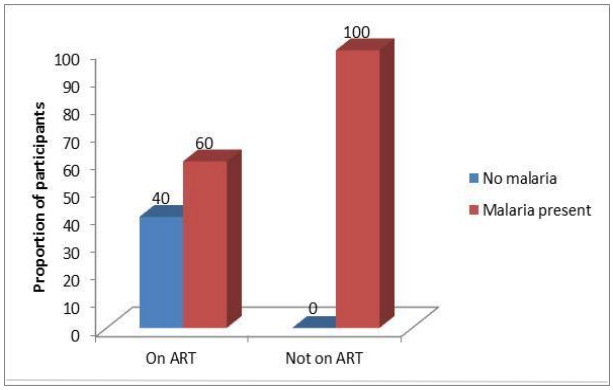

Figure 2: Prevalence of malaria by type of treatment

Severity of malaria among participants

Among the 60 HIV-infected children on ART who had malaria, 12(20.0%) had severe malaria compared to 34 (85.0%) of the 40 cases of malaria among the HIV-infected children that were not on ART (χ^2 = 25.6, p < 0.001) [Figure3]. Among the HIV-infected children on ART who had malaria, the severe form of malaria was significantly (p < 0.05) associated with sex, age and socioeconomic class (Table 3). The mean parasite density was 70,636 ± 52,821 among the HIV-infected children that were not on ART as compared with 62,357 ± 45,520 among the HIV-infected children that were on ART, but the difference was not statistically significant (t = 0.841, p = 0.09). Also, the mean $CD4^+$T cells count was 403 ± 168cells/ul among the HIV infected children on ART compared with 194 ± 67cells/µl in the treatment naïve patients, and the difference was statistically significant (χ^2 = 33.70, p < 0.001).

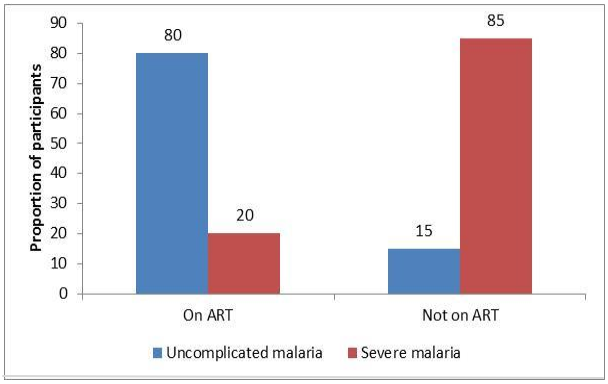

Figure 3: Distribution of severe malaria by type of treatment

Table 1: Socio-demographic characteristics of participants

Variables	Type of treatment		Test of significance
	On ART (n = 100) Frequency (%)	Not on ART (n = 40) Frequency (%)	
Age (years)			
Minimum	0.25	0.25	t = 0.11,
Maximum	15	15	p = 0.315
Mean	6.01 ± 4.10	4.2 ± 3.91	
Age group (years)			
0.25-5.0	43 (43.0)	26 (65.0)	χ^2= 11.848, df = 2
6.0-10.0	37 (37.0)	14 (35.0)	p = 0.003*
11.0-15.0	20 (20.0)	0 (0)	
Sex			
Male	60 (60.0)	12 (30.0)	χ^2= 11.504, df = 1
Female	40 (40.0)	28 (70.0)	p = 0.001*
Socioeconomic status			
Upper class	12 (12.0)	0 (0)	χ^2= 11.848, df = 2
Middle class	18 (18.0)	6 (15.0)	p = 0.049*
Lower class	70 (70.0)	34 (85.0)	

*Statistically significant, t = unpaired t test; χ^2= Pearson's chi-square test

Table 2: Distribution of malaria by socio-demographic variables among the study participants

Variables	HIV infected on ART (n = 100)		HIV infected not on ART (n = 40)	
	Malaria present Frequency (%)	Malaria absent Frequency (%)	Malaria present Frequency (%)	Malaria absent Frequency (%)
Sex				
Male	33 (55.0)	27 (45.0)	12 (100)	0 (0)
Female	27 (67.5)	13 (32.5)	28 (100)	0 (0)
	χ^2= 1.439, df = 1, p = 0.230		#	
Age group (years)				
0.25-5.0	19 (44.2)	24 (55.8)	26 (100)	0 (0)
6.0-10.0	29 (78.4)	8 (21.6)	14 (100)	0 (0)
11.0-15.0	12 (60.0)	8 (40.0)	0 (0)	0 (0)
	χ^2= 9.918, df = 2, p = 0.007*		#	
Socioeconomic status				
Upper class	4 (33.3)	8 (66.7)	0 (0)	0 (0)
Middle class	14 (77.8)	4 (22.2)	6 (100)	0 (0)
Lower class	42 (60.0)	28 (40.0)	34 (100)	0 (0)
	χ^2= 4.921, df = 2, p = 0.085		#	

*Statistically significant, χ^2= Pearson's chi-square test; # = no statistics were computed because malaria parasite was a constant

DISCUSSION

The significantly lower prevalence of malaria among the subject on ART may be because ART boosted immunity and increased CD4+T cell count thereby making CD4+T cells available to protect against malaria infection; this may be achieved by the destruction of pre-erythrocyte stages of the parasite in the liver by cytotoxic T-cells, and also by the production of anti-malarial antibodies by CD4+T-cells to control parasitaemia.[22,23] The lower prevalence could also mean that ART has direct anti-malaria property. Most of the available studies on prevalence of malaria in HIV-infected patients were carried out among HIV-infected patients that were not on ART in the era before the wide availability and high uptake of ART; Omoti et al[24] in Benin reported a malaria prevalence of 74% in HIV infected adults that similarly had fever (clinical malaria) but were not on ART. Okonko et al[11] in Ibadan, Nigeria reported a significantly lower malaria prevalence of 9.1% among HIV-infected children aged 3 days to 15 years that were not on ART, but only antibody testing for HIV was carried out, viral DNA PCR confirmation for children aged less than18 months was not done. As such, the HIV–infected population could have been under represented, thus resulting in the relatively low prevalence of malaria that was reported. Ahmed et al.[25] in Abuja, Nigeria, reported a malaria prevalence of 13.3% among HIV infected children aged 3-15 years that had no fever, it means the specificity of absence of fever in identifying correctly those that were free of malaria was 86.7%. This when compared with the overall prevalence of malaria of 71.4% among the HIV-infected

Table 3: Distribution of the clinical forms of malaria by socio-demographic variables among the study participants

Variables	HIV infected on ART		HIV infected not on ART	
	Uncomplicated (n = 48) Frequency (%)	Severe malaria (n = 12) Frequency (%)	Uncomplicated (n = 6) Frequency (%)	Severe malaria (n = 34) Frequency (%)
Sex				
Male	30 (90.9)	3 (9.1)	1 (8.3)	11 (91.7)
Female	18 (66.7)	9 (33.3)	5 (17.9)	23 (82.1)
	χ^2= 5.695, df = 1, p = 0.017*		χ^2= 0.5, df = 1, p = 0.452	
Age group (years)				
0.25-5.0	14 (73.7)	5 (26.3)	0 (0)	26 (100)
6.0-10.0	28 (96.6)	1 (3.4)	6 (42.9)	8 (57.1)
11.0-15.0	6 (50.0)	6 (50.0)	0 (0)	0 (0)
	χ^2= 21.99, df = 2, p < 0.001*		χ^2= 10.649, df = 1, p = 0.001*	
Socioeconomic status				
Upper class	4 (100)	0 (0)	0 (0)	0 (0)
Middle class	12 (85.7)	2 (14.3)	2 (33.3)	4 (66.7)
Lower class	32 (76.2)	10 (23.8)	4 (11.8)	30 (88.2)
	χ^2= 6.109, df = 2, p = 0.047		χ^2= 4.141, df = 1, p = 0.42	

*Statistically significant, χ^2= Pearson's chi-square test

children that presented with fever, meaning that the sensitivity of fever in identifying correctly those that had malaria was 71.4%. This may mean that fever is a possible sensitive clinical case definition for malaria and that in its absence, malaria may be unlikely.

The significantly lower proportion of participants with the severe form of malaria in the HIV group on ART could be because ART improves $CD4^+$Tcell count, controls malaria parasiteamia and also keeps malaria parasite density low; and according to the mechanical hypothesis of severe malaria, organ affectation is proportional to the number of sequestrated parasite within it.[26] The findings of this study highlight the benefits of ART in reducing the burden of malaria among HIV-infected children, and therefore provide additional evidence in support of the need to intensify efforts towards early diagnosis of HIV infection and prompt commencement of ART in HIV-infected children.

CONCLUSION

ART boosted immunity and reduced malaria prevalence and severity among febrile HIV-infected children. Efforts should be intensified towards early diagnosis of HIV infection and prompt commencement of ART in HIV-infected children.

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Source of support

Nil.

Conflict of interest

None declared.

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