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MALARIA PARASITAEMIA AMONG FEBRILE CHILDREN INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS IN THE CONTEXT OF PROPHYLACTIC COTRIMOXAZOLE AS STANDARD OF CARE: A CROSS- SECTIONAL SURVEY IN WESTERN KENYA

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ABSTRACT

***Objective*: To document the prevalence of malaria parasitaemia among the HIV infected febrile children in a malaria endemic area.**
***Design*: A cross-sectional study.**
***Setting*: An ambulatory paediatric HIV clinic in Western Kenya, between November 2011 and December 2012.**
***Subjects*: A total of 245 febrile HIV infected children aged less than 14 years attending the HIV clinic in the Webuye level IV hospital were included in the study. A systematic sampling method was used.**
***Main outcomes*: A blood sample was taken for malaria parasite testing. Presence or absence of malaria parasites was documented. Clinical and socio-demographic characteristics of the participants were also recorded.**
***Results*: A total of 245 participants were recruited mean age being 5.53 years. Malaria prevalence was 81.9%. Most participants (97%) were on cotrimoxazole prophylaxis. Some of the factors found to be positively associated with malaria parasitaemia were; male sex, care taker category (parent), WHO stage 3 and 4 of HIV disease, and a high absolute CD4 count. However, only the caretaker association was statistically significant.**
***Conclusion*: The frequency of malaria parasitaemia among febrile HIV infected children is still high regardless of the high cotrimoxazole prophylaxis uptake. It is also noted that there is a shift in the age group of fever among children toward the older age group. This implies that policies may need to be relooked at to include the older age group in the aggressive malaria prevention measures to avoid losing on the already made gains.**

INTRODUCTION

Fever is one of the most common reasons why parents bring their children to the outpatient setting of any health facility. The causes of fever in children in resource-limited settings, such as is in rural Kenyan health facilities, is rarely investigated; often diagnostic investigations are limited to the more readily available blood slide for malaria parasites and widal test (serology for Salmonella typhi). Even where these tests are available, clinicians often do not pursue them (1, 2)

Clinicians follow the Integrated Management of Common Childhood Illnesses (IMCI) protocol for fever management in addition to disease epidemiological pattern. These factors might not however always apply especially to an HIV-infected child, who is not only at risk of atypical infections but also likely to have atypical presentation of illness due to immunosuppression (3).

There is little data on common pathogens responsible for fever among HIV-infected children, especially in the context of cotrimoxazole use. Therefore, fever in HIV-infected children is commonly

managed in a similar manner like it is in HIV-uninfected children. This can result in inaccurate diagnosis, delay in proper management, and ultimately, serious morbidity and mortality.

Malaria and HIV co- infection is common especially in sub-Saharan Africa.In Kenya malaria transmission rates vary from one area to the other with areas around the large water bodies having the highest and the cooler areas experiencing the least. Nearly half, (49%), of Kenyan population lie in high transmission areas though concentrated in a small area of Kenya. The areas in Western province are high Malaria regions. Kenya has an HIV prevalence rate of6.7% (4,).

The effect of HIV on malaria seems not to have consensus especially in the paediatric population. Whilst in adults there seems to be clearer associations, in children there is scarce data (5).

Generally HIV appears to increase the incidence of malaria in adults. However, not many studies have evaluated this effect in children. A recent study in Tanzania (2012) provides the closest evidence to the effect that HIV infection is a risk for development of malaria (6). Villamor *et al.* had earlier in 2003 concluded that among the children they studied, 11.4% of HIV-infected versus 27.6% of HIV-uninfected developed malaria in the same country, Tanzania (7). Malaria associated morbidities have been shown to be worse in children co-infected with HIV. In Kenya and Malawi among others, HIV has been associated with increased incidences of severe anaemia (5). Hendriksen *et.al* showed that the prognosis of malaria in children with HIV was worse with 26% likely to die compared to 9% of those HIV-uninfected (3).

While in adults worsening immunity(declining CD4) is associated with increased malaria attacks, current data from children living in malaria endemic regions is limited and inconclusive (5,8). There has also been no demonstrated difference in risk of developing malaria among children when one is on ARVs (Antiretroviral) versus when not on ARVs (6). However, Akyalalshaku *et.al* showed being on ARVS was protective, he however considered all age groups (8).

While breast feeding and use of cotrimoxazole were shown to be protective in Tanzania (6), a review published three years earlier, had pointed out that data on the protective effect of cotrimoxazole on HIV infected children on malaria is scarce. This is unlike the clear statement that cotrimoxazole protects against malaria in HIV-uninfected (5).

WHO recommendation also state that confirmatory malaria test is necessary before starting children on anti-malarial contrary to the guidelines earlier on. However, the guidelines do not specifically guide on the management of febrile HIV infected children in malaria endemic areas especially considering the already documented high morbidity and mortality in this population (3, 5).

It is also recommended that all children who are HIV infected should be on cotrimoxazole prophylaxis. This also is known to be protective against malaria (9, 10). It is therefore expected that in a cohort of HIV infected children on cotrimoxazole the malaria burden should be low.

We set out to determine the prevalence and describe the clinical and socio-demographic factors associated with malaria parasitaemia in a cohort of febrile HIV infected children with high uptake of cotrimoxazole prophylaxis in malaria –HIV co endemic area. This study serves as an eye opener to the development of a management guideline specific for febrile HIV infected children in malaria endemic zone where cotrimoxazole prophylaxis uptake is high. The study seeks to answer the question is malaria still a priority cause of fever among HIV-infected children in the context of prophylactic cotrimoxazole as standard of care in a malaria-endemic region.

MATERIALS AND METHODS

A cross-sectional study of HIV-infected children with acute fever was carried out in an ambulatory clinic in malaria –HIV co endemic region of western Kenya.

The study was conducted at a level IV health facility, Webuye District Hospital, in Bungoma East District, Western Kenya which serves as a referral centre to several health centers and dispensaries; Webuye is a malaria-endemic area with annual transmission ranging from 20-40%; HIV transmission rate is about 5.1%(4,). The hospital houses one of the AMPATH (Academic Model for Providing Access to Healthcare) clinics, which serves HIV-infected children. AMPATH was founded in 2001 to address HIV / AIDS pandemic in Western Kenya; AMPATH now manages a cohort of over 22,000 HIV-infected or HIV-affected children in more than fifty-five clinical sites throughout the region. All children diagnosed with HIV are put on cotrimoxazole prophylaxis and may be protected from common organisms that cause fever including malaria.

Sample size was determined using Fischer's formula at 95% confidence level and a standard error of 5%. The estimated transmission rate among febrile children was estimated as is 17% from a study done in a Malaria endemic area in Kenya (11). This gave a minimum sample size of 217.

The study recruited 245 febrile children (axillarytemperatures of >37.5 degree Celsius) below 14 years with confirmed HIV infection following a consenting process with the parents or the guardian. Those children already on anti-malarial drugs or those with other obvious cause of fever were excluded.

A local research nurse performed patient recruitment and consenting. Data was collected by a trained research assistant and investigators and

stored on a password-protected study computer for subsequent analysis by co-investigators.

A peripheral venous blood sample was obtained from each child who met the eligibility criteria, and put into an EDTA bottle. This was used to prepare a thick blood smear which was then stained using Giemsa stain and examined under oil emersion power 100 for malaria parasites.

Two laboratory technicians examined the samples separately and a third one was used to resolve discrepancies for purpose of quality assurance.

Data analysis was done using the STATA version 10. Measures of central tendency were used to describe continuous variables while frequency tables were used for categorical data. Chi square and Kruskal Wallis test were used to test associations between the dependent and independent variable. All analysis was done at 95% confidence level.

Consent was obtained from the guardian or the parent of these children before any data was taken and before the samples were taken. No names were used instead subject numbers were assigned to each participant. The blood slide results were communicated to the primary care giver as soon as it was possible. No information deemed useful for the patient management was withheld from the primary care giver. Approval to carry out the study was sought from all the necessary authorities including Institution Research Ethics Committee of Moi University / Moi Teaching and Referral Hospital.

RESULTS

A total of 245 participants were recruited into the study with a male female ratio of 1.35:1. The mean age of the participants was 5.53 years with a range of 0.3 -12.78 years. Table 1 and 2 provides the characteristics of the study participants.

Table 1
Anthropometric and clinical characteristics of the study participants

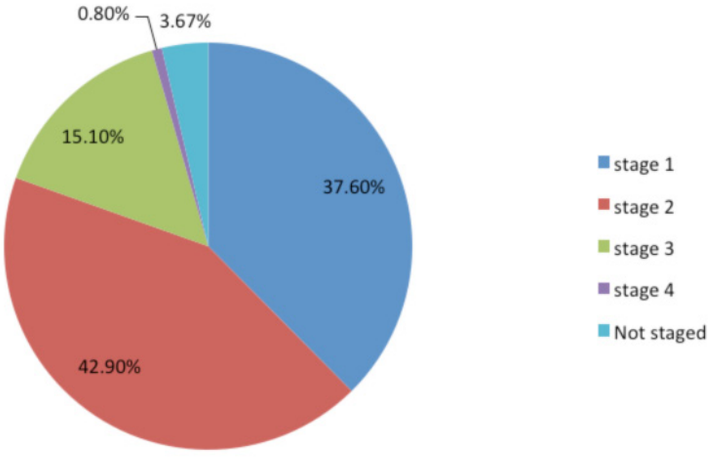
Variable	Mean(sd)	Range
Weight(kg)	19.3 (7.39)	5-48
Temperature oC	38.5 (0.44)	37.5-40.2
Respiratory rate (/min)	37.9 (8.31)	22-68
Pulse rate (/min)	109.3(18.28)	76-196
CD4 count (absolute)	239.4(1261.18)	2-18360

Table 2
Socio-demographic characteristics of study participants

Variable		Frequency(n)	% of n
Sex	Male	141	57.6%
	Female	104	42.4%
Residence	Bungoma East	136	55.5%
	Outside Bungoma East	109	44.5%
Informant	Mother	164	66.9%
	Father	35	14.3%
	Relative	30	12.2%
	Others	16	6.5%
Referrals	Yes	47	19.18%
	No	198	80.81%
Primary caretaker	Parent	199	81.2%
	Grandparent	12	4.9%
	Others	30	12.2%

A total of 80.5% of all subjects were in WHO clinical stage 1 and 2 with only 0.8% being in stage 4.

Figure 1
WHO clinical staging of HIV disease among the participants.



Most of the recruited participants were on cotrimoxazole prophylaxis for opportunistic infections (97%).

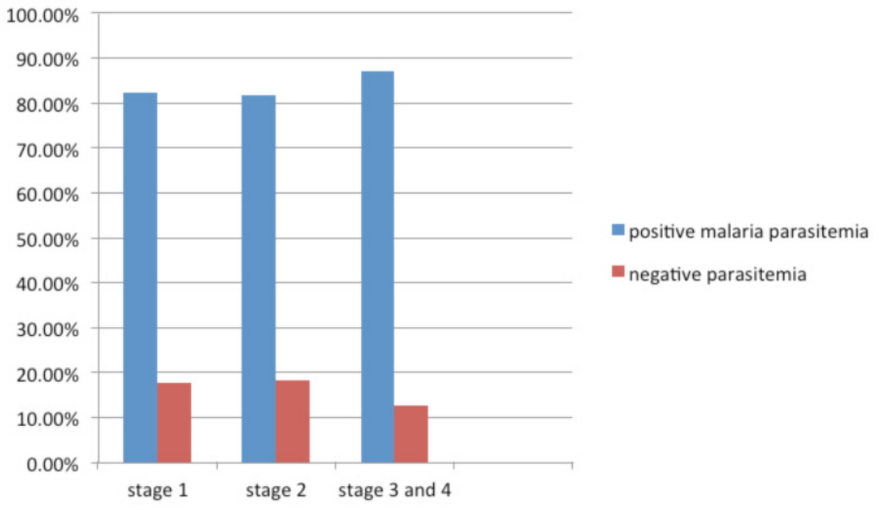
Apart from fever the other common clinical presentations found were general malaise in 85.3% of the participants, joint pains in 75% and vomiting in 34.7 %.

Malaria parasitaemia prevalence among the participants was found to be 81.9 %. Several clinical and socio-demographic factors were found to be positively associated with malaria parasitaemia among the febrile HIV infected children example male sex, caretaker (parent), WHO stage 3 and 4, and a high absolute CD4 count. However, only the caretaker factor was found to be statistically significant. Those children who had other persons or grandparents as care takers had a lower risk of malaria parasitaemia as compared to those who had a parent for a primary caretaker with an odd ratio and P-value of 0.164 (0.001) and 0.570 (0.520) respectively. Other persons in this case referred to children's homes and guardian's other than the grandparents (Table 3).

Table 3
Association between socio-demographic and clinical characteristics of the participants with presence or absence of malaria parasitaemia

Variable		Positive parasitaemia	Negative parasitaemia	p-value
Sex	Male	117 (83.6%)	23 (16.4%)	0.4281
	Female	82 (79.6%)	21 (20.4%)	
Caretaker	Parent	168(85.7%)	28(14.3)	0.0211
	Grandparent	9 (75%)	3(25)	
	Others	19(65.5%)	10(34.5)	
WHO HIV stage	Stage 1	75(82.4%)	16 (17.6%)	0.7341
	Stage 2	85 (81.7%)	19(18.3%)	
	Stage 3and 4	34(87.2%)	5 (12.8%)	

Figure 2
Malaria parasitaemia status by WHO clinical staging of HIV disease



The children with malaria parasitaemia were older, had higher mean weight, had a higher mean absolute CD4 count, and had a higher mean temperature, and a higher mean respiratory rate but all these associations were not statistically significant (Table 4).

Table 4
Malaria parasitaemia status versus means of clinical and demographic characteristics of participants

Variable	Mean for positive parasitaemia(s.d)	Mean for negative parasitaemia(s.d)	P-value
Age (years)	5.52(2.68)	5.51 (2.94)	0.9745
Weight in kg	19.45 (7.39)	18.44 (18.44)	0.5782
CD4 absolute	234.9 (1372.1)	112.39 (24.78)	0.4993
Temperature 0C	38.52 (0.44)	38.41 (0.46)	0.2090
Respiratory rate/min	38.04 (8.19)	37.22 (9.04)	0.4491
Pulse rate /minute	108.79 (16.46)	112.39 (24.78)	0.8945

Fever was found to have a positive predictive value of 81.9% for malaria parasitaemia among these febrile HIV infected children.

DISCUSSION

In our study there was a high male preponderance of the participants with a male to female ratio of 1.35:1. This is similar to a study conducted in Nigeria where they found a male /female ratio of 1.43:1 (12). The age distribution was almost equal with a slight shift to the older age group with a mean age of 5.53 years. This was unlike the Nigeria study where they found a high number of febrile children among the HIV population to be more in the age group of less than two years (12). Our findings somewhat supports the shifting epidemiology of febrile illness among children in malaria endemic areas towards the older children. This has been attributed to the extensive campaign on malaria control by the roll back malaria team. Some of the strategies focus mainly on the under five year olds and pregnant women, an example is the use of mosquito nets. This is a worrying trend that may lead to a loss in the already achieved gains in malaria control. Considering that these are HIV infected children and as we know the natural history of disease, we are most likely having lower immunity among the older children compared to the younger and therefore more prone to malaria and other opportunistic infections that will give you febrile illness. A recent study in Kilifi Kenya suggests that among febrile children admitted with severe malaria those infected with HIV were older than those were not infected (median 38 months and 19 months respectively). Also the older children had higher peripheral parasite density. However, there was no relationship between HIV infection and severe malaria among the infants hence suggesting stunting

age related acquisition of immunity to malaria among the HIV infected children (13).

Most of the children recruited had their primary caretaker being the parents (81.2 %) followed by grandparents. This is similar to the findings by Nyandiko *et al* who found an orphan hood prevalence of 10% in a cohort of HIV infected children in western Kenya (14). It was also a surprising finding that most of the children with malaria parasitaemia were those whose primary caretakers were the parents. It is expected that worse outcomes or findings are associated with other caretakers other than the parents. Nyandiko *et al* in western Kenya found that those with severe malnutrition were orphans (14). However the health seeking behaviour may be different for the different caretakers. It is expected that parents will seek more prompt health care and in health facilities while others will go for over the counter medications and therefore may get away without being seen in a health facility. It has also been reported in some studies that people tend to seek health care from the community level providers which are their areas of proximity especially if their economic status is poor (15).

The prevalence of malaria parasitaemia in this population of febrile HIV infected children was found to be quite high at 81.9%. This is much higher than in the general population of the area (Bungoma East district) which currently stands at 44.9% (16).However our population being a hospital based study may have been biased since these are sick children and are HIV infected. Imade et.al showed similar high prevalence in children below five years infected with HIV of up to76% in Nigeria (17). The number of fever episodes attributable to parasitaemia however cannot be determined from this study considering the study design. In another study in Nigeria a 65.8 % prevalence of parasitaemia was reported among febrile children and fever was reported to be highly predictive of malaria (18). It is necessary to conduct a cohort study to document this. It is also well known that not all parasitaemia episodes will result in clinical disease.

High asymptomatic parasitaemia have been reported in several studies hence the fever may be due to other bacterial infections or even drug reaction (19). Other causes of fever will include bacteraemia,urinary tract infections, and pneumonia with increased risk of serious disease in the more immunosuppressed (20). Some drugs used by the HIV infected children (Abacavir) have occasionally been reported to cause hypersensitivity that manifests with fever among other symptoms (21). Not all fevers equal infection. Fever is therefore a diagnostic challenge to the emergency physician; differential diagnosis is broad especially among HIV infected children in a malaria endemic area. Fever is a common presentation to the clinic among the HIV infected children. Nyandiko *et al* in his study in western Kenya reported that 15%of the children presented with fever at enrolment (14).

No differences were noted between the clinical characteristic of those with parasitaemia and those without parasitaemia. Clinical presentation of malaria is non- specific and hence the diagnostic dilemma of presumptive diagnosis.

CD4 count is one of the best predictors of the risk of an opportunistic infection. In our study we found the contrary that the meanCD4 count was higher among the children who had a positive parasitaemia as compared to those with negative parasitaemia (234.9 and 112.4 respectively). This was contrary to some studies in Malawi where incidence of clinical malaria episodes was higher in participants with CD4 cell count of less than 200 cells /mm3 than in those with a CD4 count of >75. Also higher density parasitaemia in patients with low CD4 count. This is however in adults and also varies on whether the patient is on ARVs or not. This trend was preserved even when more specific definitions of malaria were made (22). This however was not the case with the WHO staging where we found more of the febrile children to be in stage 3 and 4 and more parasitaemia frequency in the same advanced stages. It is good to note that the CD 4 count used in our case was the latest CD4 usually done six monthly in the clinic. This may have changed with time especially if the child had already been started on ARVs. The CD4 percentage was not available for all the children hence the absolute values were used. For the WHO staging the research assistants staged the children at the point of enrolment hence it reflects the actual stage at enrolment.CD4 count is also influenced by the disease state, for example, acute illness.

Most of the patients seen (97.1%) were on cotrimoxale (septrin) prophylaxis. This confirms the widespread scaling up of cotrimoxazole use as recommended by WHO. In the year 2007,in western Kenya only 25 % of the HIV infected children were on cotrimoxazole (14).Several studies previously have suggested that cotrimoxazole prophylaxis yields a reduction in malaria episodes though no reduction in the incidence of severe malaria. A study by Sandison *et al* in Uganda yielded a 39 % reduction in malaria incidence. In another study cotrimoxazole was also associated with an 83% protective efficacy (9, 10). We would thus have expected probably a lower prevalence of malaria parasitaemia. It is known that in the setting that this study was conducted that there is a high prevalence of malaria resistance to anti-folates however it has been shown that even in areas of high anti-folate resistance the protective effect of cotrimoxazole exists. In a study in Uganda a group of HIV infected population was found to have a high mutation dhfr 164l which is highly associated with anti-folates resistance and yet the cotrimoxazole yield significant protection (9, 10). Some of the anti-

retroviral drugs are also known to inhibit CYP 344 pathway involved in Lumefantrine metabolism hence causing high levels of lumefantrine which provides a prolonged post treatment effect hence reducing subsequent episodes. Most of the children usually have received anti-malaria (artemether / lumefantrine) drugs before coming to a level IV facility. Some though not documented in this study are on ritonavir hence we expected a lower level of parasitaemia. However we are unable to proceed with this argument due to limiting study design. We did not have sufficient numbers of patients not on cotrimoxazole to act as a control and hence make comparisons. Such a study would not be possible due to ethical reasons as cotrimoxazole has already been proven to provide protection against other opportunistic infections and hence cannot be withheld from the patient.

In conclusion, the frequency of malaria parasitaemia among HIV infected febrile children is still high regardless of the aggressive control methods being instituted. It was noted that those with malaria parasitaemia had a higher CD4 count. It is possible that most of the malaria we are seeing are carrier asymptomatic states and hence need to look for other possible causes of fever. Cotrimoxazol eprophylaxis uptake rate in the study population was quite high but still the parasitaemia rate remained high. There is an age shift towards the older children for malaria parasitaemia that requires urgent attention before the already made gains are lost.

RECOMMENDATION

Further studies need to be carried out to ascertain the fever that is attributable to malaria.

Studies require to know whether the wide spread use of septrin is contributing to high malaria prevalence by causing anti-folates resistance. The anti-folates anti-malarial are still being used by many of our primary providers before the patient gets to the health facility.

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