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Research Article

Prevalence of malaria among deceased HIV-infected patients: A comparative study of patients on versus those not on antiretroviral therapy in Western Kenya

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Abstract: Background: HIV and malaria infections coexist in patients in sub-Saharan Africa causing substantial morbidity and mortality. HIV infection has been associated with an increased risk of malaria. Objective: Our objectives were: 1) to determine the prevalence of malaria in HIV-infected patients who die while on antiretroviral therapy versus those not on antiretroviral therapy. Methodology: This was a cross-sectional study that was conducted among deceased HIV patients. The study targeted 268 patients in each group HIV-infected who are on ART and those not on ART through consecutive sampling method. Peripheral blood was collected and smear made, air dried and stained using GIEMSA staining technique. Slides were taken for microscopy examination from which quantification of the parasite, species identification and other microscopic features were observed. The participants were grouped as HIV infected who died while on ART and HIV infected who died while not on ART but *p. falciparum* status not known. The study applied univariate and bivariate analysis using SAS version 9.3 statistical package. We performed modified Poisson regression model using robust error variance to compare malaria prevalence rates among different groups. Results: The study had 258 patients in each group; patients who died while on ART and those not on ART. majority were female. Among those not on ART, 79.1% were in WHO stage III and IV compared to 68.4% among those on ART. The overall malaria was 15% with significant difference between those on ART and those not on ART (12.8% and 3.5% (RR 3.7, 95% CI 1.8-7.5). Patients aged 18-35 and 36-55 years, who died while on ART, had significantly higher prevalence of malaria compared to those not on ART (RR 6.2, 95% CI 1.5-26.9; RR 2.6, 95% CI 1.1-6.0 respectively). Malaria prevalence across CD4 levels was only significant for the CD4 cell > 200 cells/mL for those on ART compared to those not on ART (RR 5.5, 95% CI 1.3-23.2). Patients who were on Co-trimoxazole prophylaxis exhibited malaria prevalence (12.3%) comparable to the overall prevalence, for those who died while on versus those not on ART (3.3%) albeit lower rates. There was significant difference in anemia detected among patients dying while on ART and using Zidovudin regimen compared to those not using Zidovudin (p-value=0.001). Anemia was detected in 44.4% among those on Zidovudin compared to 66.4% among those not on Zidovudin. Conclusion: Malaria prevalence appears to be higher in deceased patients who died while on ART compared to those patients not on ART. Patients who were on Co-trimoxazole prophylaxis had partial protection against malaria. Deceased patients on Zidovudin had a higher rate of anemia.
Keywords: Malaria, HIV, Antiretroviral.

INTRODUCTION

In parts of the world where HIV and malaria overlap, co-infections are prevalent. This is particularly true in sub-Saharan Africa, where an estimated 40 million people are living with HIV and more than 350 million episodes of malaria occur yearly (Hewitt *et al.*, 2006, Saracino *et al.*, 2012). HIV and malaria impact each other: HIV increases the risk of acquiring malaria infection and development of clinical malaria and malaria increases HIV replication. However there are limited data on prevalence of malaria in HIV-infected

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patients who die while on antiretroviral therapy versus those not on antiretroviral therapy.

Even though malaria is not among the leading causes of death in HIV-infected patients (Saracino *et al.,* 2012, Rana *et al.,* 2000) it has been identified as the third most important source of HIV-related morbidity in Africa (Saracino *et al.,* 2012, Holmes *et al.,* 2003). HIV infection is expected to increase the morbidity and mortality attributed to malaria, since immunosuppression impairs the immune response to Plasmodium, determining more frequent occurrences of clinically severe malaria (Flateau *et al.,* 2011). However, the use of cotrimoxazole (CTX) prophylaxis and antiretroviral therapy (ART) in HIV-infected patients seems to provide a protective effect from malaria (Flateau *et al.,* 2011).

HIV may be associated with an increased risk of susceptibility to malaria infection (kublin *et al*.2005). Host immunity, as measured by CD4 cell counts, appears to increase the probability of development of malaria in HIV-infected patients (Laufer *et al.,* 2007, Whitworth *et al.,* 2000, Francesconi *et al.,* 2001, Patnaik *et al.,* 2001). There are conflicting reports as to whether HIV contributes to the severity of malaria infection (Laufer *et al.,* 2007, Grimwade *et al.,* 2004). Since HIV and malaria co-infection leads to a near one-log increase in viral load in chronically HIV-infected patients, and HIV increases susceptibility to malaria infection, there are concerns that co-infection may be contributing to further spread of both diseases. The potential impact of HIV on falciparum malaria has been difficult to determine because of diagnostic challenges and insufficient epidemiological data.

We conducted this study to determine the prevalence of malaria in HIV-infected patients who died while on ART and compared this in those who were not on ART

METHODOLOGY

Study design

This was a cross-sectional study.

Study Site

The study was carried out at AMPATH/MTRH clinics at MTRH Eldoret, Kenya (catchments population – 16 million; HIV prevalence – 7%). MTRH is the 2nd National Hospital in Kenya and serves as a referral center for the western Kenya region. It also serves as a teaching hospital for Moi University College of Health Sciences. The hospital has a bed capacity of 720.

Study population

The study was carried consecutively on participants who are AMPATH deceased patients, HIV-infected who are on ART and those not on ART between 2009 - 2014. HIV-infected patients who died while on ART were drawn from the Academic Model Providing Access to Healthcare (AMPATH) HIV care and treatment program.

Inclusion Criteria

Subjects who fulfilled the following criteria were included in the study: (1) deceased person was HIV-infected and enrolled in any AMPATH clinic; (2) on ART; (3) age >13 years ; (4) the next of kin signed the study informed consent form and; (5) The participant's Ampath adult clinical summary was present.

Exclusion criteria

Subjects who did not fulfilled the following criteria were excluded in the study: (1) Not deceased person; (2) not HIV-infected; (3) not enrolled in any AMPATH clinic; (4) on ART; (5) age <13 years ; (6) absence of the next of kin signed informed consent form and; (6) The participant's Ampath adult clinical summary was missing.

Human subjects' protection

The Moi University School of Medicine (MUSoM)/Moi Teaching and Referral Hospital (MTRH) Institutional Review and Ethics Committee (IREC) and the Indiana University School of Medicine (IUSOM) Institutional Review Board (IRB) approved the study.

Study Procedures

In order to minimize post mortem changes, specimen collection was done within 48 hours of death and a blood slide for malaria is taken immediately. Blood was collected from peripheral and blood smear were made, air dried and stained using GIEMSA staining technique. Once stained and dried, the slides were taken for microscopy examination from which quantification of the parasite, species identification and other microscopic features were observed.

Parasitemia was quantified using a semi-quantitative method give the scores as 1(+=1–10 parasites per 200 fields); 2 (++=11–100 parasites per 200 fields); 3 (+++=1–10 parasites per field); 4 (++++= more than 10 parasites per field). During the study, the following parameters were also examined; the blood smear quality (preparation), staining quality, sample quality and microscopic examination of smears.

Clinical and laboratory data was available for all adults admitted to a medical ward at the MTRH. Diagnosis was assigned by the ward clinicians based on fever and symptoms suggestive of malaria in the ward absence of signs of other infections and verified malaria.

The participants were grouped as follows; ***Group 1:*** HIV infected who died while on ART. Their HIV status is known but their *p. falciparum* Malaria status is not known. The study will screen them for *p. falciparum*. ***Group 2:*** HIV infected who died while not on ART. Their HIV status is known to be seropositive but *p. falciparum* status not known.

Statistical analysis

The primary outcome was positive malaria based on smear test. The explanatory variables included patients' age, gender, baseline CD4 count, latest CD4 count, HB, WHO stage, weight, and Co-trimoxazole (septrin) prophylaxis. Socio-demographic and clinical characteristics of the study participants were described using descriptive statistics, where appropriate. We compared proportions for categorical variables using chi-square test. Continuous variables were compared using the Wilcoxon rank-sum test. We performed modified Poisson regression model using robust error variance to compare malaria prevalence rates among different groups. Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) and p-value of less than 0.05 was used to define statistical significance.

RESULTS

The study had 268 patients in each group, that is, patients who died while on ART and those not on ART. Overall the study enrolled 536 patients in the study including an equal numbers of patients in the on ART and those not on ART. Comparing those on ART vs. those not on ART, there were significant difference in the hemoglobin among those who were not ART and those on ART were fairly similar (40.0 vs 38.0, 50.0 vs 50.0, and 11.1 vs 11.3 respectively) (table 1). The baseline CD4 count between the two samples was significantly different (p-value < 0.05) with patients not on ART having a lower CD4 count on average (Median 54A0 cell/mL, IQR 27.0-142.0) compared to those on ART (Median 165.0 cell/mL, IQR 50.5-333.5). There was significant difference (p-value < 0.05) in the proportion of patients' WHO stage between those not on ART and those on ART with majority of patients being in WHO stage III and IV. Among those not on ART, 79.1% were in WHO stage III and IV compared to 68.4% among those on ART. See results in table 1.

The overall malaria prevalence was 15% across the two group. There was a significantly difference among deceased patients on ART prior to their death compared to those not on ART (PR 12.8% vs 3.5% respectively; RR 3.7, 95% CI 1.8-7.5). When compared across various characteristics, the prevalence of malaria was high for patients on ART compared to those not on ART. For sex, male who died while on ART had malaria prevalence 6-folds higher than those not on ART (RR 6.6, 95% CI 2.0-22.0). Patients aged 18-35 and 36-55 years, who died while on ART, had significantly higher prevalence of malaria compared to those not on ART (RR 6.2, 95% CI 1.5-26.9; RR 2.6, 95% CI 1.1-6.0 respectively). The difference in malaria prevalence across CD4 levels was only significant for the CD4 cell > 200 cells/mL for those on ART compared to those not on ART (RR 5.5, 95% CI 1.3-23.2). Similar trend was exhibited for patients weighing ≥ 50 kgs (RR 5.4, 95% CI 1.9-15.4). Patients who were on Co-trimoxazole (septrin) prophylaxis exhibited malaria prevalence comparable, but slightly lower, to the overall prevalence for those who died while on ART versus those not on ART (PR 12.3% vs 3.35 respectively; RR 3.8, 95% CI 1.7-8.4). These results are presented in table 2.

Among those with HIV/Malaria co-infection, the prevalence of Anemia was lower in HIV-infected patients who die while on ART (44.8%) versus those not on ART (55.6%). However, the difference was not statistically significant (RR 0.8, 95% 0.4-1.6). There was significant difference in anemia detected among patients dying while on ART and using Zidovudin regimen compared to those not using Zidovudin (p-value=0.001). Anemia was detected in 44.4% among those on Zidovudin compared to 66.4% among those not on Zidovudin (Table-3).

Table-1.Baseline characteristics among HIV infected patients in Moi Teaching and Referral Hospital (MTRH), Eldoret, Kenya

Participants characteristics	Patients not on ART *(n=258)* **n(%) or median (IQR)**	Patients on ART *(n=258)* **n(%) or median (IQR)**	p-value
Demographic characteristics			
Sex (female)	134 (50.0)	153 (57.1)	0.0999
Age in years	40.0 (33.0-48.0)	38.0 (33.0-46.0)	0.2258
Weight (Kgs)	50.0 (42.5-60.0)	50.0 (43.0-59.0)	0.5031
Microbiological and clinical characteristics			
Baseline $CD4^+$ count(cell/mL)	54 (27.0-142.0)	165.0 (50.5-333.5)	0.0003*
Hemoglobin (g/dL)	11.1 (9.4-13.1)	11.3 (9.1-13.1)	0.6092
ART duration		8.0 (1.0-38.0)	-
WHO stage			
I and II	24 (9.0)	34 (17.4)	<.0001*
III and IV	212 (79.1)	134 (68.4)	
Missing	32 (11.9)	28 (14.3)	
ART regimen			
Second-line regimen		232 (86.6)	
Missing		36 (13.4)	

* Significant at α=0.05

Table-2.Comparison of patients' characteristics among HIV- malaria co-infected patients on ART versus those not on ART at Autopsy

Participants characteristics	**Patients not on ART n/N (PR)**	**Patients on ART n/N (PR)**	**Rate Ratio (95% CI)**
Overall	9/268 (3.5)	33/268 (12.8)	3.7 (1.8-7.5)
Sex			
Female	6/134 (4.5)	16/153 (10.5)	2.3 (0.9-5.8)
Male	3/134 (2.2)	17/115 (14.8)	6.6 (2.0-22.0)*
Age (years)			
18-35	2/93 (2.2)	13/97 (13.4)	6.2 (1.5-26.9)*
36-55	7/142 (4.9)	19/148 (12.8)	2.6 (1.1-6.0)*
>55	0/33 (0.0)	1/23 (4.3)	-
CD4 count (cells/mL)			
0-49	5/111 (4.5)	8/68 (11.8)	2.6 (0.9-7.7)
50-199	2/74 (2.7)	8/71 (11.3)	4.2 (0.9-19.0)
>200	2/58 (3.4)	13/69 (18.8)	5.5 (1.3-23.2)*
WHO stage			
I and II	4/24 (16.7)	5/34 (14.7)	0.9 (0.3-3.0)
III and IV	5/212 (2.4)	16/134 (11.9)	5.1 (1.9-13.5)*
Weight (kgs)			
< 50	5/123 (4.1)	11/105 (10.5)	2.6 (0.9-7.2)
≥ 50	4/145 (2.8)	19/128 (14.8)	5.4 (1.9-15.4)*
Co-trimoxazole prophylaxis	7/215 (3.3)	33/268 (12.3)	3.8(1.7-8.4)*

PR = Prevalence rate

* Significant at α=0.05

Table-3.Prevalence of Anemia in patients with HIV/Malaria co-infection who die while on ART versus those not on ART.

Characteristic	**HIV patients not on Zidovudin n (%)**	**HIV patients on Zidovudin n (%)**	**P-value**
Anemia			
No	51 (33.6)	45 (55.6)	0.001
Yes	101 (66.4)	36 (44.4)	

All the malaria cases among those on ART were taking Septrin. Therefore we were not able to assess the effect of combination of Septrin and ART on malaria prevalence since the comparison group should be malaria cases among those who were not using Septrin.

From the data, every patient among the group who were on ART was using Septrin. As such, since no one was not using Septrin, we were not able to deduce or make any comparison to the extent that we can quantify the effect of Septrin on CD4 count.

DISCUSSION

The findings of this study revealed that the overall malaria prevalence among deceased HIV patients was higher than the general population in Kenya (KDHS_) Comparing deceased patients on ART and those not on ART, there was s statistically significant higher prevalence among the patients ART. This study is one of few studies addressing the issue of malaria and HIV co-infection. This study findings are consistent with other study conducted in other studies. These findings also might imply that, the prevalence of malaria infection in hospitalized patients does not directly reflect the disease distribution throughout the entire population, due to the greater number of pathologies, especially AIDS-related opportunistic infections, which could require hospitalization in HIV-infected individuals (Saracino et al., 2012; Berg et al., 2008; Evans, 2004; Archibald, 2000). It also highlights that when evaluating HIV positive patients, results show that, malaria is not the most frequent diagnosis hence there is need for a rigorous approach for timely diagnosis of malaria among this population. Additional studies to better under these difference are needed to confirm our findings. Concerns have been raised regarding the reliability of malaria diagnosis in HIV patients (Laufer, 2006; Kublin, 2005; Brentlinger, 2007; Cohen, 2005).

According to the previous guidelines HIV Patients in care receive Co-trimoxazole (septrin) regardless of whether they are on ART as part of daily management of patients. Patients who are on Co-trimoxazole prophylaxis had partial protection against malaria. This could mean that treating HIV patients who are not on ART with Co-trimoxazole prophylaxis provide a cover by reducing the prevalence rate of malaria. These findings are in agreement with other studies as the protective effect of co-trimoxazole on parasite infection has been observed in clinical trials in children (Gasasira, 2010), pregnant women (Kapito-Tembo, 2011) and adults (Thera, 2005; Walker, 2010). However, Rates of resistance to co-trimoxazole and sulfadoxine-pyrimethamine ranging from 1% to 41% have been documented in malaria in other parts of sub-Saharan Africa. The substantial effect of co-trimoxazole prophylaxis on the frequency of malaria suggests that the prophylactic efficacy of an antimicrobial agent might not be accurately estimated by clinical resistance to treatment (Mermin, 2006; Kilian, 1998; Dorsey, 2002). Not forgetting that Co-trimoxazole targets dihydrofolate reductase and dihydropteroate synthetase, the same folate pathway enzymes as the antimalarial combination sulfadoxine-pyrimethamine. However in this study, Patients who were on Co-trimoxazole prophylaxis and on ART exhibited a higher malaria prevalence than those not on ART and on Co-trimoxazole. Additional studies are needed to understand the effect of combination of ART and Co-trimoxazole on malaria infection.

Anemia was associated with Zidovudin use. We were also able to show that among those with HIV/Malaria co-infection, the prevalence of Anemia was lower in HIV-infected patients who die while on ART (44.8%) versus those not on ART (55.6%). However, the difference was not statistically significant (RR 0.8, 95% 0.4-1.6). There was significant difference in anemia detected among patients dying while on ART and using Zidovudin regimen compared to those not using Zidovudin (p-value=0.001). Anemia was detected in 44.4% among those on Zidovudin compared to 66.4% among those not on Zidovudin. This finding is in agreement with other studies (Flateau, 2011).

The difference in malaria prevalence across CD4 levels was only significant for the CD4 cell > 200 cells/mL for those on ART compared to those not on ART (RR 5.5, 95% CI 1.3-23.2). The study findings support the theory that HIV increases the incidence of malarial fever and that ART, by restoring immune function, counters that effect. Other studies have also report the same (Mermin, 2006). Adverse effects of antiretrovirals and immune reconstitution syndrome further complicate the diagnostic process (Brentlinger, 2007).

Diagnostic challenges due to a multitude of factors, including high workload, poor facilities, unavailability and underuse of equipment and laboratory tests (Chilundo, 2004; Chandler, 2008; Reyburn, 2004; Thang, 2008) have contributed to the low prevalence of malaria observed in this study. The findings of this study emphasize that there is need to consider qPCR or immunochromatographic test as well together with microscopy in future analysis since the foregoing assays are highly sensitive and specific tools for post-mortem malaria diagnosis.

Majority of people in endemic areas have asymptomatic malaria parasitemia which increases the diagnostic challenges (Mayor, 2007; Imperato, 1986; Cohen, 2005; Makani, 2003; Whitworth, 2000; Laufer, 2006; Kublin, 2005; Mwangi, 2005; Kamya, 2006).

The low prevalence of malaria seen may be as a result of increased government eradication effort in Western Kenya region, but may also be as a result of

false negative malaria tests due to intake of effective or ineffective antimalarials prior to admission. Also as a result of inaccurate laboratory diagnosis. When diagnosing malaria using thick malaria blood smears only, this may result in an increased number of false negative blood slides (Chandler, 2008; Saracino et al., 2012).

Limitations

All the malaria cases among those on ART were taking Septrin. Therefore this study was not able to assess the effect of combination of Septrin and ART on malaria prevalence since the comparison group should be malaria cases among those who were not using Septrin. As such, since no one was not using Septrin, we were not able to deduce or make any comparison to the extent that we can quantify the effect of Septrin on CD4 count. Hence, further studies are needed to validate this association. While previous studies on the outcome of malaria largely used other treatment regimens (Patnaik, 2005; Chirenda, 2003; Shah, 2006; Djimde, 2003), this study was not able to document if the participants were treated with other malaria treatment regimens.

CONCLUSIONS

In conclusion, malaria prevalence appears to be higher in patients who died while on ART compared to those patients not on ART. Patients who were on Co-trimoxazole (septrin) prophylaxis exhibited malaria prevalence comparable, but slightly lower, to the overall prevalence for those who died while on ART versus those not on ART. Therefore the use of Co-trimoxazole prophylaxis provide partial protection against malaria infection. Anemia should be suspected and treated when patients are on Zidovudin regimen.

Recommendations

Since the trophozoite (ring-form) was somewhat degraded in some of the samples-perhaps secondary to autolysis, this may have compromised malaria diagnosis in some cases. We recommend the need to consider qPCR or immunochromatographic test as well together with microscopy in future analysis since the foregoing assays are highly sensitive and specific tools for post-mortem malaria diagnosis.

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