Health Sciences & Disease
The Journal of Medicine and Biomedical Sciences

Original Article

Features of Malaria among Patients HIV Infected in a Department of Infectious Diseases in Bamako

Caractéristiques du paludisme chez les patients infectés au VIH dans un service des maladies infectieuses de Bamako

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Keywords: Coinfection, malaria, HIV, Bamako, Mali
Mots-clés : Coinfection, paludisme, VIH, Bamako, Mali

ABSTRACT

Introduction. We studied malaria in HIV infected subjects hospitalized in the department of infectious diseases at Point G Teaching Hospital in Mali, with the objective to have current data on malaria in patients infected by HIV. **Materials and methods.** We conducted a prospective study from October, 1st 2016 to September 30th 2018 in patients seropositive for HIV having positive thick smear for Plasmodium and hospitalized in the department of infectious diseases at Point G Teaching Hospital. We collected sociodemographic, clinical and lab data form those patients. Data have been entered and analyzed using SPSS20.0 software. **Results.** Hospital frequency of malaria among People living with HIV was 24.4% (151/618). This population has a mean-age of 44.1±12.4 y/o and a sex-ratio (M/F) of 0.86. Majority of patients were at WHO stage IV of HIV infection (63.4%). Symptoms were by decreasing frequency: fever (98.3%); headache (86.4%); anorexia (72.9%); asthenia (61.0%) and vomiting (42.4%). the mean parasitemia was 172.9±352.1 trophozoite/mm^3. Mean hemoglobin level was 9.1±3.2 g/dl and the mean CD4 count was 9±3 cell/mm^3. Severe malaria was independent from WHO HIV stage and from immunologic deficiency. The malaria treatment when correctly followed conduct to good improvement of the anemia (p = 0.03) and the negativity of the parasitemia (p = 0.00). Death in our HIV patient is linked to association with severe malaria (p = 0,012). **Conclusion.** Malaria is relatively common and severe among PLWHA in Mali. Prompt treatment is still effective and must be implemented to ensure a good prognosis. Despite cotrimoxazole chemoprophylaxis, a certain number of PLHIV suffer from malaria, raising the hypothesis of plasmodium resistance to antifolates.

RÉSUMÉ

Introduction. Nous avons étudié le paludisme chez les sujets infectés par le VIH hospitalisés dans le service des maladies infectieuses du CHU du Point G au Mali, avec pour objectif de disposer de données actuelles sur le paludisme chez les patients infectés par le VIH. **Matériels et méthodes.** Nous avons mené une étude prospective du 1er octobre 2016 au 30 septembre 2018 chez les patients séropositifs au VIH ayant une goutte épaisse positive au Plasmodium et hospitalisés dans le service des maladies infectieuses du CHU du Point G. Nous avons recueilli les données socidémographiques, cliniques et de laboratoire de ces patients. Les données ont été saisies et analysées à l'aide du logiciel SPSS20.0. **Résultats.** La fréquence hospitalière du paludisme chez les personnes vivant avec le VIH était de 24,4% (151/618). Cette population a un âge moyen de 44,1±12,4 ans et un sex-ratio (M/F) de 0,86. La majorité des patients étaient au stade IV de l'infection au VIH selon l'OMS (63,4%). Les symptômes étaient par fréquence décroissante : fièvre (98,3%) ; céphalées (86,4%) ; anorexie (72,9%) ; asthénie (61,0%) et vomissements (42,4%). La parasitémie moyenne était de 172,9±352,1 trophozoïtes/mm3. Le taux moyen d'hémoglobine était de 9,1±3,2 g/dl et le taux moyen de CD4 était de 9±3 cellules/mm3. Le paludisme grave était indépendant du stade VIH de l'OMS et de la déficience immunologique. Le traitement du paludisme, correctement suivi, a conduit à une correction de l'anémie (p = 0,03) et à la négativité de la parasitémie (p = 0,00). Le décès de notre patient VIH était lié à l'association avec le paludisme grave (p = 0,012). **Conclusion.** Le paludisme est relativement fréquent et grave chez les PVVIH au Mali. Une prise en charge rapide reste efficace et doit être mise en œuvre pour avoir un bon pronostic. Malgré la chimioprophylaxie au cotrimoxazole, un certain nombre de PVVIH souffrent de paludisme, faisant évoquer l'hypothèse d'une résistance du plasmodium aux antifoliques.

INTRODUCTION

Malaria and HIV infection are two endemic infections with high burden in sub-Saharan Africa [1,2]. They are widespread and constitute overlapping diseases in the tropics [3]. World Malaria report states, despite recent advances, overall progress against global malaria control has stalled. In 2016, there were an estimated 216 million cases of malaria, about 5 million cases more than in 2015.

Ninety percent of these cases occurred in sub-Saharan Africa, where 25.6 million of the 36.7 million HIV-infected individuals live [4, 5]. In Sub-Saharan Africa most of HIV positive subject bear Plasmodium and/or antimalarial antibody [6]. In Mali, for HIV, according to UNAIDS, in 2016 the number of case was estimated to 110 000, with the majority in adults, women are the most affected with 66000 estimated cases [5]. For malaria, Malian health statistics in 2017 reported 2 097 797 cases of malaria of which 673 574 case were severe malaria. Among those cases, 1 050 deaths were observed giving a lethality rate of 0.050 per thousands. The HIV and Malaria association have been studied in Africa and the cause to effect relation between these two infections is controversy [7,8,9]. In Fact, HIV related cellular immunosuppression could increase the frequency and the severity of malaria by the loss of immunity in autochthone populations of endemic area. By the same, the occurrence of repeated malaria episodes could activate HIV replication which would result in a decrease of CD4 lymphocytes and then to a faster evolution toward Aids [13]. In Mali, a number of studies were conducted on HIV and malaria co-infection [10-14], both in population of blood donors and in hospital setting. Nevertheless those study were done since more than ten years while in the last decade, with new strategies, the configuration of both pathologies has changed principally in Africa. It is thus interesting to have current data on malaria in patients living with Aids in the main department of Infectious disease in Mali located in Point G teaching hospital.

MATERIALS AND METHODS

This study was conducted in the Infectious disease's department of Point G teaching hospital. This is the third level health care structure in Mali located in Bamako the capital town. The enrollment was prospective from October 2016 to September 2017. Study population consisted of in-patients of the department with positive HIV serology. Inclusion criteria was positive thick smear for Plasmodium, in patients who voluntarily give their informed consent to participate to the study.

The sample size was calculated by Schwartz formula [n=((〖z)〗^2 p(1-p))/d^2] using a confidence level of 95%, and the estimated proportion of malaria in HIV population from a previous study of 21.69 %. With error margin of 8 % the minimal size was 101.76 e.g. 102 patients.

For enrolment, after informed consent, all patients with HIV positive serology two tests "Immuno comb" and "Genie II" as recommended by the national HIV testing guideline, underwent Thick smear testing for malaria and all patient diagnosed positive for malaria were tested for HIV. All patient positive for the two diseases were enrolled. A biological check-up by T CD4 count, complete blood count was done at the time of malaria infection. Other lab test such as liver enzyme, blood creatinine, blood sugar, HIV viral load were also assessed. Treatment of malaria and other opportunistic infection were conducted according to national guideline of treatment. Highly Active Antiretroviral Therapy was also initiated after malaria treatment for HIV treatment naive patient.

Data were collected on individual previously tested case report form containing the following parameters: sociodemographic (age, sex, residence, job, marital status and schooling level); clinical examination: History researching disease on set and malaria risk factors; physical examination; complementary examination with previously cited lab test but also test for the diagnosis of opportunistic infections as needed; and clinical outcome. Data were entered and analyzed with SPSS 21.0 software. Chi square or Fisher- exact test were used according to convenience to compare proportions and Mann-Whitney test used to compare means in non-Gaussian distributed data. The significance threshold was set at $p \leq 0.05$.

All patients gave informed consent prior to enrolment. Confidentiality of data was guaranteed for all patient trough attribution of anonymous study number use in all record.

RESULTS

Sociodemographic data

From October 1st, 2016 to December 10th, 2017, 453 patients were admitted in the ward of infectious disease of Point G teaching hospital, of which 404 were tested positive for HIV, meaning a prevalence of 89,2% for HIV. Among these 404 patient, 101 (25%) had positive thick smear for malaria. The occurrence of malaria variate significantly according to months [Figure 1].

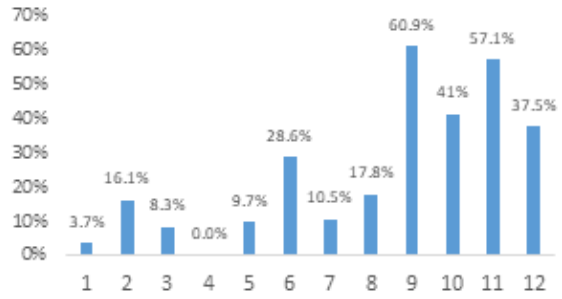

Figure 1: Monthly frequency of malaria cases among People living with HIV in infectious diseases department, Point G teaching Hospital, Bamako.

The mode of patient's age-group is 21 to 45 years old (y/o), the mean age was 41.9 ± 12.1 y/o with extremes of [17 and 75 y/o]. There were a majority of female with 58.4 %. Bambara and Fulani ethnicity were the most frequent with respectively 26.7 % and 22.8 %. Traders and housewives were the most represented social and professional class with respectively 28.7 and 24.8 % of the population. Patients in majority were living in Bamako (61.4%) principally in the sixth district. Patients were married in 70.3 % of case of which 39.6% were under monogamy regimen. For schooling, 65.3% went to French school with 47.5 % reaching primary level, 12.9 % secondary level and 5.0 % upper level [Table I].

Table I: Sociodemographic characteristics of malaria cases among People living with HIV in infectious diseases department, Point G teaching Hospital, Bamako

Variables		n (%)
Age group (Years)	[0 – 20]	2 (2)
	[21 – 45]	59 (58.4)
	[46 – More]	40 (39.6)
Sex	Female	48 (47.5)
	Male	53 (52.5)
Profession	Household	25 (24.8)
	Trader	29 (28.7)
	Farmer/Breeder	11 (10.9)
	Official	11 (10.9)
	Student	2 (2)
	Driver/Mechanic	8 (7.9)
	Worker/Artisan	13 (12.9)
	Retirement	2 (2)
Bamako Residence	District I	8 (7.9)
	District II	2 (2)
	District III	3 (3)
	District IV	10 (9.9)
	District V	12 (11.9)
	District VI	27 (26.7)
	Out of Bamako	39 (38.7)
Marital status	Single	12 (11.9)
	Married Polygamous	31 (30.7)
	Monogamous	40 (39.6)
	Widower	12 (11.9)
	Divorced	6 (5.9)
Schooling	Koranic school	14 (13.9)
	Primary	48 (47.5)
	French-speaking school Secondary	13 (12.9)
	Superior	5 (5)
	No schooling	21 (20.8)

Table II: Clinical characteristics of malaria cases among People living with HIV in infectious diseases department, Point G teaching Hospital, Bamako

Variables		N (%)
Use of mosquito nets	Yes, Impregnated	68 (67.3)
	Yes, Not impregnated	8 (7.9)
	No	25 (24.8)
Cotrimoxazole chemoprophylaxis	Yes	46 (45.5)
	No	55 (54.5)
Functional signs	Feeling feverish	92 (91.1)
	Asthenia	89 (88.1)
	Weight loss	80 (79.2)
	Anorexia	77 (76.2)
	Headache	56 (55.4)
	Vomiting	49 (48.5)
	Chills	36 (35.6)
Condition	Good	12 (11.9)
	Fair	20 (19.8)
	Altered	69 (68.3)
Temperature (°C)	≤ 37.5	36 (35.6)
	[37.6 – 37.9[	17 (16.8)
	≥ 37.9	48 (47.5)
Form of malaria	Uncomplicated malaria	36 (35.6)
	Severe malaria	65 (64.4)
Signs of severity	Neurological	38 (37.6)
	Anemia	26 (25.7)
	Renal failure	11 (10.9)
	Respiratory distress	8 (7.9)
	Jaundice	7 (6.9)
	Hypoglycemia	4 (4)
	Hemorrhagic abnormalities	4 (4)
	Macroscopic hematuria	2 (2)

Clinical and biological data

Malaria related

As prevention method, 67.3% of patients used impregnated bed net but also 45.5% of patient were taking trimethoprim-sulfamethoxazole chemoprophylaxis. Feeling fever, asthenia were the most frequent symptoms respectively in 91.1 % and 88.1 % of cases. Most of the patients had impaired general condition e.g. 68.3%. Patients presenting fever at the time of malaria diagnosis accounted for 64.3% of cases [Table II]. The most frequent clinical form was severe malaria with 64.4%, of which 37.6% presenting cerebral malaria and 25.7% severe anemia [Table II].

All parasitemia where due to *Plasmodium falciparum*. Patients with plasmodium parasitemia less to 200 trophozoïtes/µl where the most frequent (82.2%). The mean parasite density was 196.22 ± 412.85 trophozoïtes/µl of blood with extremes of [10 to 3000 trophozoïtes/µl]. Patients presenting anemia were the most frequent with 56.4% of moderate anemia and 25.7% of severe anemia. The mean hemoglobin level is 8.99 ± 2.85 g/dl of blood with extremes of [3.49-15.66 g/dl]. Few patients (3.4%) presented thrombopenia that was severe and moderate in 25.0% of cases. The mean count of platelet was 222780.68 ± 118470.13/µl of blood with extremes of [13300-573000/µl]. Patients presenting severe hypoglycemia accounted for 4.0% of cases, the mean glycaemia was 5.18 ± 2.06 mmol/l [1.3-18.40 mmol/l]. Kidney failure was noted in 10.9% of patient. The mean of creatininemia was 142.94 ± 183.25 µmol/l [33-1144 µmol/l].

HIV related

The majority of patient had severe immunosuppression du to HIV1, 63.4 % was classed at WHO stage 3 or 4. They have in majority a CD4 count < 200 cells/µl (69.4 %) with a mean CD4 count at 181.96 ± 216.75 [1-1114 cells/µl]. Patients with a viral load (VL) ≥100000 copies/ml were the most frequent 52.8 %, means VL was 925100.58 ± 1890475.91 [0-9150000 copies/ml].

Treatment of Malaria

Most of the patients were treated by Artemether + Lumefantrin combination (49.5%), injectable Artemether (38.6%), Artesunate (32.7%) and Quinine (3%).

After treatment the majority of patients (56.8%) recover. The mean hemoglobin before antimalarial treatment that was 7.9 ± 2.1 g/dl increased to 9.5 ± 2.3 g/dl after malaria treatment (p=0.03).

The mean glycaemia did not significantly changed before as compared to after the treatment of malaria (5.3 ± 2.7mmol/l vs 5.1 ± 2.3mmol/l ; p=0,64).

The mean creatininemia did not significantly changed between pre antimalarial and post anti-malarial treatment testing (196.5 ± 241.1 vs 143.1± 205.3 µmol/l; p=0.16).

Worsening factors of malaria among HIV infected subject

Patients with CD4 count lower than 200 Cells/µl with severe malaria were most frequent with 64 % as compared to those with higher CD4 count. But this difference were not significant (p=0.30). Most of the patients suffering of severe malaria (62.5%) were at WHO stage IV for HIV, but there were no statistically difference in the distribution of malaria clinical form and the WHO clinical stage of HIV infection (p=0.61).

HIV and malaria co-infected patients with hemoglobin level < 7 g/dl have a higher lethality (56.0%). But there were no statistically difference in the disease outcome related to hemoglobin level (p=0.13).

There were no statistically difference in the distribution of glycaemia and the disease outcome (p= 0.54). Nor in the distribution of malaria clinical form and trimethoprim-sulfamethoxazole chemoprophylaxis (p= 0.50). The mean parasitemia in patients taking trimethoprim-sulfamethoxazole chemoprophylaxis was higher as compared to patients without trimethoprim-sulfamethoxazole chemoprophylaxis (207 vs 187.2 trophozoites/mm^3). But this difference was not significant (p= 0.94). Patients with hospital acquired malaria had a significantly longer hospital stay than those with community acquired malaria (32.66 ± 23.63 days vs 15.57 ± 44.22 days; p= 0.05). CD4 count less than 200 cell/mm^3 increased the risk of nosocomial malaria (22.4% vs 5.8%; p=0.02).

Table III: Biological characteristics of malaria

Variables		N (%)
Parasitaemia (Trophozoites / µl)	< 200	83 (82.2)
	[200 – 800[	13 (12.9)
	≥ 8000	5 (5)
Pre-therapeutic hemoglobin level (g / dl)	< 7	26 (25.7)
	[7 – 12[	57 (56.4)
	≥ 12	18 (17.8)
Glycemia (mmol/l)	< 2.2	4 (4)
	≥ 2.2	97 (96)
Creatininemia (µmol/l)	>265	11 (10.9)
	≤ 265	90 (89.1)
CD4 count (Cells/mm^3)	< 200	50 (69.4)
	≥ 200	22 (30.6)
Viral load (Copies/ml)	< 100 000	17 (47.2)
	≥ 100 000	19 (52.8)

DISCUSSION

Frequency of malaria HIV infected patients

Thick smear confirmed malaria in seropositive HIV patients was 25% the peak of transmission was in the months of September, October and November with respectively 60.9%, 41.0% and 57.1% of admission. Dembélé found in his study a higher prevalence (33.1% e.g. 83/251 patients) but Keita a lower prevalence (21.6% e.g. 46/212 patients) [12,13]. These different results may be explained by the difference in the duration between these studies, our study covered two transmission seasons as previously described by Doumbo et al [20].

Socio-demography of malaria and HIV co-infected patients

Our patients were mostly females 52.5% (53/101). Almost all authors made the same finding because female are more exposed to HIV infection dues to social and economic conditions but also their biological constitution [10,13,14]. Only Dembélé found male predominance because his study was conducted in national blood bank in Bamako where the majority of volunteer blood donors were males [12]. As previously described in studies on HIV in Africa, the majority of our patients were young (58.4% aged between 21-45 y/o). But the mean age of 41.9 ± 12.1 y/o found in our study was slightly higher than the one found in studies conducted in Mali around 10 years before by Bane A and Keita PM respectively whose found a mean age of 32.5 ± 12.1 y/o and 34.4 ± 9.4 y/o [13,14]. With HAART, the HIV infected population expectancy of life is increasing, we are facing more and more an aging pattern in HIV epidemiology.

Patients were married in 70.3% of cases. This corresponds to the pattern in general population in Mali principally in the sexually active age groups [EDS V]. Our results are similar to Keita's one (69.6%) but higher than Dembélé and Bane's one respectively 56.6% and 42.6% [4,12, 14]. Most represented professions are traders (28.7%) and housewives (24.8%). Dembélé found (21.2%) of trader (17.3%) of students [12].

Clinic of malaria and HIV co-infected patients

In this study patients admitted were referred by outside doctor in 73.3% of case, generally in the hospital when in the other ward HIV serology is found positive doctor send patients to the infectious diseases department. But also HIV patients followed up in the ward as out-patient come back to the ward and can be hospitalized when severe illness occur. As antecedent, tuberculosis was found in 7.9% of patient e.g. 8/101. Biapo found a lower rate [10]. Main symptoms found in our patients were feeling of fever and asthenia in respectively 91.1% and 88.1% of cases. Our results was different from Biapo's one who found diarrhea, Bane's who found headache and arthralgia and Keita who found anorexia and asthenia as main symptoms [10,14].

Majority of patients had fever e.g. 64.3% at admission, this proportion was higher than the one in Keita's study (60.9%) and lower than the one in Biapo's (75%) [10,13]. The importance of fever despite the variations in signs shows the need to evoke malaria in case of fever in an HIV positive patient in a malaria endemic area. The majority

of HIV and malaria coinfected patients (63.4%) were at WHO stage IV. This proportion is higher than the result of Keita who found 52 % [33]. Moreover the majority of HIV patients who were at WHO stage IV for HIV suffered from severe malaria e.g. 62.5%. This result is higher than the finding of Bané A and Diapo K who respectively were 19.7% and 11.1 % [10,14]. Keita PM found 56.1% of patient at WHO stage IV suffering of severe malaria [13]. But there was no statistically significant influence of WHO stage. Other study in Mali found relation between severe malaria and WHO stage [12,14].

Biology

HIV1 was the serogroup mostly observed in our patients (93.1%). Dembélé and Biapo made the same observation with a lower frequency (respectively 85.7% and 88.8%) and Keita with a higher frequency (97.6%) [10,12,13]. We also found HIV2 in 4 patients and both HIV 1 plus 2 in 3 patient. This predominance of HIV1 is well known in the literature in our sub-region.

The majority of patients had anemia (82.1%), including severe anemia in 25.7% of cases. The hemoglobin level in patient appeared to be significantly improved after antimalarial treatment, an average increase of 1.52 g / dl (p=0.03). The frequency of anemia found in our study is higher than the one found by Kone in 2000 (70%) and Biapo (78.1%) [10,10]. Anemia can be related to malaria but also to HIV because of the effect of the virus itself, or opportunistic infection, or also of some antiviral drug like zidovudine or anti-opportunistic drug such as cotrimoxazole.

Sixteen percent of our patients with a CD4 count <200 cells/mm^3 had parasitaemia ≥ 200 trophozoites/mm^3. Our study did not show a significant relationship between parasite density and CD4 count as well as WHO classification. Bane in his study on HIV and Malaria Association, found a higher rate of 50% of seropositive patients with a parasite density of [101-1500] [14], he found then statistically significant association between parasite density and immunosuppression. This could be explained by the fact that in his study he made a comparison between patients immunocompromised to HIV and not.

Regarding the other criteria of severity of malaria few patients presented hypoglycemia lower than 2.2 mmol/l e.g. 4% and functional renal failure with creatininemia higher than 265 µmol/l e.g. 10.9% of our patients. There was no link between the evolution of blood glucose and antimalarial treatment. Our results show a lower frequency of hypoglycemia than Bane, which found 11.8% of hypoglycemic forms [14]. In his study the threshold for hypoglycemia was <3.5 mmol /l.

Treatment of malaria and HIV co-infected patients

The most commonly used route of administration for antimalarial drug in our study was injection (48.5%), similarly Keita in Bamako found 50% in 2007 [13]. This is linked to the national guidelines for severe malaria treatment. Even if this route is used at the beginning of the treatment, the relays was made by oral route with Artemether + lumefantrine as soon as possible. Keita in Mali in 207 used infusion of quinine in 80% of cases and Biapo in Cameroon used oral chloroquine in 55.5% of case [10,13]. This difference in used drugs is due to the change in the National guideline for Malaria Control Program through the time. Presently guideline recommends to use in first-line injectable artesunate for severe malaria and ACTs for uncomplicated malaria.

Outcome of malaria and HIV co-infected patients

We found an efficacy of antimalarial treatment with mean thick blood before treatment which was 1.0 ± 0 which increased by 0.81 ± 0.397. The difference was significant with a $P<10^{-3}$.

We found that the occurrence of nosocomial malaria could increase the duration of hospitalization of our patients. In his study, Biapo K found an average hospital stay of 24 ± 14 days in HIV + subjects with malaria at extremes of 2 and 60 days [10].

The clinical outcome after treatment in the majority of our patients was good but 38.9% of then died. Thus, this lethality rate could be due to the associated diagnosis. Our result is lower than that of Keita and Bane who found respectively 67.4% and 86.8% but higher than that of Biapo who found 8.33% [10,13].

Occurrence of malaria in HIV patient under Cotrimoxazole chemoprophylaxis.

In our study Among patients taking cotrimoxazole chemoprophylaxis prior to their hospital admission, and who were diagnosed for malaria, we observed more severe malaria (60.9%) than uncomplicated malaria (39.1%). Thus our study don't show a protection against severe malaria by cotrimoxazole chemoprophylaxis. In contrary, Bane A in his study on cotrimoxazole chemoprophylaxis in Bamako in 2009 found a low incidence of severe forms of malaria in patient taking correctly cotrimoxazole chemoprophylaxis: in 40 patients 36 had uncomplicated malaria vs 4 cases of sever malaria [14]. This difference could be related to the study population that was hospitalized patients with severe illness with confusing signs making malaria to be qualified as severe. Most of authors in the literature found cotrimoxazole chemoprophylaxis to protect against severe malaria [15-18]. We can formulate the hypothesis that malaria in HIV patient under Cotrimoxazole chemoprophylaxis could be caused by Plasmodium resistant to anti folate. The emergence of resistant parasite was a concern since the beginning of the use of cotrimoxazole as prophylaxis against major HIV opportunistic infection. Some authors thought that largescale use of Cotrimoxazole might accelerate parasitic resistance to this drug and limit its efficacy in the long term [19,20].

CONCLUSION

Malaria is common in HIV hospitalized patient in the ward of infectious diseases in Mali, it can be event hospital acquired. Severe form are frequent principally neurological malaria and severe anemia. Malaria seems to not be linked to immune suppression but had seasonal variation. Cotrimoxazole chemoprophylaxis doesn't avoid malaria occurrence but anti-malarial treatment shown their efficacy without avoiding patient's death because of comorbidities.

Conflicts of interest

The authors declare no conflicts of interest.

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