Malaria and HIV/AIDS in Cameroon: Antenatal care attendees as a case study in management of both infections.

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Abstract Malaria and HIV are common in Cameroon. In order to identify the possible relationships between these two infections we studied their occurrence among pregnant women in two districts (Kumba and Bamenda) where HIV testing is performed within the context of the prevention of mother to child transmission of HIV. Our study subjects were 870 pregnant women, aged between 14 and 45 (mean 25.1 years) of whom over 75% were in the 3rd trimester at booking. Positive *P. falciparum* blood smears were identified in 535 of the subjects, i.e. 61.5% of them while antibodies to HIV-1 were detected in 150 (17.2%) of the subjects.None had HIV-2. Among the 535 who had positive *P. falciparum* blood smears, 99 were HIV-1 positive (18.5%), compared to 51 (15.2%) in those who were smear negative. Also, among the 150 women who were HIV-1 positive, 99 (66%) were *P. falciparum* smear positive, compared to 436 (60.6%) of those who were HIV-1 negative. Thus, we found a higher ratio of *P. falciparum* positivity among HIV infected women than in those who were HIV-negative as well as a higher ratio of HIV seroprevalence among women who were *P. falciparum* smear positive than in those who were smear negative. Although these differences were not statistically significant, current evidence suggests that the diagnosis of either infection as well as therapy and preventative actions need to be done with due consideration of the possible effects on the other. The effect of these diseases on human development are sufficiently important to warrant an integration of HIV and Malaria control programmes as much as possible. It is at this price that we might achieve the Millennium development goals related to the control of these diseases.

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Introduction

Malaria and HIV/AIDS are common in most countries of sub Saharan Africa[1]. The World Health Organization estimates that together malaria and HIV cause more than four million deaths per year worldwide[2] In Cameroon, the overall morbidity due to malaria collated from clinical data is estimated at 40.1% (± 0.06%), whilst mortality, estimated from data obtained from 608,378 hospitalized patients is at 2.2% (± 0.03%).[3] In 2002, HIV/AIDS seroprevalence among the sexually active was estimated at 11.8% [4]. A recent demographic survey carried out in 2004 put the overall prevalence in the general population at 5.5%[5]. It is recognized that the effects of either malaria or HIV are severe in pregnant women[6,7,8] and that dual infections could result in worsening of either or both HIV and malaria in pregnant women[1]. Since September 2000, global health development strategies are guided by the United Nations Millennium Declaration[9], of which Millennium Development Goal (MDG) #6[10] seeks to halt and begin to reverse the spread or incidence of HIV/AIDS, malaria, and other major diseases, worldwide, by 2015. Indicators for this goal focus on high-risk groups and areas - for instance, HIV prevalence among pregnant women aged 15 to 24.

We therefore elected to study the association of malaria and HIV infections in antenatal clinic attendants in Cameroon with a view to identifying lessons that would apply to the management of both diseases in this population as we seek to achieve the MDG #6.

Methods

Study sites and subjects

The study was conducted in two high performing[11] health districts of Cameroon. We selected health facilities where all consenting booking antenatal clinic (ANC) attendees are systematically offered HIV testing before their subsequent enrolment into the programme for the prevention of mother to child transmission of HIV. The districts were Bamenda, in the North West province and Kumba, in the South West province. Kumba is a cosmopolitan town with 17 health areas and an estimated population of 311,688 inhabitants. This region has the highest transmission of malaria. Bamenda, equally cosmopolitan, has an estimated population of 259,927 with relatively less malaria transmission than Kumba. Each district was artificially divided into four equal quadrants. In each quadrant, all health facilities providing antenatal care were serially numbered. Through a ballot, one was randomly selected from which our study subjects were recruited. Every third booking ANC attendee was requested to participate in the study until we recruited about 100 per health facility. Since testing

Table 1. Distribution of subjects according to age and place of residence

Age of subjects	Kumba		Bamenda		Total	
	N	%	N	%	N	%
14 – 19	79	19.1	61	13.3	140	16.1
20 – 29	254	61.6	290	63.5	544	62.5
30 – 39	72	17.4	94	20.6	166	19.1
40 – 49	8	1.9	12	2.6	20	2.3
TOTAL	413	100.0	457	100.0	870	100.0

for malaria is not done routinely in the health facilities of these districts, consent was requested to have their blood tested for the presence of malaria parasites. Free treatment was offered to those whose slides were positive. All booking subjects who had symptoms or signs suggestive of malaria infection[12], or who could have been in early stages of labour were excluded from the study.

Data collection, laboratory methods and data analysis
A questionnaire was administered to record relevant demographic information including information on gravidity and parity. An aliquot of each routine blood sample collected was used for malaria parasite testing.

For malaria parasite testing, two samples each of smears and thick films were prepared on glass microscope slides, air dried and stained with the Diff-Quick stain (Field's stain). Each slide was examined at least twice by two of the investigators for the presence of asexual forms of *P. falciparum* and a blood film was classified as negative if no parasites were detected after counting 200 leukocytes.

HIV testing was done simultaneously with the Organon-Teknika ELISA test and the ELISA test. Discordant results were tested with the Line Immuno-Assay of Organon Teknika. All data from questionnaires were fed in to multivariate analysis software Epi Info version 3 of October 13, 2003. Student's t-test was used to compare means of normally distributed continuous variables; the Wilcoxon rank sum test was used to compare continuous variables with non-normal distribution, and the chi-square test was used for comparison of categorical variables.

Ethical considerations
This study was approved by the Ethical Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde I.

Results

Characteristics of the study population
870 antenatal clinic attendants participated in the study, 413 from Kumba district and 457 from Bamenda district. Their ages ranged from 14 – 45 years, with a mean age of 25.1 ±5.7 years (Table 1). The majority of them 663 (76.2 %) were in the 3rd trimester at booking, the mean gestational age being at 29.5 ±6.9 weeks. Concerning their pregnancy status, 229 (26.3%) of them were primigravidae, 478 (55.0%) multigravidae and 163 (18.7%) grand multigravidae.

P. falciparum parasitaemia and HIV among the study population (Table 2)
In this study, 535 (61.5%) of the women had malaria parasites on blood smear and 150 (17.2%) were HIV-1 positive, none had HIV-2. Among the 535 who had positive *P. falciparum* blood smears, 99 were HIV-1 positive (18.5%), compared with 51 HIV-1 positives (15.2%) among those who were *P. falciparum* smear negative. Also, among the 150 women who were HIV-1 positive, 99 (66%) were smear positive, compared to 436 (60.6%) of those who were HIV-1 negative. Thus, we found a higher ratio of *P. falciparum*

Table 2: Table showing relationship between malaria and HIV infection among 870 pregnant women from Kumba and Bamenda Districts in Cameroon.

		MALARIA		
		Positive	Negative	Total
HIV STATUS	Positive	99	51	150
	Negative	436	284	720
	Total	535	335	870

Chi-square ($\div^2$), 1.55 (p value = 0.2125); odds ratio 1.26 (95% CI: 0.86-1.86)

positivity among HIV infected women than in those who were HIV-negative as well as a higher ratio of HIV seroprevalence among women who were *P. falciparum* smear positive than in those who were smear negative. These differences were however not statistically significant (see table 2).

Discussion

Although previous reports failed to show any convincing and consistent link between malaria and HIV[13], current knowledge of the human immune response to malaria and HIV leads us to expect that either infection might influence the clinical course of the other. Many other infections are associated with a transient increase in HIV disease progression and the same may be expected of malaria. Also, the control of malaria parasitaemia is immune mediated; thus the immune deficiency resulting from HIV infection should, in theory reduce the immune response to malaria parasitaemia resulting in an increased frequency in clinical attacks of malaria.[14]

Malaria and HIV in our study subjects

Our study subjects were 870 pregnant women, aged between 14 and 45 (mean 25.1 years) of whom over 75% were in the 3rd trimester at booking. We found a prevalence of positive *P. falciparum* blood smears of 61.5% among 870 pregnant women. These correspond to current estimates from other studies[2,6] The overall prevalence of HIV in these women is 17.2%. Although this is consistent with current findings in our laboratory (Ndumbe P et al, unpublished data), it is much higher than would be expected from current reports[5]. These will be the subject of discussions elsewhere.

We observed a higher prevalence of *P. falciparum* parasitaemia in HIV infected women than in those who were non-infected. Also, we recorded a higher HIV prevalence in women who were smear positive for *P. falciparum* than in those who were not. Although these differences were not statistically significant, we consider that they are worthy of attention within the context of our control programmes. The non-inclusion of women with obvious signs and symptoms suggestive of malaria could have biased our population by eliminating those with major disparities as a result of the interaction of HIV and malaria[22]. The discussions that follow further substantiate this thesis.

How HIV affects malaria

Infection with the HIV-1 causes progressive cellular immunosuppression, and any resulting impairment in immune response to malaria might be associ-

ated with failure to prevent infection or to suppress parasitaemia and clinical disease[15]. Studies from Kenya[16] an Uganda[17] have reported an increase in the prevalence of *P. falciparum* in adults with HIV infection. HIV infected pregnant women with *P. falciparum* malaria have also been shown to have greater parasite densities in peripheral blood and placenta and are at a greater risk of fever, severe anaemia and adverse birth outcomes than HIV uninfected women[1]. In addition, HIV infection was associated with severe/complicated malaria and death from falciparum malaria in an area of unstable malaria transmission in KwaZulu Natal in South Africa[18]. Also, symptomatic malaria appears to increase HIV load.[19]

How malaria affects HIV infection

In Uganda, studies on 746 HIV pregnant women reported that HIV was transmitted to babies in 40% of cases where the mother also had malaria, compared to 15% for those without malaria[20].In pregnant Malawian women, placental malaria has been associated with a 1.7-fold increase in geometric mean peripheral HIV-1 RNA concentration and a 2.0 fold increase in geometric mean placental HIV-1 RNA concentration[21]. Another study in the Thyolo District of Malawi involved 367 HIV infected persons[22]. Among 334 aparasitaemic at baseline, viral load measurements were done at baseline, during malaria and after anti-malarial treatment (when possible). During the study, 148 developed malaria; complete data was collected from 77 of these. It was noted that levels of HIV in the blood almost doubled when patients got malaria; eight to nine weeks after being treated for malaria, HIV levels returned to what they were at the start of the study. This may be explained by the increase in production of lymphocytes in response to the malaria infection, leading to the activation and subsequent replication of the HIV. Thus malaria, especially if frequent, unrecognized, inadequately treated, or untreated, might lead to sufficient elevation of viral loads in HIV-infected adults to result in increased rates of HIV transmission and disease progression. Given the number of cases of HIV and malaria, even small increases in relative risks of HIV transmission and progression are important[23]

Antimalarial and Antiretrovial Drug interactions

The rapid increase in access to antiretroviral drugs coupled with the increased use of combination antimalarial drugs might lead to potential interactions which may be disadvantageous or indeed advantageous to the host[24]. Chloroquine and its analogue hydroxychloroquine have been shown to suppress HIV-1 and HIV-2 replication in vitro; also, there is some additivity between chloroquine and zidovudine in HIV infected cells and synergy with some PI drugs in T cell lines [25,26,27]. The anti-HIV activity recorded for chloroquine and mefloquine have been modest at best , and no anti-viral activity has been observed for halofantrine, amodiaquine and mepacrine.[28] The clinical significance of these findings is uncertain[16,29]. There is some evidence that HIV protease inhibitors may alter disease outcomes of coinfected patients. This is based on the observed antimalarial effects with protease inhibitors saquinavir and ritinavir *in vitro*[30] ; possibly due to the down regulation of CD36, a key receptor mediating the cytoadhesion of parasitized erythrocytes to endothelial cells[31].

Prospects for more concerted control of both malaria and HIV infections

Policy

Malaria and HIV are two of the most common diseases in Sub-Saharan Africa; it is estimated that at least 38 million Africans are infected with the HIV-1[32], and that 300 million to 500 million suffer from malaria each year[33]. Therefore any interaction between these two diseases will be of public health importance. Public policy should therefore be towards a coordinated effort in the control of malaria and HIV in areas where both diseases are endemic. These two diseases overlap on both the social and biological levels, as the poorest in society are most likely to be infected by HIV and least likely to have access to preventative interventions against malaria. Thus, it is crucial that health services in developing countries integrate programmes treating HIV/AIDS and malaria. The very first action would be the implementation of the malaria control programmes and the HIV control programmes in all countries in a manner that would increase the efficiency of both programmes.

Diagnosis

Despite the availability of the technology, universal blood screening is not yet achieved in most parts of Africa, including Cameroon. The process of equipment of HIV laboratories should be accompanied with the equipment and training in malaria diagnosis. It is worth noting that patients with HIV infection may have a false positive test for malaria; therefore serological tests for malaria may not be useful as surrogate tests for assessing the travel status of individuals[34]. However, the current point-of-care serologic tests are more specific than the first generation ones which were evaluated in the study. The process of conducting tests for malaria by peripheral smear examination, without adequate protective measures might increase the transmission of HIV infection through needle pricks[35]. It is noteworthy that the presence of malaria might influence the quality of the HIV antibody response of the host thus resulting in either false positive (cross reacting antibodies to other infectious agents), or false negative (poor quality of antibodies produced due to immunoregulation).[36] ,[37]

Therapy

Antimalarial measures might be important for HIV infected persons who may not yet be eligible for antiretroviral therapy. Also, antimalarials should be made available to all subjects who might be at risk of malaria such as HIV infected persons, and pregnant women amongst others. Programmes should think about making antimalarials free or subsidized in the same manner as anti-retrovirals. The use of blood transfusions in the treatment of anaemia needs to be very well regulated as this might be a source of infection with the HIV.

Preventative actions

HIV infected persons should be encouraged to avoid malaria infections. Preventative interventions such as the use of insecticide treated bednets should be expanded to the poor in general and to those likely to have HIV or who are living with HIV/AIDS. Other personal actions such as the use of

mosquito repellents on skin or clothing should be encouraged and where possible provided for, as well as the use of antimalarial chemoprophylaxis. These should be reinforced in the vulnerable groups such as pregnant women and children. Indeed preventing and treating malaria during pregnancy could be a beneficial and cost-effective means of reducing the transmission of HIV from mother to newborn. Messages given to persons who attend antenatal clinics should include both HIV and malaria as should messages given to STI clinic attendees or HIV infected persons on routine follow-up visits. The latter should be provided insecticide treated nets free of charge. Also laboratory services as well as maternity services should be reinforced to ensure proper barrier nursing and the use of gloves in delivery. This will help protect both the health worker and the user of health services. Finally, it will be essential that ours services are solicited in time to permit any useful interventions. The fact that over three quarters of the women in our study went to the antenatal care services in the third trimester of pregnancy is quite telling on the efforts that need to be made in ensuring the timely use of services.

Conclusions

The knowledge of how malaria and HIV diseases interact is still not clear because of gaps in many key areas. Some interactions between treatments of these two diseases may occur, but the magnitude of these and their eventual effects are still not clear. Whatever the case, there is sufficient evidence that these diseases affect each other negatively. It is necessary that current intervention strategies for both HIV and malaria are implemented as they ought, with special emphasis towards ensuring appropriate cover to the poor and vulnerable of our societies and to the integration of these services whenever possible.

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