Malaria/HIV Interactions in Nigeria - A Review

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ABSTRACT

BACKGROUND
Malaria and HIV are two of the most common and important health problems facing developing countries and Nigeria being the most populous African country bears a very high percentage of this burden. This article is an attempt to review the published articles on the co-infection of the two diseases available in literature from Nigeria.

METHODS
A review of the literature on the subject was done utilizing google search, Medline, PubMed and other available literature. The keywords were Malaria and HIV; Interactions and Nigeria.

RESULTS
Malaria and HIV constitute major public health threats responsible for significant morbidity and mortality in the country. Malaria and HIV are diseases of poverty resulting in over 4 million deaths a year. Both diseases are highly endemic, with a wide geographic overlap in sub-Saharan Africa and Nigeria. The management of the co-infection is a major challenge to the public health system. Of particular importance is the potential drug-drug interactions involved in the management of the co-infections as a result of co-administration of the drugs which have not been adequately investigated.

CONCLUSION
Despite the endemicity of both diseases in Nigeria, there is paucity of data on the interaction of the two diseases.

KEYWORDS: Malaria; HIV/AIDS; Co-infection; Nigeria; Review

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INTRODUCTION

Malaria is a protozoan infection in humans caused by the parasite Plasmodium which until recently was thought to be classified into four species *P. falciparum, P. ovale, P. malariae* and *P. vivax*. However current studies has shown that there are two non-recombining species of *ovale* (*ovale curtisi* and *ovale wallikeri*) which are non-sympatric in nature1,[2]. Of all these species, *Plasmodium falciparum* malaria is the commonest specie in virtually all parts of Africa accounting for up to 98% of the confirmed malaria cases[3]. *Plasmodium falciparum* is the agent of the most malignant form of malaria, usually presenting with severity mostly in children in sub-Saharan Africa[3]. *P falciparum* malaria is also associated with the highest rates of complications, morbidity and mortality in Nigeria[3].

The first symptoms of malaria are non-specific and similar to the symptoms of minor systemic viral illness. The characteristic presentation of uncomplicated malaria includes fever, headache, joint pains, weakness, muscle pains, chills and rigors, anorexia, nausea and vomiting. Orthostatic hypotension and abdominal pain may also occur and in children and in severe cases with hemolysis[4].

The severity of clinical malaria depends very much on the acquired immunity and intensity of malaria transmission in the area of residence[4,5]. In areas of stable transmission which prevail in much of sub-Saharan Africa, partial immunity to clinical malaria has been acquired in early childhood therefore clinical diseases is almost always confined to young children who suffer high parasite densities and acute clinical disease[4]. The risk of severe malaria is also higher in pregnant women and in immunosuppressed individuals.

Half of the world population is at risk of malaria and an estimated 243 million cases occurred in 2008[4,5]. Of these, there was an estimated 863,000 malaria deaths, 767,000 (89%) of which occurred in Africa where malaria is the leading cause of mortality in children under 5 years [5,6]. However the World Malaria Report, 2011 indicates that over a period of two years, the malaria cases have reduced from 243 million cases in 2008 to 216 million in 2010 and the number of deaths have reduced to 655, 0007. Despite this reduction, the global burden of malaria has remained very high especially in the tropics.

The National Population Commission and National Malaria Control Programme reports that malaria is responsible for 30% childhood death, 25% of death in children below one year and 11% maternal death8. Nigeria bears up to 25% of the malarial disease burden in Africa, hence contributing significantly to the one million lives lost per year in the region 9. Treatment of malaria illnesses accounted for 40% of the curative health care cost incurred by households10. The indirect cost of malaria cannot be quantified, but malaria has been shown to have a long term effect on the cognitive function and educational attainment in children[11,12].

HIV/AIDS

The acquired immune deficiency syndrome (AIDS) is defined as the state of profound immunosuppression produced by chronic infection with human immunodeficiency virus (HIV). Many theories have been projected as the origin of HIV. It has however been accepted as a descendant of the African Green monkey virus, the Simian immunodeficiency virus (SIV) virus because of the similarities between the two viruses[13] .

HIV is a retrovirus that belongs to the family of Lentiviruses from the retroviridae. There are two types of HIV -types 1 and 2. Both HIV-1 and HIV-2 replicate in CD4 T cells and have been documented as causative agents of AIDS. HIV-1 is more virulent than HIV-2, more easily transmitted and is the cause of the vast majority of infections globally[14]. In Nigeria, HIV-1 sub-types A and G are predominant ones in circulation 15. Report (UNAIDS, 2011) shows that by 2010, about 34million people were living with HIV/AIDS of which 2.7million are new infections and the greatest burden is in sub-Saharan Africa where an estimated population of 22.9million (68%) of HIV-infected people live[16].

Nigeria is ranked second in the number of people living with HIV/AIDS after South Africa and accounts for about 9% of the global HIV burden[17]. AIDS was first reported in Nigeria in 1986. Currently an estimated 3.1 million people are living with HIV/AIDS with a national prevalence of 4.1%[18]. Nigeria has the second highest number of new infections yearly and about 80% of HIV transmission is through the heterosexual route[17]. Another major route of transmission is the mother to child accounting for about 360,000 children with HIV. In settings as obtained in Nigeria, where heterosexual transmission is common, women are more likely to be affected in the epidemic thereby increasing the burden of mother to child transmission. The high prevalence of HIV in women of reproductive age has led to a growing population of HIV–infected and affected children. It is estimated that one HIV- positive child is born every five minutes, in Nigeria[19] .

Malaria/HIV interactions

The interaction between malaria and HIV is made manifest in three main ways namely disease, treatment and transmission issues

and these can be reflected in any of the areas such as increased prevalence of malaria, severity of malaria in HIV disease or as increased immunosuppression in HIV persons infected with malaria. The interaction of these two conditions has been described as a collision of two titans[20] due to the impact of the co-infection on public health[20].

In stable malaria situations there is acquired immunity with increasing age due to continued exposure. HIV erodes this immunity leading to increased parasitaemia and fever[21].

HIV co-infection is thought to contribute to 3 million additional malaria cases, higher malaria parasite densities in immunosuppressed children and a 5% greater mortality. [22,23].

Malaria has been associated with a rise in viral load and a fall in CD4 cell count potentially worsening the clinical course of people with HIV infection[24,25,26]. An important study from Malawi showed that HIV-1 plasma viral loads were significantly higher in patients with malaria infection than in those without and these levels remained higher for up to 10 weeks after treatment[24]. The increases in viral load were greatest in those with clinical malaria and high levels of parasitaemia. This is supported by another Malawian study which revealed that HIV-1 viral burden is higher in patients with *Plasmodium falciparum* than in controls and thus viral burden can in some patients be partly reduced with antimalarial therapy[25].

Malaria/HIV interactions have been clearly demonstrated in young children in whom malaria induced anaemia leads to blood transfusions which may transmit HIV[24]. In pregnant women HIV also contributes to higher malaria infection rates, higher parasite density, more clinical illness, more anaemia and a diminished response to treatment[27]. Another study on malaria in HIV observed that HIV-1 infected malaria patients had lower haemoglobin (Hb) compared to HIV-1 uninfected patients[28]. It is thought that malaria/HIV interaction is a contributing factor to the reversal of the gradual declines in malaria mortality in the 1990s, the period during which HIV was at its peak[29].

The control of malaria parasitaemia in untreated individuals is immune mediated, and this prevents most malarial infections from becoming clinically apparent in semi-immune adults in endemic areas[21]. This suggests that HIV-associated immunosuppression interferes with parasite control. The above report also stated that HIV infection may reduce the efficacy of immunity which protects persons with parasitemia from clinical disease and may reduce the effectiveness of the acquired protective immune response that prevents parasitemic persons from developing clinical illness[30].

HIV infection impairs T-cell immunity, which is of crucial importance for antimalarial responses[31]. The immunosuppression caused by HIV infection, affects the acquisition and persistence of immune response to malaria[32]. On the other hand, malaria infection activates T cells, potentially promoting HIV replication [33,34]. Since increased HIV RNA levels are associated with accelerated disease progression, malaria could potentially facilitate faster progression to AIDS and death[35]. In areas of stable malaria transmission, as obtained in sub-Saharan Africa, malaria infection rates and the frequency of clinical illnesses (fever and other findings) appear to be increased in HIV infected adults particularly those with immunosuppression as measured by low CD4 T cell counts. A study involving Ugandan adults, observed that the odds of parasitemia, and risk of malarial fever increased with decreasing CD4 cell count, such that individuals with CD4 cell counts<200cells/μl were more than twice as likely to suffer malarial fever as individuals with >500 cells/μl[21,36]. Increased prevalence of severe malaria has also been reported in HIV-infected adults in South Africa[37].

With the above reports and records it can be predicted that the efficacy of antimalarial therapy will be lower in immunosuppressed individuals co-infected with HIV and malaria living in regions of stable transmission. Increasing parasite burdens and reduced host immunity, both of which occur with HIV infection, are associated with increased treatment failure rates[4]. A Ugandan study observed that HIV-1 infection was associated with a >3-fold hazard ratio [HR] increased risk of clinical treatment failure of adults treated with three different antimalarial regimen including an ACT[38]. In a study of delayed clearance of *Plasmodium falciparum* in patients with human immunodeficiency virus co-infection, Birku et al, demonstrated a prolongation in fever and parasite clearance time in adults following Artemisinin treatment for uncomplicated malaria[39]. Further study established clinical failure to chloroquine therapy in HIV-positive children in comparison with HIV- negative children[38]. This decrease in response to antimalarial therapy in immunosuppressed individuals could be attributed to the fact that HIV infection impairs T- cell immunity, which is of crucial importance for antimalarial responses[31]. It could also be because of increased susceptibility to malaria re-infection or because of recrudescence of infection since antimalarial therapy is most effective in individuals who already have some acquired immunity[30,40].

Influence of HIV on the emergence of antimalarial drug resistance.

The effect of malaria/HIV interactions on transmission issues is reflected in the area of antimalarial drug resistance. Gametocytes of Plasmodium parasite which circulate in the blood stream of the infected individual and are taken up from the blood stream of the victim by the vector Anopheles. These gametocytes undergo sexual reproduction in the midgut of the mosquito and ultimately produce sporozoites which are injected into the blood stream of another victim during a blood meal. Mosquitoes carrying gametocytes of resistant parasites are through this means transmitted and thereby continue the spread of antimalarial drug resistance in the environment. Hence the drugs that have effect on gametocytes can be used to reduce the spread of resistance[41].

Among factors that influence antimalarial drug resistance are host immunity, high parasite density and drug pressure[21,36,40,42]. In HIV-positive individuals, immunity is compromised. Other factors contributory to drug resistance are frequency at which resistance mutation occurs in a population and the number of parasites exposed to drugs. In HIV-infected individuals, there is increased probability of malaria infection progressing to symptomatic illness and to higher parasite densities, thereby increasing the probabilities of treatment being required and thus of contact between parasites and the drug.

The resulting effect is increased drug exposure and thus selective drug pressure[21,36,43]. Other consequences which include the prolongation in fever and parasite clearance time in HIV-infected patients; higher risk of treatment failure and higher rates of recrudescence, accelerate the spread of resistant parasite biomass in both symptomatic patients and asymptomatic HIV-infected people[38,39,44,45].

Effect of the Co-infection in the areas of Drug-Drug Interactions

Management of co-infection with malaria and HIV is a major challenge to public health yet potential drug-drug interactions between antimalarial and antiviral regimen have not been adequately investigated in people with both infections. Djimde and Lefevre (2009) in their study on the pharmacokinetics of artemether-lumefantrine (Coartem) stressed the need for additional data on the pharmacokinetics of artemether-lumefantrine in patients undergoing HIV/AIDS chemotherapy[46]. The mortality and morbidity of the two diseases is already high, and if the interaction of the treatment undermines the efficacy of the antimalarial drug, the risks of adverse outcomes will be increased. This scenario may necessitate the modification and

optimization of therapy; it may even worsen the problem of drug resistance, or result in the elevation of the concentration of the antimalarial leading to a possible increase in toxicity. On the other hand, the elevation may be an advantage in enhancing the antimalarial effect especially with antiretrovirals that possess antimalarial activity[47,48,49].

The choice of antimalarial drug for the treatment of HIV-positive patients therefore is of utmost importance considering the dangers of co-morbidity. However sufficient pharmacokinetic and parasitological evidence to make this choice is currently lacking because very few studies have been focused on this area. Dosages of ACTs currently used for the treatment of malaria are based on trials among HIV- negative people. Since this does not reflect the true picture of the HIV-infected persons, there is need for research and studies in this area so as to ensure that the doses currently in use are adequate for HIV-infected persons.

The Nigerian Situation

In a study of malaria infection among HIV-seropositive and seronegative people in Jos, Uneke et al, reports a dearth of information on the prevalence of malaria-HIV co-infection in Nigeria[50]. Unfortunately the situation has not changed much since there is still a paucity of data in this area. The aim of this paper is to review the malaria-HIV co-infection in Nigeria as reported in literature.

The Influence on Disease Condition

A study in Ahmadu Bello University Teaching Hospital, Kaduna, Nigeria reported that 70% of HIV-1 patients have concurrent malaria parasitaemia compared to HIV-negative adults and children with parasitaemia of 22.5% and 57.5% respectively[51]. In another study of Seroprevalence of malaria infection among human immunodeficiency virus patients in Ondo state, Western Nigeria by Onifade and Ogudare, it was observed that 33.5% of HIV patients examined were positive for malaria and the highest prevalence of malaria infection in the patients was 66.7% for age range 0-9 years[52]. A study on the prevalence of malaria as a co-infection in HIV infected individuals in South Eastern Nigeria, showed 3 times higher prevalence of *Plasmodium falciparum* malaria in symptomative HIV seropositive group compared to seronegative group[53]. Another study[54] in Nnewi a sub-urban town in South-Eastern Nigeria reported a 46.7% prevalence in asymptomatic-malaria in HIV-positive patients compared to 26.9% in the HIV-negative group. The results of the Nnewi study are similar to the result obtained in Lagos[54,55]. The incidence of febrile malaria infection was reported to be three times higher and recurrence of fever nine times higher among HIV-infected pregnant women in Kano[56]. Studies in Jos, North Central Nigeria, established a 24% prevalence of malaria parasitaemia in HIV-positive adults compared to 9% in HIV-negative controlled group as well as increased clinical malaria in HIV-persons with advanced immunosuppression[57,58].

The influence of malaria/HIV interaction has also been reported on the biochemical / laboratory values in co-infected patients with specific reference to reduced antioxidant status, reduced serum iron and albumin as well as reduced CD4 cell count in HIV-persons infected with malaria[59,60]. The studies found in published literature are summarized in Table 1.

Effect of the Co-infection in the areas of Drug-Drug Interactions

Studies of drug-drug interactions between antimalarials and antiretrovirals in Nigeria are lacking as opined by Uneke and Ogbonna[61]. Search of published literature has shown some reports that are of interest. In a study of concurrent administration of nevirapine on disposition of quinine in healthy volunteers, Soyinka et al, established significant decrease in quinine concentration[62]. Other studies on interactions between antimalarials and antiretrovirals in Nigeria include interaction between Quinine and ritonavir, Proguanil + efavirenz. Both studies were carried out in

healthy volunteers and in both cases; the concentration of the antimalarial drug was increased in the presence of antiretroviral drug[48,63] (Table 2).

Another study of interest is the report of decreased concentration of quinine in the presence of nevirapine in a HIV-positive Nigerian man after returning to the UK from a three-week trip to Nigeria[64]. Fehintola and colleagues reported increased exposure to DHA and artesunate in HIV-positive patients receiving NVP-based ART when compared to ART-naïve patients who were both administered artesunate-amodiaquine[65].

A more recent study on the use of artemether-lumefantrine (CoartemR, first-line ACT in Nigeria) for the treatment of asymptomatic malaria in HIV-positive Nigerian adults, established elevated level of day 7 lumefantrine concentration when compared to the concentration in HIV-negative control group66. This was in consonance with earlier study among un-infected malaria HIV-positive patients in South Africa[67]. Another recent study on the impact of nevirapine-based ART on the disposition of amodiaquine and its metabolites, reports a lower exposure to both amodiaquine and desethylamodiaquine (DEAQ) in subjects on nevirapine-based ART compared to ART-naïve subjects68.

The above studies on drug-drug interactions emphasize the importance of the knowledge of potential antimalarial drug interactions with ART when prescribing medications to co-infected patients. There is need for increased research and studies on drug-drug interactions between antimalarials and ART because this will help in better management of co-infected patients.

Apart from drug-drug interaction between antimalarials and antiretroviral drugs, there is sparse data on the importance of resistance to antimalarials in HIV-infected individuals. Various studies have established the influence of host factor on resistance with particular reference to the immune status[40,69]. These reports have shown that drug resistance is usually genetically related because of polymorphic changes, and is influenced by host immune status which is of particular importance in HIV-infected persons and pregnant women as well. Review of published literature yielded no result on antimalarial drug resistance among HIV-infected persons in Nigeria indicating that the published studies on antimalarial drug resistance did not involve HIV-infected subjects. There is urgent need to design studies to address the relationship between immune status and antimalarial drug resistance especially in the HIV-infected persons since this will be beneficial in the monitoring and surveillance of resistance to antimalarial drug in use in the country.

Table 1 Summary of Malaria/HIV Interactions

Study	Criteria	Outcome
Uneke et al, 2005 (adults in Jos)	Influence of HIV on malaria	Higher percentage of malaria positives in HIV+ve people (21% vs 11.6%)
Eni et al, 2005 (Kaduna, adults and children)	Influence of HIV on malaria	Higher percentage of malaria positives in HIV+ve people (70% vs 22.5%)
Onifade & Ogundare, 2006 (Ondo, 0-59yrs)	Influence of HIV on malaria	Higher percentage of malaria positives in HIV+ve people (33.5%)
Onyenekwe et al, 2007(2-70yrs Awka)	Influence of HIV on malaria	3X fold higher prevalence of malaria in HIV+ve people
Onyenekwe et al, 2008 (Awka)	Influence of malaria on HIV	Reduced serum iron and albumin in malaria co-infected HIV group
Goselle et al, 2009 (Jos, 10-50yr)	Influence of malaria on HIV	Decreased PCV among malaria co-infected HIV people
Ukibe et al, 2010 (Nnewi, Anambra)	Influence of HIV on malaria	Higher prevalence of malaria compared to HIV-negative group (46.7% vs 26.9%)
Wariso & Nwauche, 2011 (18-45 yrs in Port Harcourt)	Influence of HIV on malaria	High percentage of malaria (26.5%
Omole-Ohonsi and Nwokedi, 2011	Influence of HIV on malaria	Increased frequency of febrile malaria parasitaemia (OR 3.09) among HIV-infected women compared to HIV-negative counterparts
Onyenekwe et al, 2012	Influence of malaria on HIV	Reduced antioxidant status in HIV/malaria co-infected patients compared to those without malaria
Osuji et al, 2012 (Anambra)	Influence of HIV on malaria	Lower antioxidant status and CD4 in malaria/HIV co-infection
Iroezindu et al, 2012a, 2012b (adults in Jos)	Influence of HIV on malaria	Higher percentage of malaria positives in HIV+ve people (24% vs 9%,); low CD4 count with higher rates of clinical malaria
Sanyaolu et al, 2013 (Lagos)	Influence of HIV on malaria	Higher percentage of malaria (47.7% vs 25.8%) and mixed malaria infection in HIV-positive people; also higher anaemia in the HIV/malaria group than in those with malaria alone
Falade et al, 2013	Influence of HIV on malaria	Malaria percentage 19.3% by RDT
Chijioke-Nwauche et al, 2013	Influence of HIV on malaria	Higher percentage of malaria in HIV-positive group (OR 2.05) than in the HIV-negative group

Table 2: Summary of Antimalarial/ARV interactions

Soyinka et al, 2009	Quinine and nevirapine	Significant decrease in quinine concentration
Soyinka et al, 2010	Quinine and ritonavir	4-fold increase in quinine concentration
Soyinka & Onyeji, 2010	Proguanil + efavirenz	Increased exposure of proguanil
Uriel & Lewthwaite, 2011	Quinine and nevirapine	Decreased quinine concentration
Fehintola et al, 2012	Artesuante- amodiaquine + nevirapine	Increased exposure to DHA and artesunate
Chijioke-Nwauche et al, 2013	Artemether-lumefantrine + nevirapine	Elevated day 7 lumefantrine concentration
Scarsi et al, 2014	Artesunate + amodiaquine	Reduced exposure to amodiaquine and desethyl amodiaquine (DEAQ)

CONCLUSION

In summary, these reports on malaria/HIV interaction cited are studies carried out in the areas of disease and treatment with an obvious lack of information on resistance. Considering the endemicity of both diseases in Nigeria, more research is required in the understanding and dynamics of the co-infection of the two diseases. In order to sustain the life of the current ACTs in use in Nigeria, there is clear need for studies on interaction between ACT use in HIV-positive individuals who have been established to harbor more resistant parasites[21,27]. The information obtained from the study may be useful to advise policy on the choice of antimalarial drug use in HIV-positive persons and help in the monitoring and transmission of resistant parasites. More studies and evaluation of current studies from Nigeria on the malaria/HIV interaction are recommended to provide the needed evidence for the policy and guidelines on the treatment of Malaria in HIV.

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