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Review Article

Malaria and HIV/AIDS Co-infections

Desalegn Amenu

College of Natural and Computational Science, Biology Department, Wollega University, Nekemte Ethiopia, P.Box, 395

*Corresponding author: *wadadesalegn@gmail.com*

Abstract

Malaria and HIV/AIDS are the major priority medical challenges facing sub-Saharan Africa in general and Ethiopia in particular and yet little has been known so far on the clinical and public health implications of HIV and Malaria co-infection. Even if the statistical effect is modest, any interaction between these two infections would have public health significance. The study concluded that the current HIV prevalence among P.faciparum malaria patients was not different from the HIV seroprevalence in the general population in the area, based on the prevalence findings from the national sentinel reports. No strong evidence suggesting an association between HIV and malaria was identified. The need for further studies with improved methodologies and designs is emphasized.

Keywords: HIV, Malaria, Co infection, Health Institution, Ethiopia.

Introduction

Two of the greatest medical challenges facing Africa today are human immunodeficiency virus (HIV) and malaria infections. Although these two infections are of major public health and clinical importance in the Sub Saharan Africa (SSA) in general and in Ethiopia in particular, their interaction is little understood (1). It is estimated that over 40% of the world's population lives in areas where there is high risk of malaria infection (2, 3). WHO estimates 300 - 500 million cases and 1.5 - 2.5 million deaths a year globally; Africa accounts for 90% of cases and the great majority of deaths (3, 4). According to UNAIDS's latest report in July 2002; approximately 70% of the world's 40 million HIV positive population live in Sub-Saharan Africa. UNAIDS also reports that out of the 5 million newly infected persons in 2001, 3.5 million live in Sub-Saharan Africa (5).

Man has known malaria for centuries and HIV has been around only for two decades.

Malaria has already killed millions and continues to kill nearly three million every year.

As of 1999 nearly 36 million people around the world have been infected with HIV and five million have died of AIDS related illness. In the coming millennium both diseases are expected to infect and kill many more around the world. And the biggest tragedy is that HIV infection is on the dramatic increase in those countries where

malaria is already an uncontrollable problem (6). Being the two most common infections in sub-Saharan Africa and to a lesser extent in other developing countries little is known on the clinical and public health implications of HIV and malaria co-infection. And yet the association between the two infections has important implications. It is estimated that 22 million Africans are already infected with HIV-1 and 500 million Africans get infected with malaria every year. Therefore, any interaction between these two infections will have public health significance, even if the statistical effect is modest (7).

On a population basis, an increased prevalence of malaria and parasite density in HIV infected individuals could lead to increased malaria transmission affecting both HIV positive and negative individuals, assuming that the frequency, duration and density of gametocytemia rise in parallel with asexual parasitemia, which is currently unproven. The increased risk of clinical malaria in HIV positive subjects could also increase the burden on clinical services in areas where HIV-1 is prevalent. The population attributable fraction of adult malaria due to HIV-1 would be expected to rise in parallel with HIV-1 prevalence. In a region with HIV-1 prevalence of 30% such as parts of Southern Africa, the population attributable fraction could reach 20% for parasitaemia and 35% for clinical malaria (7).

Research questions that need addressing in the relationship between these two illnesses include establishing the precise mechanism whereby immunity to malaria is impaired by HIV-1; whether mortality from severe malaria is increased by HIV-1 in some situations; whether response to malaria treatment is diminished by HIV-1; whether the current HIV-1 epidemics is having an effect on malaria control programs in Africa and whether improved clinical management of malaria in HIV-1 infected subjects, such as avoiding mosquito bites or chemoprophylaxis, slows the progression of HIV disease (7).

Recent studies have shown presence of interaction between malaria and HIV-1 in pregnant women and non-pregnant adults in Africa. In East and Southern Africa, where HIV-1 prevalence approaches 30%, about a quarter to third of clinical malaria in adults and malaria in pregnancy can be accounted for by HIV-1. If confirmed by further study, this has significant public health implications (8). Thus, the worsening of malaria in Africa could in part be due to the expanding HIV-1 epidemic. Also, if present observations of a transient increase in viral load during malaria episodes and its reversibility with effective treatment of malaria hold in, malaria control may be beneficial in curbing HIV-1 transmission and the rate of disease progression.

The interaction between HIV infection and malaria could work in either direction. HIV infection might reduce immunity to clinical malaria resulting in more frequent infection among the semi-immune and more severe disease among the semi-immune and nonimmune; conversely malaria might enhance the progression of HIV infection to clinical AIDS (1). The effect of HIV infection on the pattern of malaria might take the form of an increased incidence of successful as opposed to aborted infections, an increased incidence of clinical as opposed to asymptomatic infections, or an increased incidence of severe rather than mild malaria (1).

Perhaps the other most critical challenge would be to make the most out of increasing resources for control of malaria and HIV-1. Anemia related deaths could be reduced by a joint program of prevention of malaria associated anemia and provision of a safe blood supply. High rate of attendance at antenatal clinics in Africa suggests that the effect of HIV-1 and malaria in pregnancy could be countered in routine antenatal care by the incorporation of malaria prevention, through intermittent preventive treatment and the use of insecticide treated bed nets, and access to HIV diagnoses and antiretroviral drugs (8). Therefore, continued investigation in to the interaction of HIV-1 and malaria, and joint programming of key intervention strategies could lead to immediate and long-term benefits in disease control. Such studies also could help in dealing with certain

misconceptions in HIV transmission in malarious areas (9). Our improved understanding of HIV disease progression combined with newer laboratory techniques for easier diagnoses of HIV infection and quantification of viral load provide an opportunity to revisit and further investigate these important areas of potential overlap between malaria and HIV.

The Situation of Malaria and Its Epidemiology in Ethiopia

Malaria is one of the country's foremost health problems top ranking in the list of common infectious diseases. Three quarter of the total land mass is regarded as malarious and about 68% of the total population is at risk of malaria infection (10). Reports indicate that clinical malaria accounts for 10% - 40% of all out patient consultations, with corresponding proportional morbidity among children under 5 years in age being 10% -20%. In recent years, on average, about 400,000 to 600,000 people with positive blood films for malaria are treated every year. It is estimated that the actual number of malaria cases seen at health facilities without microscopic diagnostic services and by the community health workers is 3-4 times the number of cases treated at health institutions with diagnostic facilities. In addition, since quite a significant number of people do not have access to health services, the actual number of malaria cases that occur annually throughout the country is estimated in the range of 4-5 million. According to MOH reports, malaria accounted for 13% - 26% of all inpatient admissions in the various health facilities with proportional mortality and case fatality rates of 13 - 35 % and 15 -17 %, respectively (10,11). Malaria is also a significant impediment to socioeconomic development in Ethiopia. Fertile lowlands and major river valleys have not been fully inhabited and developed largely due to high malaria transmission in these areas. Due to fear of malaria in these areas the population has settled largely on the highlands; this has caused over population, ecological degradation, reduced productivity and hence famine and poverty (10, 12). In endemic and malaria epidemic prone areas, the disease strikes during planting and harvesting seasons, cutting down productivity capacity at a time when there is the greatest need for agricultural work. The disease is also associated with loss of earning, low school attendance, and high treatment cost. Malaria also impedes flow of trade, foreign investment and commerce. During epidemics, malaria generally causes panic in the general population; economic activities, particularly agricultural activities are paralyzed. Health facilities are also overwhelmed and lots of resources are spent on dealing with the emergency situation. Generally, malaria accounts for 30% of the disease burden (DALYs) in all age groups (10, 11, and 12).

In Ethiopia, *Plasmodium falciparum* and *Plasmodium vivax* are the two most dominant malaria parasites, distributed all over the country and accounting for 60% and 40% of malaria cases, respectively. *P. malariae* accounts for less than 1% and *P. ovale* is rarely reported. The parasite is principally transmitted by the major mosquito vector known as
Anopheles arabiensis (10, 11).

Altitude and climate (rainfall and temperature) are the most important determinants of malaria transmission in Ethiopia. Areas with bimodal pattern of transmission are limited and restricted to a few areas that receive the small (*Belg*) rains. The major transmission season occurs almost in every part of the country. Accordingly, there are four eco-epidemological strata of malaria transmission in the country:

Current Malaria Control Activities

The control of malaria in Ethiopia has a history of more than four decades, which initially began as a pilot control project in 1950s and launched a national eradication campaign in the 1960s followed by a control strategy in the 1970s. In 1976 a vertical organization known as the National Organization for the Control of Malaria and other Vector Borne Diseases (NOCMVD), evolved from the Malaria Eradication Services (MES). Some of the major contributions attributable to malaria control program activities

in the country include reduced prevalence and level of transmission in many areas, the opening up of the fertile arable lowlands and major river valleys for expanded agriculture and settlement, rapid growth of many urban centers in the lowlands and the general population increase in these areas (10). Currently, the major malaria control measures being employed in the country include vector control and prompt case management. The vector control activities mainly rely on insecticide sprays, environmental management and insecticide treated nets (ITNs). The anti malarial drugs being used for malaria case management include chloroquine, sulfadoxine-pyremethamine and quinine. To this effect, the federal MOH has developed national guidelines for professionals involved in malaria case management (10, 13).

Concurrently, the global Roll Back Malaria (RBM) initiative, which aims at reducing the malaria burden by half in ten years, was initiated in 1998. In line with the global RBM objectives, malaria control in Ethiopia aims at reducing overall burden of malaria by 25% as compared to the 2000 level, over the coming five years. Furthermore it aims to maintain malaria free areas from introduction and establishment of the disease through strong surveillance and preventive measures (10). Despite decades of sustained control efforts, malaria still remains as the major cause of morbidity, mortality and socioeconomic problem in Ethiopia. Various reports from health institutions in the country show that the problem is growing intense and there is a general build up and increase of malaria nationwide with common occurrence of epidemics. The problem is partly due to development of chloroquine resistant strains of *P. falciparum*, the commonest cause of malaria in Ethiopia and other possible factors (10, 14).

HIV / AIDS

HIV/AIDS is a new emerging phenomenon. The disease was first recognized in the United States in 1981. AIDS is characterized by presence of HIV infection together with presence of reliably diagnosed opportunistic infections that are indicative of underlying deficiency in cell mediated immunity in the absence of known causes of other underlying immune defects. The etiologic agent for AIDS is *human immune deficiency virus* (HIV), which belongs to the family of human retroviruses and the subfamily of *lentviruses*. The virus has two serotypes and the most common cause of HIV disease throughout the world is HIV-1(15). HIV is transmitted by sexual contacts; by blood or blood-products; and from infected mother to infant intrapartum, perinatally, or via breast milk. There is absolutely no evidence that HIV is transmitted by casual contact or that the virus can be spread by insects such as by a mosquito bite (15). The clinical consequences of HIV infection encompass a spectrum ranging from an acute syndrome associated with primary infection, prolonged asymptomatic state to advanced disease. The diagnoses of HIV infection is based on demonstration of antibodies to HIV or the direct detection of HIV or one of its components. The standard screening test for HIV is *enzyme linked immunosorbent assay* (ELISA). This solid-phase assay is an extremely good screening test, with a sensitivity of over 99.5 percent. The majority of diagnostic kits contain both HIV-1 and HIV-2 and thus either will be detected on routine screening. Though extremely sensitive, ELISA is not optimal with regard to specificity.

Areas of Potential Overlap between HIV and Malaria Infections

With what we know of HIV infection, it is only natural that one expects as far poorer outcome for malaria infection in HIV patients. But on the contrary, the reports available indicate either no effect or even a protective effect of HIV infection against death from complications of *P.falciparum* malaria (6). Studies showed that although high level of malaria parasitaemia has been observed in African children with symptomatic HIV infection, these children have been found to be ‘protected’ against cerebral malaria. This has been attributed to lower levels of TNF in HIV infected children. TNF is reported to have a potentiating effect on the endothelial adherence and clogging of microcirculation by parasitized red cells. In an

animal study using mice, murine AIDS was found to confer protection against the severity of neurological manifestations of experimental cerebral malaria and this protection was higher with longer duration of immunodeficiency. IL-10 from splenic cells was shown to play a crucial role in this protection (6).In Africa, human immunodeficiency virus type-1 (HIV-1) infection is a serious emerging infectious disease, and *P.falciparum* malaria infection is the most prevalent infectious diseases. Studies to date have not demonstrated a direct, biologic association between HIV infection and *P.falciparum*; that is, malaria has not appeared as an opportunistic infection, nor does it accelerate progression of HIV related diseases. However, altered cell mediated immunity in HIV infected person could influence the frequency and course of malaria infection. Inadequate sample sizes and the cross sectional nature of previous studies might have limited their ability to adequately asses any interaction between the two infections. The one confirmed area of overlap reported was the increased risk of HIV transmitted through blood transfusion to persons with severe malarial anemia (16). There are also evidences that T-cell function is impaired during acute episodes of malaria. Proliferate responses to a variety of antigens are depressed during acute episodes of malaria when assessed by tests carried out on peripheral blood mononuclear cells. It is possible, however, that this anergy is due in part to sequestration rather than depletion of competent cells. Of particular importance here is the observation that T-cell control over EB virus infection is lost transiently in children with acute *falciparum* malaria. Thus, one might expect malaria infection to have an adverse effect on HIV infection both by stimulating T-cell turn over and by impairing T-cell cytotoxic function. Malaria infection may damage the placenta in such a way as to facilitate transmission of HIV in-utero (1).

HIV and Severe Malaria

In two studies done in urban Burundi, and Zambia among admitted adults with severe malaria, the case fatality ratio (CFR) was more than twice as high in the HIVSP compared to the HIVSN group. However, the sample sizes of these studies were too small to draw any statistically significant conclusion (1). In another study done in Zimbabwe, after adjusting for confounders, the risk of developing severe and complicated malaria was significantly more in HIV positive patients than in HIV negative patients (17)

HIV and Malaria in Pregnancy

In a secondary analysis of data, from a cohort of mothers enrolled in a trial chemoprophylaxis during pregnancy undertaken in rural Malawi from 1987 to 1989, it was observed that the prevalence of parasitaemia at the time of enrollment was similar among HIVSP and HIVSP primigravidae, but it was higher among HIVSP multigravidae compared to HIVSN multigravidae. The geometric mean density of parasitemia (GMPD) was higher in HIVSP primigravidae than HIVSN primigravidae. While the GMPD decreased with gravidity it was consistently higher in HIVSP than HIVSN pregnant women at all parities. The incidence of placental malaria was also higher among HIVSP than HIVSN women, and this difference was more marked among multigravidae (1).

HIV and Response to Antimalarial Treatment

Chloroquine, the most commonly used ant-malarial drug in Africa has in-vitro anti HIV-1 activity. Prospective studies addressing the role of chloroquine as an anti-HIV-1 agent are being planned in sub-Saharan Africa (8). Two studies have examined the prevalence of treatment failure on day 7 following treatment with Quinine given a dose of 20 mg/kg daily for 5 days in HIVSP and HIVSN children in urban Zaire; there was no significant difference in the level of treatment failure in the two groups (1). In an Ethiopian study, nineteen hospital admitted adult malaria patients with *P. falciparum* infection (7 HIV sero positives and 12 HIV sero negatives), were followed for their response to anti malarial therapy (*artemisinin*) so as to investigate the effect of *artemisinin* on the rate of clearance of *P. falciparum* in patients with or without human immune deficiency virus (HIV) co-infection.

The findings of the study indicated for the first time that clearance of *P.falciparum* after administration of *artemisinin* is delayed in patients with HIV co- infection (18

Malaria and Progression to HIV Infection

In community based study in Guinea Bissau, no significant difference in provirus load of HIV- 2 was found between subjects who had peripheral parasitemia and those who did not; the geometric mean provirus load in the two sub groups were 103 (95% CI : 37-287) and 146 (95% CI : 96-220) respectively (18).

Conclusion and Recommendation

The prevalence of HIV in the study subjects was similar to the figures of HIV prevalence in Ethiopia for the rural population and with the findings of ANC sentinels reports in the same area.

Though studies like this one were used to verify associations between HIV and certain diseases like TB, no evidence of association between HIV and malaria was found, since this study design may not be an appropriate one to investigate the possibly existing association between these two diseases.

Overall the study population has a better knowledge on the occurrence, means of transmission and prevention of malaria as well as in treatment seeking behaviors.

Except that they had certain misconceptions and deficiencies in the knowledge that malaria could be transmitted from person to person and the modes of malaria transmission

Further studies should be done in the area with a relatively improved study designs and methodologies, which employ follow up for outcomes of treatment and case fatality rates of cases and control groups.

Most of the studies that drew conclusions that there are associations between HIV and malaria are cohort studies.

Appropriate messages on malaria transmission and prevention methods including ITN promotion should be provided.

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