

A PERSPECTIVE ON ANTIINFECTIVE AGENTS INTERACTION IN HUMAN IMMUNODEFICIENCY VIRUS PATIENTS WITH MALARIAL INFECTION

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ABSTRACT

Despite recent research advances in anti-infective agents (achievements), Human immunodeficiency virus (HIV), and malaria infection are currently considered two main global human health problems. Given the considerable geographical overlap between malaria and HIV, a substantial number of co-infection incidences occur in human. The purpose of this review is to summarize the information on the clinical impact of co-infection, therapeutic anti-infective agents' interaction in human and future research priorities.

Keywords: Malaria, Human immunodeficiency virus, Co-infection, Anti-malarial drug and anti-retroviral drug interaction, Public health, Clinical epidemiology, Anti-infective agents.

INTRODUCTION

Human immunodeficiency virus (HIV) and malaria infection often co-exist in patients in many parts of the world [1]. Patients with such dual infection are a source of spreading both the diseases [2]. Anti-malarial treatment failure is reported in HIV-infected adults as compared to uninfected adult [3]. Annual mortality due to these infections is estimated very high around 4 million [4]. The incidence of infections may increase in near future because of the potentially co-infected population with HIV and malaria. One of the major problems is anti-malarial agents' drug failure in efficacy probably due to lack of immunity in HIV patients. The present article provides in the brief clinical impact of co-infection, therapeutic problem in the treatment of malaria infection in HIV patients due to the interaction between anti-retroviral and anti-malarial drugs and future research priorities.

BACKGROUND

HIV, a retrovirus that causes acquired immunodeficiency syndrome (AIDS), is transmitted by sexually contact through infected blood and from the infected mother to child [5]. HIV patients due to depletion of immune systems' CD4 T-cells are likely to be exposed to the risk of opportunistic infections and may lead to malignancy [5]. Malaria is a protozoan parasitic disease of human caused by various species of *Plasmodium* such as *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium Malariae*, and *Plasmodium knowlesi*. Among these species, *P. falciparum* infection may be usually fatal. Malaria infection is transmitted in human through the bite of infected female *Anopheles* mosquito and introducing infective sporozoites in the blood stream and developing in hepatocytes as schizonts which ruptures and release merozoites into the blood stream. These merozoites invade erythrocytes where they develop to schizont stage and burst erythrocytes and merozoites are released and invade erythrocytes and the cycle continues. Some parasites differentiate into sexual erythrocytic stages (gametocytes) which are ingested by *Anopheles* mosquito. The clinical manifestations of malaria are fever, anemia, cerebral malaria, multiorgan failure, and coma [1]. The incidence of malaria has been reported very high, nearly 104 countries in the world are declared an endemic zone of malaria constituting nearly half of the global population. The highest mortality due to malaria is reported from African countries followed by South-East Asia [6].

Currently, around 35.3 million (including 52% women) people in the world are infected with HIV and among these most of the people are from Sub-Saharan Africa mainly Zambia, Malawi, Mozambique, and Zimbabwe, this region remains most heavily affected by HIV followed by an estimated 4.8 million people living across South/South-East Asia [7].

It is apparent from these geographical areas that high incidence of HIV and malaria are most prevalent in sub-Saharan Africa and next in East and South-East Asia and dual infections co-exist in population in these regions. Visitors traveling in the endemic countries of HIV and/or malaria may be at high risk of dual infection and develop serious clinical complication.

CLINICAL IMPACT OF CO-INFECTION

HIV infection alone is a slow progressive disease and without treatment, the disease takes about 7-10 years to develop into AIDS. During this period, HIV infection impairs T-cell immunity, causes progressive cellular immune suppression leading to failure in the prevention of infections [8]. It is reported that malaria infection in HIV-infected patients' favors multiplication of HIV to significantly increased HIV viral load [9]. Several studies showed an increased HIV RNA replication in patients with malarial parasites [8,10,11]. Due to severity acute malarial infection, HIV RNA concentration may be as high as 7-10 folds increases as compared to HIV patients without malarial infection [2,12,13,14]. One of the possible explanation is given for such situation is that malaria parasites stimulate T-cell activation, leading to the production of interleukin-6, tissue necrosis factor- α by activated lymphocytes, which promote HIV replication and viral load RNA [8].

Further, HIV disease may rapidly progress to AIDS due to CD4 T-lymphocyte depletion during repeated malarial infection and may lead to early death and high mortality despite prompt treatment [1,8,10]. The effect of HIV on malaria in patients is more apparent in children than in adults in high transmission areas because young children have a high incidence of symptomatic malaria [8].

HIV-infected persons are more likely to develop severe and complicated malaria infection, acute renal failure, jaundice, and severe anemia as compared with non-HIV-infected individuals and non-pregnant women [8,15]. Pregnant women infected with HIV are

highly susceptible to malaria infection and transmission of disease to the child. Such mothers are also at high risk of anemia and children born are with low-birth weight [1]. Malaria infection during pregnancy may increase the risk of mother to child transmission of HIV [1,16]. Kenyan children had a significant increase of severe anemia and nearly 10-folds greater mortality reported 3 months after exposure to HIV infection [15]. The incidence of malaria and HIV/AIDS is very high in sub-Saharan Africa, and annually approximately 1 million pregnant women get co-infections [4]. The high-risk of HIV and malaria during pregnancy poses a great challenge to treat such patients due to the limited drug of choice.

THERAPEUTIC INTERACTION

HIV patients co-infected with malaria are treated with a combination of the anti-malarial drug along with HIV therapeutic agents. However, such combination poses the problem of drug interaction since their mode of action follow the same metabolic pathways. Most of the national government in sub-Saharan Africa follows the WHO recommendation of a combination therapy of artemisinin based anti-malarial that include artemether, artesunate or dihydroartemisinin with non-artemisinin derivatives such as amodiaquine, lumefantrine, and mefloquine [17].

Three major classes of anti-HIV drugs include: (1) Nucleosides nucleotide reverse transcriptase inhibitors and drugs include in this class are zidovudine, emtricitabine, tenofovir, didanosine, lamivudine, stavudine, and abacavir; (2) Non-nucleoside reverse transcriptase inhibitors and drugs are efavirenz and nevirapine, and (3) Protease inhibitors and drugs include lopinavir, saquinavir, indinavir, atazanavir, and ritonavir [17]. In Africa, the most commonly recommended first line of treatment includes artemether-lumefantrine and nevirapine-based anti-retroviral therapy for malaria and HIV, respectively. Two recent incidences showed that co-administration of artemether-lumefantrine with efavirenz or nevirapine resulted in a reduction in artemether and dihydroartemisinin exposure, but the findings on the impact on lumefantrine were conflicting [18-20]. It is also indicated that reduction in nevirapine exposure [19].

The risk of development of drug resistance in the treatment of malarial infection might increase due to drug interaction of artemether/lumefantrine and nevirapine. Most of the HIV protease inhibitors also have anti-malarial activity. Improvement in the treatment of malaria infection has been shown in a study due to the synergistic effect of ritonavir-boosted lopinavir and artemether-lumefantrine [21]. Similarly, protease inhibitors indinavir, ritonavir, and saquinavir in a combination of chloroquine at prophylaxis dosing suppressed HIV infection by synergistic effects of drugs combination therapy [22]. Prevalence of placental malarial infection in HIV-infected women has been shown to decreased using Co-trimoxazole as prophylaxis drug as compared to sulfadoxine-pyrimethamine intermittent preventive treatment used in HIV-uninfected women [23]. International travelers (HIV-infected) should be aware while traveling to the high incidence of malaria infection zone regarding drug interaction of anti-retroviral and antimalarial prophylactic drugs to avoid disease complication. Therefore, HIV-infected travelers taking highly active anti-retroviral therapy should be taken into consideration, chemoprophylaxis drugs to avoid antimalarial drug interactions.

FUTURE RESEARCH PRIORITIES

1. Effect of co-infection of malaria and HIV should be studied in *in-vitro* co-culture models, animal models and further in clinical studies toward detailed understanding of the impact of co-infection on public health
2. HIV interaction with other plasmodium species should be assessed
3. Pharmacokinetic and drug interactions between antimalarial and anti-retroviral drugs should be studied in detail.

CONCLUSION

From the available literature, it is obvious that interaction between malaria and HIV-infective agents are bidirectional and synergistic in aggravating both diseases. It is emphasized here that HIV and malarial infections are complementary to each other because HIV replicate in the malarial infected patients thereby threatening efficacy anti-retroviral treatment. HIV and malaria co-infection challenge a significant public health and economic concern in sub-Saharan African and Asia. Finding the answers to some of the unexplored disease areas questions will help us to improve our current strategic for the treatment of HIV-malaria co-infection.

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