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Drug Interactions in the Treatment and Chemoprophylaxis of Malaria in HIV Infected Individuals in Sub Saharan Africa

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Abstract

Malaria and HIV/AIDS remain diseases of public health importance in sub-Saharan Africa as both infections are responsible for high morbidity and mortality rates. Malaria disproportionately affects young children and pregnant women and HIV/AIDS affects mostly adolescents and young adults. The widespread nature of both infections has led to co-infection in many residents of sub-Saharan African countries. HIV-infected individuals are more susceptible to frequent attacks of malaria thus requiring combination antiretroviral therapy and antimalarial drugs. There is, in general, lack of information on the influence of the chronic use of antiretroviral medicines on the outcome of repeated treatment of malaria. Pharmacokinetic drug interactions with HIV medications that lead to sub-therapeutic concentrations of antimalarial drugs will promote drug resistance in patients with malaria. The objective of this review is to summarize the available information on the adverse drug reactions and drug interactions of commonly used antimalarial drugs in the context of combination antiretroviral therapy and propose a clinical pharmacology research plan to develop dosing recommendations for patients with malaria and HIV co-infection.

Keywords

Drug interactions; HIV infection; malaria; antiretroviral therapy; chemoprophylaxis; sub-Saharan Africa

INTRODUCTION

Malaria remains a disease of public health importance in sub Saharan Africa where it is responsible for high morbidity and mortality rates. The Plasmodium species infect an

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estimated 300–500 million people resulting in annual deaths of over 1 million mostly in sub Saharan Africa [1–3]. Prior treatment of malaria involved the use of a single drug but the emergence of drug resistant strains of mostly *Plasmodium falciparum*, the commonest species in Africa, has compelled the use of combination therapy [4–6]. About 40 million people are living with HIV, 60% of who are in Africa [7]. Global HIV/AIDS related mortality was estimated at 2 million in 2006, 90% of which was documented in Africa. Combination antiretroviral therapy (cART) with three or more drugs has been found to be effective to decrease mortality and morbidity in patients with advanced HIV disease in this region [8].

In most of sub-Saharan Africa, malaria transmission is perennial and disproportionately affects young children and pregnant women [9]. HIV/AIDS is more common in adolescents and young adults but the widespread nature of both conditions has led to their common co-existence requiring concurrent drug antimicrobial therapy for both infections. Although therapy with cART is life-long and malaria requires only a few days of treatment with combination therapy, HIV-infected individuals are more susceptible to frequent attacks of malaria [10, 11] thus making it imperative for such individuals to combine their cART with antimalarial drugs. There is minimal information on the influence of chronic use of cART on short, repeated treatments of malaria in patients in sub-Saharan African countries. Since all anti-malarial drugs are available as non-prescription medicines in most sub-Saharan African countries, it has been difficult to obtain pharmacokinetic data from well controlled studies. For example, in Nigeria individuals who have active medical problems often obtain medicines from chemists or pharmacy outlets without a prescription. Often the identity or quality of these products is unknown [12, 13]. How this practice of self-care impacts on HIV/AIDS treatment in Nigeria and other sub Saharan African countries remains to be investigated. Since negative pharmacokinetic drug interactions may lead to sub-therapeutic anti-malarial concentrations, promoting drug resistance, rigorous pharmacokinetic evaluation is needed to determine optimal dosing regimens. It may also help identify other new pharmacological responses, such as the positive additive anti-HIV effect of chloroquine [14].

This review considers the available information for the drug interactions and adverse effects of commonly used antimalarial drugs in the context of antiretroviral therapy.

STATUS OF MALARIA THERAPY

Malaria is one of many infectious diseases requiring combination drug therapy, primarily due to the widespread resistance that has emerged after the early successful use of chloroquine, amodiaquine and sulphadoxine-pyrimethamine [6]. Other available antimalarials in sub-Saharan Africa include mefloquine, quinine, dapsone-chlorproguanil and artemisinin derivatives notably artesunate, artemether and dihydroartemisin, which have been commended for use in combination with other potent antimalarial drugs. The rationale for the use of combination therapy is to reduce the probability of the development of drug resistance. Documented high rates of resistance to chloroquine and sulphadoxine-pyrimethamine have led most national governments in sub Saharan Africa not to recommend their use, even as partner drugs in combination therapy [6, 15]. Relative to East African countries of Kenya and Tanzania, the evolution of antimalarial drug resistance was relatively slow in Nigeria and West Africa [16–18]. It is unknown if the concurrent use of cotrimoxazole with chloroquine has contributed to such a trend. Cotrimoxazole possesses similar antimalarial activity to chloroquine and both have been used together for malaria and respiratory tract infection [19, 20]. The World Health Organization (WHO) recommendation which has been adopted by most national governments in sub-Saharan Africa includes the use of artemsinin-based combination therapy (ACT) based on efficacy data [6, 9].

Artemisinin-based therapy usually consists of artemether, artesuante or dihydroartemisinin with non-artemisinin derivatives like amodiaquine, lumefantrine, and mefloquine. Although the use of drugs with high level resistance like chloroquine and sulphadoxine-pyrimethamine is discouraged, the latter is the WHO-approved drug for the intermittent preventive treatment in pregnancy (IPTp) [21, 22].

CHLOROQUINE

Chloroquine remains an effective antimalarial drug in areas other than sub-Saharan Africa where *Plasmodium falciparum* accounts for about 85–90% of malaria cases [23, 24]. The other species that naturally cause malaria in humans, *P. malariae*, *P. ovale* and *P. vivax* are responsible for 10–15% of cases and more importantly, severe disease and drug resistance are almost non-existent with these species compared to falciparum [4–6]. Chloroquine is generally not recommended for use either alone or in combination in sub-Saharan African countries.

The mechanism of action of chloroquine is incompletely understood despite being the most used and apparently the safest antimalarial drug to date. Chloroquine prevents the detoxification of heme by the heme polymerase, resulting in toxic accumulation of heme within the parasite. Resistant strains of the parasite probably adapt so that the drug does not accumulate to critical intracellular concentrations required for its antimicrobial effect with multidrug resistance protein (MRP) presumed to be responsible for drug efflux [25]. Prior attempts to reverse chloroquine resistance focused on inhibition of the efflux process. Both *in vitro* and *in vivo* studies suggest reversal of resistance in resistant strains by verapamil and chlorpheniramine [26–28].

Chloroquine has been used extensively for many years and its pharmacology is well documented [29]. Chloroquine is almost completely absorbed when taken orally and binds to plasma proteins with subsequent hepatic metabolism via CYP2C8 and CYP3A4 to desethylchloroquine and bis-desthylchloroquine. Both of these metabolites have reduced activity against the malaria parasite. The parent drug and metabolites are renally excreted and clearance is reduced in renal impairment cases although dose adjustment may not be necessary. The volume of distribution of chloroquine is very large at about 100L/Kg and the half-life is 30–60 days. Prolonged use of chloroquine may cause macular deposits resulting in visual impairment. Chloroquine may also cause gastrointestinal upset and abnormalities in the PR interval on eletrocardiographic study. Chloroquine-induced pruritus is common amongst black Africans and the mechanism remains poorly understood. Chloroquine is well tolerated and safe in pregnancy. Interestingly, chloroquine has antiretroviral activity and this effect may be enhanced by co-administration with HIV protease inhibitors such as lopinavir or ritonavir due to the inhibition of CYP3A4 with resultant increases in chloroquine plasma concentrations [30]. NNRTIs such as efavirenz and nevirapine, both of which are commonly included in cART may reduce chloroquine plasma concentrations from induction of CYP3A4 activity. Tenofovir-associated renal dysfunction may reduce chloroquine clearance but additional data are needed to fully elucidate this. Effects of cART on chloroquine may not be of clinical significance since the drug has been removed from the approved list of drugs for malaria treatment in most of the sub-Saharan African countries. It may nonetheless be important to evaluate how chloroquine may impact on HIV and HIV treatment especially considering its antiretroviral effect and the ease of accessibility of the drug.

AMODIAQUINE

Amodiaquine is a 4-aminoquinoline congener of chloroquine and both are presumed to have a similar mechanism of action [29]. Amodiaquine and one of its major metabolites, desthylamodiaquine possess slightly more activity than chloroquine. Amodiaquine use was

discontinued for many years consequent upon reports of hepatoxicity and agranulocytosis while being used for chemoprophylaxis. Amodiaquine was recently re-introduced in combination regimens to reduce drug resistance. Amodiaquine in combination with artesunate in a 3-day regimen has similar efficacy to the combination of artemether and lumefantrine and both are included in the treatment guideline of some national governments as recommended by the WHO. Hepatotoxicity of amodiaquine has been ascribed to the amodiaquine-quinoneimine metabolite [31], the extent of which may be increased by CYP3A4 induction. It may be inferred from the foregoing that the elevation of aminotransferases observed, and subsequent discontinuation of a study to assess pharmacologic interactions between efavirenz and amodiaquine [32], might have been due to increased production of amodiaquine-quinoneimine during efavirenz CYP3A4 induction. It is noteworthy that activation of artemisinins requires CYP3A4 thus the effect of administration of artesunate plus amodiaquine in patients receiving an efavirenz-based regimen may be difficult to analyze. Additional studies are needed to accurately evaluate these interactions. Nevi-rapine, another NNRTI is widely used as a component of cART in Nigeria where there is minimal information on the potential for pharmacokinetic interactions with amodiaquine plus artesunate.

MEFLOQUINE

Mefloquine was developed at the Walter-Reed Army Institute, USA and it has good activity against chloroquine-resistant strains of *Plasmodium falciparum*. With the advent of combination therapy, products that combine mefloquine with artesunate are available. In Nigeria, and probably the entire sub-Saharan Africa region, *Plasmodium falciparum* remains largely sensitive to mefloquine [33, 34]. Both the mechanism of action and resistance are under investigation. Increased efflux of mefloquine mediated by MDR1 has been postulated as a mechanism of parasite resistance to mefloquine similar to what has been reported with chloroquine and amodiaquine [29].

Mefloquine and chloroquine have similar activity against HIV and tends to be potentiated by lopinavir/ritonavir [30]. However, drug interaction studies are needed to determine the pharmacokinetics of mefloquine plusartesunate with lopinavir/ritonavir since a complex inhibitory and induction of CYP3A4 effects will influence both the antimalarials and antiretrovirals. Similar interaction studies are also needed between mefloquine, artesunate and nevirapine- or efavirenz-containing cART regimens.

ARTEMISININS

All artemisinins possess a sesquiterpene lactone ring and are hypothesized to influence redox reactions within the parasite. Artemether, artesunate and dihydroartemisinin are commonly used derivatives that are active against multidrug resistant strains of *Plasmodium falciparum* and are recommended for use in combination with other potent antimalarial drugs [9]. Artemether has comparative efficacy to quinine in the treatment of severe or complicated malaria and has a good safety profile. In addition to the activity of artemisinins against asexual forms of *Plasmodium species*, this class of drugs also possesses gametocytocidal effects and may therefore play a role in reducing transmission of the parasite [35, 36].

Artesunate and artemether are metabolized to dihydroartemisinin by CYP3A4 and, are substrates and inducers of CYP2C19 [36]. It is expected that inducers and inhibitors of CYP3A4 and CYP2C19 will alter the pharmacokinetic profile for artemisinins though additional information will be needed to confirm its clinical relevance. Information on interactions between artemisinins and approved antimalarial drugs like amodiaquine and lumefantrine require investigation.

QUININE

Since the introduction of quinine in the 17th century this drug has continued to be relevant in the treatment of all forms of malaria and severity especially in sub Saharan Africa where the quinine sensitivity remains relatively intact. Quinine is presumed to act through an influence on the metabolism of heme in a similar manner to chloroquine, and resistance develops through reduced intra-parasite accumulation of quinine. Quinine is well absorbed and binds extensively to alpha-1 acid glycoprotein, an acute phase reactant that increases in malaria [37]. The extent of quinine plasma protein binding in acute malaria usually increases and this may explain why high concentrations of quinine are tolerated in individuals who have malaria [37].

Quinine is metabolised by CYP3A4 and 2C9, and CYP1A2 and 2D6 may also contribute to hepatic clearance; quinine is both a substrate and inhibitor of CYP2D6 [29, 37]. Quinine also inhibits enterocyte P-glycoprotein [38]. In HIV-infected individuals receiving nevirapine or efavirenz, or 3A4 inhibitors such as lopinavir/ritonavir requiring quinine treatment, sufficient pharmacokinetic information is largely lacking to guide dosing recommendations for use [37, 39]. This has great importance as cerebral malaria, the most common cause of non-traumatic encephalopathy worldwide, is treated with quinine as first line treatment in most of the sub-Saharan African countries.

LUMEFANTRINE

Lumefantrine has been co-formulated with artemether. It is one of the widely recommended ACTs in sub-Saharan Africa countries. Lumefantrine and halofantrine are closely related in their chemical structures and they have a similar mechanism of action although lumefantrine presents a more favourable safety profile. Absorption of lumefantrine is erratic and is improved with high fat meals [40]. Lumefantrine undergoes oxidation with CYP3A4 and plasma concentrations may be reduced or increased, respectively by NNRTIs (e.g., efavirenz and nevirapine) and PIs (e.g., lopinavir/ritonavir) [37]. The combination of lumefantrine and artemether is efficacious and well tolerated in the treatment of acute uncomplicated malaria. However, research into the efficacy and tolerability of this combination in HIV-positive individuals receiving lumefantrine-containing antimalarial regimen along with PIs and NNRTIs are still lacking [37].

OTHER ANTIMALARIAL DRUGS

Other antimalarial drugs including chlorproguanil-dapsone, atovaquone-proguanil, pyronaridine, piperaquine, pyrimethamine-suphadoxine and related cotrimoxazole as well as tetracyclines and clarithromycin may be indicated as partner drugs and/or used as prophylaxis [21, 22, 35]. The use of pyrimethamine-sulphadoxine is now recommended in pregnant women for chemoprophylaxis of malaria in sub Saharan African countries. In contrast to the traditional weekly use of pyrimethamine, intermittent preventive treatment requires that at least 2 doses of sulphadoxine-pyrimethamine separated by one month be given beginning in the second trimester of pregnancy. This strategy has been found to reduce malaria associated morbidity in pregnant women and results are better in HIV negative individuals [21, 41]. Cotrimoxazole offers similar protection from malaria associated morbidity and it has been recommended that HIV infected individuals who are on cotrimoxazole prophylaxis would not require the use of sulphadoxine-pyrimethamine for intermittent preventive treatment in pregnancy [22, 23]. Comparative efficacy and tolerability of cotrimoxazole and sulphadoxine-pyrimethamine for intermittent preventive treatment in pregnancy is of urgent importance especially when considering the multiplicity of drugs that such individuals are exposed to.

COMBINATION ANTIRETROVIRAL THERAPY

The list of highly active antiretroviral therapy agents has grown exponentially over the past two decades. A comprehensive review of these new classes of drugs has been reported [37, 42]. Three major classes are widely used in sub-Saharan Africa and these include: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Newer drugs include integrase inhibitors like raltegravir and entry inhibitors like maraviroc, however, are still largely unavailable in this region of the world. Considering the ever accelerating programs on access to HIV/AIDS management, these agents may soon be incorporated. Available NRTIs in sub Saharan Africa include: zidovudine, emtricitabine, tenofovir, didanosine, lamivudine, stavudine, abacavir. Only two NNRTIs namely efavirenz and nevirapine are included in the armamentarium of HIV/AIDS treatment in most of the sub Saharan African countries. Lopinavir, saquinavir, indinavir and atazanavir are examples of PIs and are usually combined with ritonavir serving as a pharmacokinetic enhancer.

To date there are few research studies investigating NRTIs and antimalarial drug interactions. However, both recommended and alternate regimens discourage the use of all NRTI-regimen [42]. PI-based cART is usually second or third line regimen and lopinavir/ritonavir is the most common PI. Generally, PIs inhibit CYP3A4 and P-glycoprotein and in a few studies increased plasma concentrations of antimalarial drugs such as chloroquine have been reported [43]. There has been no information provided on the clinical significance of these pharmacokinetic interactions. Similarly, caution is required with the concomitant use of quinine and PIs. NNRTIs are hypothesized to have pharmacokinetic interactions with 4-aminoquinoline and amodiaquine but the extent and clinical implications are yet to be determined [37, 40]. A recent study to evaluate pharmacokinetic interactions between amodiaquine and efavirenz was stopped prematurely following a dramatic elevation of hepatic aminotransferases, perhaps due to high concentrations of amodiaquine-quinoimine, a hepatotoxic metabolite of amodiaquine via CYP3A4 metabolism [32]. It is important to note that nevirapine has a similar capability to induce CYP3A4. When this is considered along with the important role played by NNRTIs and PIs in chronic HIV treatment, drug interactions during case management of malaria in sub Saharan Africa becomes an issue of great concern. However, in a recent pilot evaluation in Nigeria on the pharmacokinetic interaction of nevirapine-containing cART in otherwise healthy HIV-positive subjects, no clinically serious untoward effects between artemether-lumefantrine or artesunate-amodiaquine and nevirapine-containing cART was observed (unpublished data).

PHARMACOGENOMICS CONSIDERATIONS FOR HIV/MALARIA DRUG INTERACTIONS RESEARCH

Although pharmacogenetic data are currently available for amodiaquine, mefloquine, primaquine, chlorproguanil and proguanil, limited sample size and lack of sound pharmacokinetic information prevent conclusions from these data. Based on their mechanism of metabolism and transport, quinine, chloroquine, artemisinin derivatives have been proposed as the candidates for future pharmacogenetic investigations. Particular attention is recommended for the use of artemisinins among patients with HIV infection, because many antiretrovirals are substrates and/or inhibitors of CYP3A and MDR1, thus, there is a potential risk of multiple drug interactions [46, 47].

Table 1 summarizes the relevant information describing these aspects of antimalarial clinical pharmacology.

ROLE OF MULTILATERAL CLINICAL RESEARCH INITIATIVES

There are numerous organizations, both governmental and nongovernmental, within and outside sub- Saharan Africa that are engaged in efforts to combat malaria and HIV/AIDS. Many of these organizations seek to provide a sustainable relationship between Europe or North America and sub-Saharan African countries. Notable initiatives include: the Malaria Clinical Trials Alliance (MCTA), African Malaria Network (AMANET), Roll Back Malaria, and Multilateral Initiative in Malaria (MIM) attempting to address malaria while initiatives like the Comprehensive International Program of Research on AIDS (CIPRA), AIDS International Training and Research Program (AITRP), and Microbicides Trials Network (MTN) primarily focus on HIV/AIDS related issues [44, 45]. In Nigeria, there is the AIDS Prevention Initiative in Nigeria (APIN) and the United States President Emergency Plan for AIDS Relief (PEFAR), both of which provide clinical program development for HIV/AIDS treatment. Some national governments also have commissions for the purpose of controlling HIV/AIDS, for example, in Nigeria there is the National Agency for Control of AIDS (NACA). The University at Buffalo School of Pharmacy and Pharmaceutical Sciences now partners with the University of Zimbabwe and has been involved in providing mentoring for research capacity building and support on HIV/AIDS related research issues [44]. Collaboration such as this and others so fashioned could easily expand their scope, taking up the drug interaction challenges that have been identified in this review.

Table 2 summarizes the current situation regarding documented or potential interactions between components of cART used in sub-Saharan Africa and commonly used antimalarial drugs. This could serve as a starting point in the prioritization of more collaborative research efforts in this area. Countries like Nigeria where the prevalence of HIV/AIDS is 4.4% of over 140 million people and an annual incidence of malaria of about 50% in the general population would be best suited to collaborate with initiatives that address these two conditions simultaneously. A sustainable relationship should be based on technology transfer and capacity building, beginning with scholarly exchanges between resource-rich and poor countries in areas of HIV clinical pharmacology and medication management. Established HIV/AIDS clinical pharmacology researchers combining forces with individuals with expertise in malaria will lead to teams that are motivated and qualified to address the issues cited in this review.

CONCLUSION

The management of malaria in HIV-infected individuals is in need of focused research efforts because of the public health importance of these two conditions. Additional evidence-based guidelines are needed, upon which important clinical decisions of treatment and/or chemoprophylaxis of malaria especially in HIV-infected pregnant women should be based. An integrated approach to research capacity building and prioritization of new research efforts through established international collaborations will facilitate the conduct of drug interaction studies that are needed to guide the management of HIV/AIDS and malaria.

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Table 1

Pharmacogenetics of Antimalarial Drugs (Modified From Reference): [48]

Drug	Mechanism of Metabolism/Transport	Single Nucleotide Polymorphisms
Amodiaquine	CYP2C8, −1A1, −1B1	*CYP2C8*3*, *CYP2C8*2*
Artemisinins	CYP2A6, −3A4/5, −2B6 (secondary), UGT1A9, −2B7, −3A4 and MDR1 inducer	--
Chloroquine	CYP2C8, −3A4/5, −2D6, MDR1	--
Chlorproguanil/proguanil	CYP2C19, −3A4	*CYP2C19*
Mefloquine	CYP3A4, MDR1, BCRP	*ABCB1 1236, −2677, −3435*, *ABCG2*
Primaquine	CYP1A2, −3A4	*G6PD*
Quinine	CYP3A4/5, −2C9, MDR1	*CYP3A5*3*

Table 2

Interactions or Potential Interactions between Components of cART Used in Sub Saharan Africa and Commonly Used Antimalarial Drugs*

	Chloroquine	Quinine	Amodiquine	Mefloquine	Artemether	LUM	S-P	Cotrim*
AZT	−	−	−	−	−	−	−	−
3TC	−	−	−	−	−	−	−	−
d4T	−	−	−	−	−	−	−	−
ABC	−	−	−	−	−	−	−	−
ddI	−	−	−	−	−	−	−	−
FTC	−	−	−	−	−	−	−	−
TDF	−	−	−	−	−	−	−	−
NVP	NA	NA	+	NA	+	+	NA	NA
EFV	NA	NA	+	NA	+	+	NA	NA
LPV	+	NA	NA	NA	NA	+	NA	NA
ATV	NA	NA	NA	NA	NA	+	NA	NA
SQV	NA	NA	NA	NA	NA	+	NA	NA
IDV	NA	NA	NA	NA	NA	+	NA	NA

*Cotrimoxazole is not recommended for treatment or prophylaxis of malaria in the general population, which is included because it has been recommended for such purpose in HIV + individuals

Abbreviations: Cotrim, cotrimoxazole (sulphamethoxazole-trimethoprim); S-P, sulphadoxine-pyrimethamine; LUM, lumefantrine; AZT, zidovudine; 3TC, lamivudine; d4T, stavudine; ABC, abacavir; ddI, didanosine; FTC, emtricitabine; TDF, tenofovir; NVP, nevirapine; EFV, efavirenz; LPV, lopinavir; ATV, atazanavir; SQV, saquinavir; IDV, indinavir

− No demonstrable interaction or clinically significant interaction is unlikely

+ Documented interactions or potential for interaction is high

NA No appreciable clinical data available or data completely lacking