SAGE-Hindawi Access to Research
Malaria Research and Treatment
Volume 2011, Article ID 703730, 5 pages
doi:10.4061/2011/703730

Review Article

Artemether-Lumefantrine Combination Therapy for Treatment of Uncomplicated Malaria: The Potential for Complex Interactions with Antiretroviral Drugs in HIV-Infected Individuals

Pauline Byakika-Kibwika,[1,2] Mohammed Lamorde,[1,2] Harriet Mayanja-Kizza,[1] Saye Khoo,[3] Concepta Merry,[1,2] and Jean-Pierre Van geertruyden[4]

[1] *Infectious Diseases Institute and Infectious Diseases Network for Treatment and Research in Africa (INTERACT), Makerere University College of Health Sciences, P.O. Box 7061, Kampala, Uganda*
[2] *Department of Pharmacology and Therapeutics, Trinity College Dublin 2, Ireland*
[3] *Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool L69 3BX, UK*
[4] *International Health, Epidemiology en Social Medicine, Universiteit Antwerpen, Universiteitsplein 1, 2610 Antwerp, Belgium*

Correspondence should be addressed to Pauline Byakika-Kibwika, pbyakika@gmail.com

Received 14 December 2010; Accepted 14 February 2011

Academic Editor: Neena Valecha

Treatment of malaria in HIV-infected individuals receiving antiretroviral therapy (ART) poses significant challenges. Artemether-lumefantrine (AL) is one of the artemisisnin-based combination therapies recommended for treatment of malaria. The drug combination is highly efficacious against sensitive and multidrug resistant *falciparum* malaria. Both artemether and lumefantrine are metabolized by hepatic cytochrome P450 (CYP450) enzymes which metabolize the protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) used for HIV treatment. Coadministration of NNRTIs and PIs with AL could potentially cause complex pharmacokinetic drug interactions. NNRTI by inducing CYP450 3A4 enzyme and PIs by inhibiting CYP450 3A4 enzymes could influence both artemether and lumefantrine concentrations and their active metabolites dihydroartemisinin and desbutyl-lumefantrine, predisposing patients to poor treatment response, toxicity, and risk for development of resistance. There are scanty data on these interactions and their consequences. Pharmacokinetic studies to evaluate these interactions in the target populations are urgently needed.

1. Introduction

Human immunodeficiency virus (HIV) and malaria have overlapping geographical distribution. Together, the two diseases account for 4 million deaths a year worldwide [1]. Over 90% of the world malaria burden occurs in sub-Saharan Africa, the region with 67% of the global HIV burden. Given the extensive overlap in geographical distribution of the two diseases, any interaction between the two could have profound public health consequences. In areas with stable malaria transmission, HIV increases risk of malaria infection and clinical malaria especially in individuals with advanced immunosuppression and in areas with unstable malaria transmission; HIV-infected individuals are at increased risk for severe malaria and death [1, 2].

This vulnerable population requires prompt, safe and effective antimalarial treatment. Current guidelines for malaria treatment advocate use of artemisinin-based combination therapies (ACTs). Treatment of malaria in HIV-infected individuals receiving ART poses significant challenges with gaps in the knowledge of ART and ACT drug-drug interactions and their consequences.

Antiretroviral drugs are among the most therapeutically risky drugs for drug-drug interactions due to the potent inhibition and induction of cytochrome (CYP) enzymes as well as transport proteins. The combination of at least

three drugs for highly active ART increases the risk for drug-drug interactions. The risk of clinically significant interactions involving ART when coadministered with substrates of CYP enzymes is considerable and may result in high concentrations with excessive toxicity or reduced concentrations with reduced efficacy and risk for development of resistance. Clinically significant CYP-mediated drug-drug interactions are more likely to occur with non nucleoside reverse transcriptase inhibitors (NNRTs) and protease inhibitors- (PIs-) based ART regimens because these are substrates, inducers, and/or inhibitors of CYP enzymes which metabolize the majority of drugs and xenobiotics [3]. Nucleoside reverse transcriptase inhibitors do not undergo CYP-mediated metabolism and are less likely to cause CYP-mediated drug interactions. They may cause interactions by influencing absorption, distribution, and elimination of coadministered drugs.

2. Artemether-Lumefantrine Use in Treatment of Malaria

Artemether and lumefantrine have different modes of action and act at different points in the parasite life cycle. Oral formulations of AL are available as tablet and dispersible formulations with similar pharmacokinetic properties [4, 5]. A six-dose regimen of artemether (20 mg) coformulated with lumefantrine (120 mg) is recommended; with first and second doses taken eight hours apart, the third dose is taken 24 hours after the first and the remaining doses 12 hours apart [6, 7]. Food enhances absorption of both artemether and lumefantrine although this effect is more apparent for lumefantrine [8–10]. The typical fat content of African diets has been demonstrated to be adequate for optimal absorption of AL [11], although the loss of appetite, nausea and vomiting in patients with malaria may compromise fat intake. Plasma concentrations of lumefantrine remain high with repeated doses over the 3 day course; however, poor adherence to the 3-day regimen may reduce effectiveness of AL. In multidrug resistant areas, day 7 lumefantrine concentration was a useful surrogate marker for AUC and concentrations of less than 280 ng/mL predicted treatment failure [9, 12].

Efficacy of the 6-dose regimen of AL is consistently greater than 95%, with rapid parasite and symptom clearance and significant gametocidal effect [4, 13–17]. A few cases of treatment failure are recorded after AL treatment; however, these are mostly reinfections [18–21]. This is of particular concern in areas with very intense malaria transmission where antimalarial drugs with longer half-life may offer the advantage of preventing reinfection. It is also of concern in HIV-infected individuals who are at increased risk for malaria infection [22]. Use of cotrimoxazole prophylaxis and insecticide treated bednets markedly reduces the incidence of malaria in HIV-infected individuals and are recommended.

AL is safe and well tolerated. Majority of adverse events are of mild or moderate severity mostly affecting gastrointestinal and nervous systems; however, most are typical of the symptomatology of malaria or concomitant infections [4, 14–17, 23]. Although lumefantrine possesses similar chemical structure with halofantrine which is known to cause cardiac arrhythmia and sudden death, safety studies have not shown lumefantrine to be cardiotoxic or to prolong QTc interval at therapeutic doses [24, 25].

3. Pharmacology of Artemether

Artemether is derived from the Chinese herb sweet wormwood (*Artemisua annua*). The antimalarial properties of artemether stem from interference with parasite transport proteins, disruption of parasite mitochondrial function, inhibition of angiogenesis, and modulation of host immune function [26]. Artemether is absorbed very rapidly after oral administration reaching peak plasma concentrations within 2 hours after dose [8, 10, 12]. It has a half-life of 1–3 hours. It is metabolized quickly via CYP450 2B6, CYP450 3A4 and possibly CYP450 2A6 [27, 28] to the more potent antimalarial metabolite DHA, which in turn is converted to inactive metabolites primarily by glucuronidation via UGT1A1, 1A8/9 and 2B7 [27]. Artemether induces CYP450 2C19 and 3A4 [28]. DHA reaches maximum plasma concentration within 2-3 hours after dosing. Artemether acts rapidly to clear malaria parasites from circulation. Both artemether and DHA offer potent antimalarial properties causing significant reduction in asexual parasite mass of approximately 10,000 fold (4 log) per reproductive cycle, with prompt resolution of symptoms [29, 30].

4. Pharmacology of Lumefantrine

Lumefantrine is an aryl-amino alcohol [27] that prevents detoxification of heam, such that toxic heam and free radicals induce parasite death [31]. Lumefantrine absorption occurs 2 hours after oral intake reaching peak plasma concentration after 3-4 hours [9]. It has a half life of 3–6 days and is responsible for preventing recurrent malaria parasitemia [32]. It is absorbed and cleared slowly acting to eliminate residual parasites that may remain after artemether and DHA have been cleared from the body and thus prevents recrudescence [8, 31]. Lumefantrine is metabolized by N-debutylation mainly by CYP450 3A4 [27, 28] to desbutyl-lumefantrine with 5–8-fold higher antiparasitic effect than lumefantrine. Lumefantrine inhibits CYP450 2D6 [28].

5. Pharmacology of Antiretroviral Drugs

Current guidelines for treatment of HIV in most resource limited settings recommend combination therapy of 2 NRTIs and 1 NNRTI as initial treatment for ART naïve patients and for patients with treatment failure; 2NRTIs and 1 PI are recommended. The NRTIs are analogues of naturally occurring deoxynucleotides needed to synthesize viral DNA. They are well absorbed after oral administration; however, NRTIs must be converted to their active metabolites, NRTI triphosphates, intracellularly, after endocytosis by addition of three phosphate groups to their deoxyribose moiety, a reaction catalyzed by cellular kinase enzymes. The triphosphate

metabolites compete with the natural deoxynucleotides for incorporation into the viral DNA chain. Their incorporation inhibits formation of phosphodiester bridges and prevents viral DNA synthesis and elongation. Most NRTIs are excreted unchanged through the kidney while zidovudine is excreted via the liver through glucoronidation.

The NNRTIs inhibit reverse transcriptase enzyme by binding directly and noncompetitively to the enzyme at a position in close proximity to the substrate binding site for nucleosides inducing conformational changes that impact enzyme catalytic activities. The resulting complex blocks the catalyst activated binding site which in turn, binds fewer nucleosides, slowing down polymerization significantly [33]. Nevirapine and Efavirenz are the two NNRTIs available for use in most malaria endemic regions [34].

6. Nevirapine

Nevirapine is administered with a dose escalation schedule starting at an adult dose of 200 mg once daily for 2 weeks followed by 200 mg twice daily thereafter because of the potential for adverse events and metabolic autoinduction of CYP450 enzymes. Absorption is not affected by food, acids, or alkali, and more than 90% of the administered dose is absorbed after oral intake [35] with bioavailability of more than 90% and about 60% protein binding.[36] The elimination half life is 25–30 hours. It is distributed throughout the body [35], metabolized by CYP450 3A4 and 2B6, and excreted via the liver and kidneys in the form of glucuronide conjugates of hydroxylated metabolites [35]. It is both a substrate and inducer of CYP450 3A4, and 2B6 [36].

Tolerability to nevirapine in majority of patients is relatively good [37]. The adverse event most commonly observed is a hypersensitivity rash, occurring in about 16% of patients with about 7% experiencing grade 3 or 4 rash with the Steven Johnson syndrome. Hypersensitivity is more common during the first 6 weeks of treatment [35]. The second common adverse event is hepatotoxicity with elevated liver enzymes. Female sex and a high CD4 cell count are associated with higher incidence of nevirapine-induced hypersensitivity [35, 38].

7. Efavirenz

Efavirenz is available as capsules, film-coated tablets and liquid formulation for oral administration. The recommended adult dose is 600 mg od, taken on an empty stomach, preferably at bedtime to diminish possible neuropsychiatric side effects that are enhanced with increased bioavailability in presence of food. It is highly protein bound (>99%), predominantly to albumin [39]. Oral bioavailability is good; reaching peak plasma concentrations within 3–5 hours after dose administration. It has a long serum half-life of 45 hours and reaches steady-state plasma concentrations in 6 to 10 days [40]. Efavirenz is a substrate, inhibitor and inducer of several CYP450 enzymes (2B6, 3A4, 2A6, 2C9, and 2C19) and induces its own metabolism [39]. It is metabolized to inactive hydroxylated metabolites that include 8-hydoxy and 7-hydroxyefavirenz. Hydroxylated efavirenz metabolites undergo subsequent urinary and biliary excretion after conjugation mainly glucuronidation.

The safety profile of efavirenz is good with minor side effects including skin rash and neuropsychiatric events. The rash is maculopapular, often of mild to moderate intensity (grade 1 or 2), occurring between the first and third week of treatment with incidence up to 34% [40]. It resolves spontaneously within one month or with treatment interruption, after which efavirenz may be reinitiated cautiously. The incidence of grade 3 or 4 rash with Stevens-Johnson syndrome is only 0.1%, and once it occurs, treatment should be stopped immediately. Neuropsychiatric events may occur including dizziness, insomnia, somnolence, impaired concentration, vivid dreams, and nightmares. More severe events like severe depression, suicidal ideation, nonfatal suicidal attempts, aggressive behaviour, paranoid, and manic reactions seldom occur [41]. Hepatotoxicity has been shown to occur during efavirenz treatment [38] with increased risk in patients with chronic viral hepatitis. Other side effects include gynaecomastia, increase in HDL-cholesterol, and elevated triglycerides.

8. Lopinavir/Ritonavir

The PIs prevent viral replication by inhibiting activity of the HIV protease enzyme and preventing HIV from being successfully assembled and released from the infected CD4 cell. HIV-1 protease is an aspartic protease that cleaves both structural and functional proteins from precursor viral polypeptide strands. Inhibition of the protease produces immature, noninfectious virions, thus preventing subsequent cellular infection [42]. Lopinavir coformulated with ritonavir is the most frequently prescribed PI in most malaria endemic regions.

Lopinavir is 3 to 4 times more active against HIV than ritonavir; however, when lopinavir is administered alone, it exhibits poor bioavailability. Lopinavir is metabolized extensibly by CYP450 3A4 and coadministration with ritonavir which is a potent inhibitor of CYP450 3A4 results in increased and sustained concentrations of lopinavir [43]. Both drugs are primarily eliminated by the fecal route with urinary excretion accounting for <2% of the eliminated drug [44]. The co-formulation is available in tablet formulation called (Aluvia) for adults, each tablet containing 200 mg lopinavir and 50 mg ritonavir.

The standard dose is 400 mg/100 mg twice daily in treatment experienced patients. Combination therapy with lopinavir/ritonavir containing regimens is well tolerated and effective in suppressing HIV-RNA and increasing $CD4^+$ T cell counts [43]. The most frequent side effects are generally mild to moderate and mainly in the gastrointestinal system where diarrhea, nausea, and vomiting may occur. Other side effects are hypertriglyceridemia, hypercholesterolemia, pancreatitis, transient elevations in transaminase levels, insulin resistance, new onset diabetes, and worsening of pre-existing diabetes. Fat redistribution occurs with central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial

wasting, breast enlargement, and cushingoid appearance. Less common adverse effects include allergic reaction, asthenia, malaise, headache, myalgias, arthralgias, myocardial infarction, seizures, and lactic acidosis [43].

9. Potential for Pharmacokinetic Interactions between AL and ART

9.1. Effect of ART on AL. Coadministration of NNRTI or PI-based ART with AL could potentially cause drug interactions with effects on the plasma concentrations of artemether and lumefantrine with unknown effects on parasite clearance and adverse effects. There are very scanty data on these interactions and their effects, yet AL and ART continue to be coprescribed in malaria endemic regions. A study that investigated the pharmacokinetics of the standard 6 dose of AL as 80/480 mg twice daily when administered with lopinavir/ritonavir 400/100 mg twice daily in healthy HIV-seronegative volunteers demonstrated 2- to 3-fold increases in lumefantrine AUC and trends towards decreases in artemether C_{max} and AUC with decrease in DHA AUC. The authors concluded that coadministration of AL and lopinavir/ritonavir can be carried out but highlighted the need for formal safety analysis of concomitant therapy [45]. Data from another pharmacokinetics study of HIV-infected participants without malaria, surprisingly demonstrated significantly increased lumefantrine exposure when coadministered with nevirapine although toxicity was not increased [46].

9.2. Effect of AL on ART. It is not known what plasma levels of ART will result if AL is administered with ART; however, since malaria infection occurs as an acute illness requiring a short course of therapy, the effect of AL on ART may only be transient with clinically insignificant results. However, in malaria endemic regions, where individuals are exposed to repeated malaria infections requiring treatment, the effect of drug interactions combined with the transient increase in viral replication and viral load [47] may be similar to effects of suboptimal adherence to ART.

10. Conclusion

There is potential for pharmacokinetic drug interactions between AL and NNRTIs and PIs in HIV-infected patients with malaria. Data on these interactions is sparse. These interactions, if not properly addressed, might have an impact on the Useful Therapeutic Lives (UTL) of the concerned drugs. Results of pharmacokinetic studies evaluating these interactions in depth and their implications are needed.

Disclosure

None to declare. None of the authors received funding from the manufactures of AL or ART.

References

[1] *Malaria and HIV and Their Implications for Public Policy*, World Health Organisation, Geneva, Switzerland, 2005.

[2] V. Chalwe, J. P. Van Geertruyden, D. Mukwamataba et al., "Increased risk for severe malaria in HIV-1-infected adults, Zambia," *Emerging Infectious Diseases*, vol. 15, no. 5, pp. 749–755, 2009.

[3] S. C. Piscitelli and K. D. Gallicano, "Interactions among drugs for HIV and opportunistic infections," *The New England Journal of Medicine*, vol. 344, no. 13, pp. 984–996, 2001.

[4] S. Abdulla, I. Sagara, S. Borrmann et al., "Efficacy and safety of artemether-lumefantrine dispersible tablets compared with crushed commercial tablets in African infants and children with uncomplicated malaria: a randomised, single-blind, multicentre trial," *The Lancet*, vol. 372, no. 9652, pp. 1819–1827, 2008.

[5] S. Abdulla and I. Sagara, "Dispersible formulation of artemether/lumefantrine: specifically developed for infants and young children," *Malaria Journal*, vol. 8, supplement 1, article S7, 2009.

[6] A. A. Omari, C. Gamble, and P. Garner, "Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria," *Cochrane Database of Systematic Reviews*, no. 2, p. CD005965, 2006.

[7] A. A. Omari, C. Gamble, and P. Garner, "Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria," *Cochrane Database of Systematic Reviews*, no. 4, p. CD005564, 2005.

[8] N. J. White, M. Van Vugt, and F. Ezzet, "Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine," *Clinical Pharmacokinetics*, vol. 37, no. 2, pp. 105–125, 1999.

[9] F. Ezzet, M. Van Vugt, F. Nosten, S. Looareesuwan, and N. J. White, "Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria," *Antimicrobial Agents and Chemotherapy*, vol. 44, no. 3, pp. 697–704, 2000.

[10] N. J. White, M. Van Vugt, and F. Ezzet, "Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine," *Clinical Pharmacokinetics*, vol. 37, no. 2, pp. 105–125, 1999.

[11] Z. G. Premji, S. Abdulla, B. Ogutu et al., "The content of African diets is adequate to achieve optimal efficacy with fixed-dose artemether-lumefantrine: a review of the evidence," *Malaria Journal*, vol. 7, article 244, 2008.

[12] F. Ezzet, R. Mull, and J. Karbwang, "Population pharmacokinetics and therapeutic response of CGP 56697 (artemether + benflumetol) in malaria patients," *British Journal of Clinical Pharmacology*, vol. 46, no. 6, pp. 553–561, 1998.

[13] M. Makanga and S. Krudsood, "The clinical efficacy of artemether/lumefantrine (Coartem®)," *Malaria Journal*, vol. 8, no. 1, article S5, 2009.

[14] M. van Vugt, P. Wilairatana, B. Gemperli et al., "Efficacy of six doses of artemether-lumefantrine (benflumetol) in multidrug-resistant Plasmodium falciparum malaria," *American Journal of Tropical Medicine and Hygiene*, vol. 60, no. 6, pp. 936–942, 1999.

[15] M. Van Vugt, S. Looareesuwan, P. Wilairatana et al., "Artemether-lumefantrine for the treatment of multidrug-resistant falciparum malaria," *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 94, no. 5, pp. 545–548, 2000.

[16] G. Lefèvre, S. Looareesuwan, S. Treeprasertsuk et al., "A clinical and pharmacokinetic trial of six doses of artemether-lumefantrine for multidrug-resistant Plasmodium falciparum

malaria in Thailand," *American Journal of Tropical Medicine and Hygiene*, vol. 64, no. 5-6, pp. 247–256, 2001.

[17] C. Hatz, J. Soto, H. D. Nothdurft et al., "Treatment of acute uncomplicated falciparum malaria with artemether-lumefantrine in non-immune populations: a safety, efficacy, and pharmacokinetic study," *American Journal of Tropical Medicine and Hygiene*, vol. 78, no. 2, pp. 241–247, 2008.

[18] A. Yeka, G. Dorsey, M. R. Kamya et al., "Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treating uncomplicated malaria: a randomized trial to guide policy in Uganda," *PLoS ONE*, vol. 3, no. 6, article e2390, 2008.

[19] M. R. Kamya, A. Yeka, H. Bukirwa et al., "Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treatment of malaria: a randomized trial," *PLoS Clinical Trials*, vol. 2, no. 5, article e20, 2007.

[20] A. M. Kabanywanyi, A. Mwita, D. Sumari, R. Mandike, K. Mugittu, and S. Abdulla, "Efficacy and safety of artemisinin-based antimalarial in the treatment of uncomplicated malaria in children in southern Tanzania," *Malaria Journal*, vol. 6, Article ID 146, 2007.

[21] H. Bukirwa, Y. Adoke, M. R. Kamya et al., "Artemisinin combination therapies for treatment of uncomplicated malaria in Uganda," *Plos Clinical Trials*, vol. 1, no. 1, article e7, 2006.

[22] J. P. Van Geertruyden, M. Mulenga, L. Mwananyanda et al., "HIV-1 immune suppression and antimalarial treatment outcome in Zambian adults with uncomplicated malaria," *Journal of Infectious Diseases*, vol. 194, no. 7, pp. 917–925, 2006.

[23] C. Falade, M. Makanga, Z. Premji, C. E. Ortmann, M. Stockmeyer, and P. Ibarra de Palacios, "Efficacy and safety of artemether-lumefantrine (Coartem®) tablets (six-dose regimen) in African infants and children with acute, uncomplicated falciparum malaria," *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 99, no. 6, pp. 459–467, 2005.

[24] Advisory Committee Briefing Book, "Coartem® (artemether/lumefantrine) tablets for the treatment of malaria in patients with acute, uncomplicated infections due to Plasmodium falciparum or mixed infections including P. falciparum," http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-02-Novartis.pdf, 2008.

[25] C. Falade and C. Manyando, "Safety profile of Coartem®: the evidence base," *Malaria Journal*, vol. 8, supplement 1, article S6, 2009.

[26] J. Golenser, J. H. Waknine, M. Krugliak, N. H. Hunt, and G. E. Grau, "Current perspectives on the mechanism of action of artemisinins," *International Journal for Parasitology*, vol. 36, no. 14, pp. 1427–1441, 2006.

[27] F. T. Aweeka and P. I. German, "Clinical pharmacology of artemisinin-based combination therapies," *Clinical Pharmacokinetics*, vol. 47, no. 2, pp. 91–102, 2008.

[28] S. Khoo, D. Back, and P. Winstanley, "The potential for interactions between antimalarial and antiretroviral drugs," *AIDS*, vol. 19, no. 10, pp. 995–1005, 2005.

[29] N. J. White, "Preventing antimalarial drug resistance through combinations," *Drug Resistance Updates*, vol. 1, no. 1, pp. 3–9, 1998.

[30] A. Djimdé and G. Lefèvre, "Understanding the pharmacokinetics of Coartem®," *Malaria Journal*, vol. 8, supplement 1, article S4, 2009.

[31] G. Kokwaro, L. Mwai, and A. Nzila, "Artemether/lumefantrine in the treatment of uncomplicated falciparum malaria," *Expert Opinion on Pharmacotherapy*, vol. 8, no. 1, pp. 75–94, 2007.

[32] M. A. Travassos and M. K. Laufer, "Resistance to antimalarial drugs: molecular, pharmacologic, and clinical considerations," *Pediatric Research*, vol. 65, no. 5, pp. 64R–70R, 2009.

[33] C. Hoffmann, J. K. Rockstroh, and B. S. Kamps, *HIV Medicine*, Flying, Paris, Farnce, 2005.

[34] A. Tseng and R. D. MacArthur, "Profile of etravirine for the treatment of HIV infection," *Therapeutics and Clinical Risk Management*, vol. 6, no. 1, pp. 49–58, 2010.

[35] D. Podzamczer and E. Fumero, "The role of nevirapine in the treatment of HIV-1 disease," *Expert Opinion on Pharmacotherapy*, vol. 2, no. 12, pp. 2065–2078, 2001.

[36] D. Back, S. Gibbons, and S. Khoo, "Pharmacokinetic drug interactions with nevirapine," *Journal of Acquired Immune Deficiency Syndromes*, vol. 34, supplement 1, pp. S8–S14, 2003.

[37] M. Colafigli, S. Di Giambenedetto, L. Bracciale et al., "Long-term follow-up of nevirapine-treated patients in a single-centre cohort," *HIV Medicine*, vol. 10, no. 8, pp. 461–469, 2009.

[38] A. Rivero, J. A. Mira, and J. A. Pineda, "Liver toxicity induced by non-nucleoside reverse transcriptase inhibitors," *Journal of Antimicrobial Chemotherapy*, vol. 59, no. 3, pp. 342–346, 2007.

[39] N. Y. Rakhmanina and J. N. van den Anker, "Efavirenz in the therapy of HIV infection," *Expert Opinion on Drug Metabolism and Toxicology*, vol. 6, no. 1, pp. 95–103, 2010.

[40] S. M. E. Vrouenraets, F. W. N. M. Wit, J. van Tongeren, and J. M. A. Lange, "Efavirenz: a review," *Expert Opinion on Pharmacotherapy*, vol. 8, no. 6, pp. 851–871, 2007.

[41] G. O. Adjei, K. Kristensen, B. Q. Goka et al., "Effect of concomitant artesunate administration and cytochrome P4502C8 polymorphisms on the pharmacokinetics of amodiaquine in Ghanaian children with uncomplicated malaria," *Antimicrobial Agents and Chemotherapy*, vol. 52, no. 12, pp. 4400–4406, 2008.

[42] C. Hoffmann, J. K. Rockstroh, and B. S. Kamps, *HIV Medicine*, Flying, Paris, France, 2006.

[43] A. H. Corbett, M. L. Lim, and A. D. M. Kashuba, "Kaletra (lopinavir/ritonavir)," *Annals of Pharmacotherapy*, vol. 36, no. 7-8, pp. 1193–1203, 2002.

[44] G. N. Kumar, V. K. Jayanti, M. K. Johnson et al., "Metabolism and disposition of the HIV-1 protease inhibitor lopinavir (ABT-378) given in combination with ritonavir in rats, dogs, and humans," *Pharmaceutical Research*, vol. 21, no. 9, pp. 1622–1630, 2004.

[45] P. German, S. Parikh, J. Lawrence et al., "Lopinavir/ritonavir affects pharmacokinetic exposure of artemether/lumefantrine in HIV-uninfected healthy volunteers," *Journal of Acquired Immune Deficiency Syndromes*, vol. 51, no. 4, pp. 424–429, 2009.

[46] K. Tamara, K. Mauff, P. Smith et al., "Nevirapine increases lumefantrine exposure in HIV-infected patients," in *Proceedings of the Conference on Retroviruses and Opportunistic Infections*, San Francisco, Calif, USA, 2010.

[47] J. G. Kublin, P. Patnaik, C. S. Jere et al., "Effect of Plasmodium falciparum malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study," *The Lancet*, vol. 365, no. 9455, pp. 233–240, 2005.