

*Full Length Research Paper*

# The pharmacokinetics of lumefantrine in adults on nevirapine-based antiretroviral therapy

<sup>\*1</sup>Dr. David Musoke, <sup>2</sup>Dr. Muhammad Ntale and <sup>3</sup> Dr. Jasper Ogwal-Okeng

<sup>\*1</sup>Department of Pharmacology, Gulu University, P.O. Box 166, Gulu, Uganda

<sup>2</sup>Department of Chemistry, Makerere University, P.O. Box 7062, Kampala, Uganda

<sup>3</sup>Department of Pharmacology, Gulu University, P. O. Box 166, Gulu, Uganda

Corresponding Author's E-mail: musoke.muweke@gmail.com

Accepted 23<sup>rd</sup> March, 2015

Pharmacokinetic parameters of lumefantrine in subjects treated for malaria and HIV-1 were obtained in two groups: antiretroviral therapy (ART) naive patients and those on nevirapine-based therapy. Both groups were on co-trimoxazole (TS) prophylaxis. Patients were enrolled prospectively. Both groups received artemether-lumefantrine (AL) combination twice daily for 3 days. Blood samples were collected just before the last dose and subsequently at 2, 4, 8, 24 and 120 h post dose. Concentrations of lumefantrine were determined by high performance liquid chromatography. Mean area under the plasma concentration-time curve ( $AUC_{0-\infty}$ ) was 589  $\mu\text{g h/ml}$  (552.4 - 627.4), mean maximum concentration ( $C_{\text{max}}$ ) was 8.67  $\mu\text{g/ml}$  (8.20 - 9.14), mean Day 7 concentration ( $C_{\text{day 7}}$ ) was 0.99  $\mu\text{g/ml}$  (0.94 - 1.04), mean elimination rate ( $K_0$ ) was 0.0214  $\mu\text{g/h}$  (0.0207- 0.0221), and mean half life was ( $T_{1/2}$ ) (h) 32.5 hrs (31.4 - 33.6) for subjects on nevirapine based ART and for ART naive subjects were 375.2 (349.7- 400.7), 6.08 (5.57- 6.59), 0.64 (0.54 - 0.74), 0.0195 (0.0185 - 0.0205), 36.0 (34.1- 37.9) respectively. Time to maximum concentration ( $T_{\text{max}}$ ) was 4 h in both groups. Nevirapine based ART significantly increases the exposure of lumefantrine but it is well tolerated.

**Keywords:** Pharmacokinetics, lumefantrine, nevirapine, HIV, Malaria.

## INTRODUCTION

Malaria and human immunodeficiency virus (HIV) are a leading cause of morbidity and mortality in Uganda and parts of sub-Saharan Africa (Proietti et al., 2011; UNAIDS, 2007). Several studies have reported an increased frequency of malaria in people with HIV (Whitworth et al., 2000; French et al., 2001; Cohen et al., 2005). Co-trimoxazole prophylaxis and antiretroviral therapy (ART) have been reported to reduce the occurrence of malaria infection in patients living with HIV (Nakanjako et al., 2011; Flateau et al., 2011; Kanya et al., 2007). Co-trimoxazole is currently prescribed for prophylaxis to all people living with HIV as a matter of health policy.

The first line treatment for malaria is by artemether-lumefantrine (AL) combination (80 mg and 480 mg respectively) administered orally, twice daily as a 3-day

treatment course based on World Health Organisation recommendation (WHO, 2010). AL is therefore by necessity being prescribed alongside antiretroviral medicines (ARVs) and Co-trimoxazole in cases of malaria and HIV co-infection. Tremendous effort and resources have been made to increase the number of people living with HIV to get started on ART. The first line treatment for HIV infection in Uganda is the triple therapy regimen composed of zidovudine (ZDV) 300 mg, lamivudine (3TC) 150 mg with nevirapine (NVP) 200 mg twice daily (Katabira and Kanya, 2003).

ZDV and 3TC are intracellularly phosphorylated and eliminated via the renal system (Khoo et al., 2005). Artemether and lumefantrine are predominantly metabolized by the cytochrome P450 (CYP) isoenzyme CYP3A4 (White et al., 1999). NVP is also mainly

metabolised by CYP3A4 but it is also reported to be an inducer of this isoenzyme (Khoo et al., 2005; Back et al., 2003). This drug-drug interaction between AL and NVP based ART has previously been investigated in HIV-1 infected adult subjects without malaria (Kredo et al., 2011).

The primary objective of this study was to determine the steady state pharmacokinetics of lumefantrine when administered to subjects co-infected with malaria and HIV with and without NVP based antiretroviral therapy. The safety of the AL combination in these subjects was also assessed.

### METHODS

#### Study site

This study was conducted at the ART clinic of Gulu Regional Referral and Teaching Hospital, Uganda during the period between December 2010 and November 2011. Malaria and HIV are prevalent in this region.

#### Study design and sample size

This was a two-arm, parallel design, open-label, pharmacokinetic study of lumefantrine at steady state after a full course of AL in adult patients co-infected with malaria and HIV. One arm was ART naive while the other was for ART experienced patients on a fixed-dose regimen of ZDV 300 mg, 3TC 150 mg and NVP 200 mg, twice daily (DUOVIR-N® CIPLA LTD, India). All patients in both arms were receiving TS for prophylaxis (COTRI®, Medreich Ltd, India). Sample size calculation was based on difference in area under the plasma concentration-time curves (AUC) between the ART naive group and the group receiving nevirapine based antiretroviral therapy. It was to detect a difference of 40% in lumefantrine AUC at a 5% significance level, given a 60% between subject co-efficient variations with a power of 80%. Twenty-two subjects were required in each arm. These subjects were recruited consecutively until the desired number was achieved.

#### Inclusion and exclusion criteria

All adult patients whose blood smears (thin and thick films) tested positive for malaria parasites and had a confirmed diagnosis of HIV-1 were eligible for recruitment onto the study. Those initiated on NVP based ART must have been on treatment for at least 4 weeks.

Individuals with complicated malaria (i.e. impaired consciousness, multiple/recurrent convulsion, deep breathing or respiratory distress, difficulty in breathing or demonstrable pulmonary oedema, circulatory collapse or shock, jaundice, generalized weakness and severe anaemia), abnormal cardiac, liver or renal function, pregnant women or breastfeeding mothers, and those on herbal medication or any other medication that may interfere with cytochrome P450 system were excluded from the study.

#### Drug administration and compliance

The subjects received the standard 6 doses of AL (80 mg artemether and 480 mg lumefantrine) [ARTEFAN® Ajanta pharma limited, India]. These were administered at 0, 8, 24, 36, 48 and 60 hours. Each subject swallowed the AL with 200 ml of milk containing 3.5% fat to ensure optimal absorption (Borrmann et al., 2010). The drug administration was directly supervised and observed by the Research Assistants. The study Nurses and Clinicians ensured that the patients strictly adhered to TS and ARVs using pill counts and self-reports at all their clinical visits.

#### Pharmacokinetic sampling

Venous blood was sampled just before the last dose and at 2, 4, 8, 24 and 120 hours post dose. Two to 3 millilitres of whole blood were collected into ethylenediaminetetraacetic acid (EDTA) containing tubes at each time point. This was then centrifuged at 2000g for 10 minutes at room temperature. The plasma was then stored at -80°C until analysis.

#### Drug assay

Plasma concentrations of lumefantrine were determined by a validated method using liquid chromatography with UV detection (Zeng et al., 1996). The absolute recovery of lumefantrine in spiked plasma samples was 90% over the concentration range 5-4000 ng/ml. The internal standard used was halofantrine whose recovery was 88% at a concentration of 300 ng/ml in spiked plasma. The detection limit of lumefantrine was 14.7 ng/ml. The total assay coefficients were < 6% for inter- and intraday precisions.

**Table 1:** Summary of baseline data in subjects co-infected with HIV-1 and malaria who were ART naive or on NVP based ART

Prescription	TS	ZDV/3TC/NVP + TS	P value <sup>a</sup>
No. (%) of females	17(81)	20(90.9)	0.11 <sup>b</sup>
Age (years)	35.0(30.6 – 39.3)	36.2(31.0 – 41.4)	0.70
Weight (Kg)	56.8(53.2 – 60.4)	57.4(53.8 – 61.0)	0.81
Height (cm)	165.5(161.8 – 169.2)	165.1(162.3 – 167.8)	0.85
CD 4 (cell/ml)	301(256 – 346)	364(316 - 411)	0.08

### Safety and tolerability assessment

Patients were continuously assessed by the clinicians for any adverse events using a checklist developed from the Division of AIDS Table for Grading the Severity of Adult adverse events (DAIDS, 2004). These were to be graded as mild, moderate, severe or life threatening.

The laboratory measurements were assessed on day 0 (at time of enrolment) before administering AL and then repeated on days 3, 7 and day 14. The hematology parameters assessed were red blood cell count, haemoglobin concentration, differential white blood cell count and platelet count. The biochemistries assessed were total bilirubin, direct bilirubin, and creatinine, serum glutamic pyruvic transaminase and serum glutamic oxaloacetic transaminase. Electrocardiographs (ECGs) were performed at enrolment and on day 4.

### Data analysis

The baseline demographic characteristics were summarised as mean with 95% confidence interval (CI) and compared using the independent *t* test.

The pharmacokinetic parameters (area under the plasma concentration-time curve, half life, maximum concentration, time of maximum concentration and elimination rate) were estimated using STATA statistical package programme (version 11.2). The area under the curve from time zero to infinity ( $AUC_{0-\infty}$ ) was calculated using the trapezoidal rule.

The pharmacokinetic parameters in the two groups were summarised as mean 95% confidence interval (CI) and compared using the Wilcoxon rank-sum test. P-value of less than 0.05 was considered statistically significant.

The changes in the biochemistry and hematological measurements on days 3, 7 and 14 were each compared to the measures on day 0 respectively using

the Wilcoxon signed rank test. P-value of less than 0.05 was considered statistically significant.

### Ethical review

Written informed consent was obtained from all literate subjects who participated in this study. For the patients who were unable to read and write, an impartial literate witness was present during the process of obtaining the consent. It was made abundantly clear to all the subjects that they were free to withdraw from the study at any time without any consequences. This study was carried out in accordance with the Helsinki declaration and adhered to Good Clinical Practice. It was approved by the Gulu University Research and Ethics Committee. Permission to carry out this study was granted by the Uganda National Council of Science and Technology (HS 877).

## RESULTS

### Patient demographics and clinical baseline characteristics

A total of 44 subjects were recruited and all were retained for the pharmacokinetic and safety and tolerability studies. One subject not yet initiated on ART was lost due to vomiting as per the study protocol. Twenty two were receiving ZDV, 3TC and NVP i.e. 300, 150 and 200 mg respectively twice daily (ART experienced) while 22 were not yet initiated on ARVs (ART naive). All patients were receiving TS. There were no statistically significant differences in demographics and clinical baseline between the two groups ( $p > 0.05$ ). There were more women than men because of the unequal distribution of gender in the patients that attend this clinic (Table 1).

**Table 2:** Pharmacokinetic parameters for lumefantrine in adults co-infected with uncomplicated malaria and HIV-1

Parameter	AL with TS	AL with ZDV/3TC/NVP+TS	P value
AUC <sub>0-∞</sub> (µg h/ml)	375.2 (349.7- 400.7)	589.9 (552.4 – 627.4)	0.0000
C <sub>max</sub> (µg/ml)	6.08 (5.57-6.59)	8.67 (8.2 - 9.14)	0.0000
C <sub>day 7</sub> (µg/ml)	0.64 (0.54 – 0.74)	0.99 (0.94 – 1.04)	0.0000
K <sub>0</sub> (µg/h)	0.0195 ( 0.0185-0.0205)	0.0214 (0.0207-0.0221)	0.0041
t <sub>1/2</sub> (hours)	36.0 (34.1- 37.9)	32.5 (31.4 - 33.6)	0.0050
T <sub>max</sub> (hours)	4.0	4.0	-

Data are expressed as mean (95% CI; n=22 for ART naive and 22 for ART experienced).

AUC, area under the plasma concentration-time curve at steady state; C<sub>max</sub>, maximum concentration; C<sub>day 7</sub>, concentration at day 7; CI, confidence interval; t<sub>1/2</sub>, half-life; K<sub>0</sub>, elimination rate, T<sub>max</sub>, time to maximum concentration.

P value was calculated using The Wilcoxon rank-sum test.

Age, weight, height and CD4 count are expressed as mean (95% Confidence interval).

<sup>a</sup> P was calculated using the independent t-test unless otherwise indicated

<sup>b</sup> P value was calculated using chi-squared test for categorical variables

found to have normalised by day 7 and remained so on day 14.

For the ART experienced group, there was a statistically significant change in total bilirubin and serum glutamic oxaloacetic transaminase (P<0.05) on day 3 as compared to day 0. They were graded as mild and were also found to have normalised by day 7 and day 14.

### Pharmacokinetic parameters of Lumefantrine

Subjects on NVP based ART had a higher area under the plasma concentration-time curve, maximum concentration, and day 7 concentration by 57% (p<0.05), 43% (p<0.05) and 55% (p<0.05) respectively. Half life was 32.5 h and elimination rate was 0.0214 µg/h in these subjects while that for ART naive subjects was 36.0 h and 0.0195 µg/h respectively. Time to maximum concentration was 4.0 h in both groups (See Table 2).

### Safety and tolerability

The adverse events in the ART naive subjects were headache (n=3), vomiting (n=1), nausea (n=1), chills (n=2) and pruritis (n=1); While those in the subjects receiving NVP based ART were: anorexia (n=1), arthralgia (n=1), fatigue (n=1), headache (n=1).

All the events were graded as mild in both groups

There were no changes in electrocardiogram parameters on admission compared to the 2 h after the last dose in both groups.

For the ART naive patients, there was a statistically significant change in total bilirubin (P<0.05) on day 3 as compared to day 0. This was graded as mild and was

### DISCUSSION

We investigated the steady state pharmacokinetics of lumefantrine in subjects co-infected with HIV-1 and uncomplicated malaria when administered with or without NVP based ART. The safety and tolerability of administering AL to these subjects was also assessed. This study demonstrates that the exposure to lumefantrine increases significantly but AL combination was well tolerated with no clinically significant changes in the haematology and biochemistry parameters during the study period.

This study confirms to the finding of increased lumefantrine exposure that has been reported in subjects receiving NVP based antiretroviral therapy but who are not infected with malaria (Kredo et al., 2011). The significant increase in lumefantrine exposure may be attributed to the action of NVP inhibiting CYP3A4 thus decreasing the metabolism of lumefantrine. It has been reported that the low substrate specificity of CYP3A4 makes it susceptible to reversible or irreversible inhibition by a variety of drugs (Zhou et al., 2005).

The ART naive subjects, on TS prophylaxis had a higher exposure of lumefantrine when compared to patients in a randomised study of Ugandan patients

undergoing treatment of malaria receiving a similar dosage of AL with fatty-food intake were the patients registered a maximum concentration of  $5.6 \pm 2.7 \mu\text{g/ml}$  and a day-7 concentration of  $460 \pm 288 \text{ ng/ml}$  (Piola et al., 2005). This may be attributed to the components of co-trimoxazole (trimethoprim + sulfamethoxazole). This combination has previously been reported to significantly influence the metabolism of other drugs used concomitantly with them (Masters et al., 2003). Much higher concentrations of lumefantrine have been reported in Asia and Europe, and this can be attributed to the highly lipophilic nature of lumefantrine and the higher fat content of the diets in these regions (Djimé and Lefèvre 2009).

Artemether-lumefantrine combination is well tolerated in both ART naive and ART experienced subjects despite the significant increase in exposure of lumefantrine in the later. There are no clinically significant changes in the laboratory parameters. The statistically significant increases of total bilirubin observed in the ART naive subjects and of total bilirubin and serum glutamic oxaloacetic transaminase observed in the ART experienced subjects on day 3 are mild and transient, and normalise on the subsequent day 7 and day 14. This good safety and tolerability profile of AL is consistent with that found in patients with uncomplicated malaria in previous studies (Rasheed et al., 2011; Tshefu et al., 2010).

Only six (14%) men were enrolled onto this study. However, all the women participants on this study were not pregnant therefore gender could not have had an effect on the pharmacokinetic parameters of lumefantrine as has been previously established (Ezzet et al., 2000). A 3-day treatment schedule with a total of 6 doses is recommended by the World Health Organisation for adult patients with a bodyweight of 35 kg and above irrespective of gender. Pregnancy has since been reported to cause rapid elimination and lower concentrations of lumefantrine (McGready et al., 2006). Therefore the pharmacokinetics of lumefantrine in pregnant women co-infected with HIV and malaria is bound to be influenced too.

## CONCLUSION

The concomitant administration of artemether-lumefantrine to subjects co-infected with malaria and HIV on nevirapine based antiretroviral therapy leads to increased exposure of lumefantrine but this combination is well tolerated.

## ACKNOWLEDGEMENTS

We highly appreciate the management and staff of Gulu

Regional Referral Hospital for the support and cooperation that was extended in carrying out all the activities in this study.

## REFERENCES

- Back D, Gibbons S, Khoo S (2003). Pharmacokinetic drug interactions with nevirapine. *J Acquir Immune Defic Syndr* 34 Suppl 1:S8-14
- Borrmann S, Sallas WM, Machevo S, Gonzalez R, Bjorkman A, Martensson A, Hamel M, Juma E, Peshu J, Ogutu B, Djimde A, D'Alessandro U, Marrast AC, Lefevre G, Kern SE (2010). The effect of food on lumefantrine bioavailability in African children receiving artemether-lumefantrine crushed or dispersible tablet (Coartem) for acute uncomplicated *Plasmodium falciparum* malaria. *Trop Med Int Health* 15(4):434-41
- Cohen C, Karstaedt A, Frean J, Thomas J, Govender N, Prentice E, Dini L, Galpin J, Crewe-Brown H (2005). Increased prevalence of severe malaria in HIV-infected adults in South Africa. *Clin Infect Dis.* 41(11):1631-7
- Division of AIDS Table for Grading Severity of Adult and Paediatric Adverse Events (2004)
- Djimé A, Lefèvre G (2009) Understanding the pharmacokinetics of Coartem®. *Malar J* 8(Suppl 1):S4
- Ezzet F, van Vugt M, Nosten F, Looareesuwan S, White NJ (2000). Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. *Antimicrob Agents Chemother* 44:697
- Flateau C, Le Loup G, Pialoux G (2011). Consequences of HIV infection on malaria and therapeutic implications: a systematic review. *Lancet Infect Dis* 11: 541-56
- French N, Nakiyingi J, Lugada E, Watera C, Whitworth JA, Gilks CF (2001). Increasing rates of malarial fever with deteriorating immune status in HIV-1-infected Ugandan adults. *AIDS* 15(7):899-906
- Kamya MR, Gasasira AF, Achan J, Mebrahtu T, Ruel T, Kekitiniwa A, Charlebois ED, Rosenthal PJ, Haviir D, Dorsey G (2007). Effects of trimethoprim-sulfamethoxazole and insecticide-treated bed nets on malaria among HIV-infected Ugandan children. *AIDS* 21(15):2059-66
- Katabira E and Kamya M (2003). National Antiretroviral Treatment and Care Guidelines for Adults and Children. Ministry of Health, Uganda. 1<sup>st</sup> edition, Earnest Publishers, Kampala pp.9
- Khoo S, Back D, Winstanely P (2005). The potential for interactions between antimalarials and antiretroviral drugs. *AIDS* 19:995-1005
- Kredo T, Mauff K, Van der Walt JS, Wiesner L, Maartens G, Cohen K, Smith P, Barnes KI (2011). Interaction between artemether-lumefantrine and nevirapine-based antiretroviral therapy in HIV-1-infected patients. *Antimicrob Agents Chemother* 55(12):5616-23
- Masters PA, O'Bryan TA, Zurlo J, Miller DQ, Joshi N (2003). Trimethoprim-Sulfamethoxazole revisited. *Arch. Intern. Med.* 163:402-410
- McGready R, Stepniewska K, Lindegardh N, Ashley EA, La Y, Singhasivanon P, White NJ, Nosten F (2006). The

## 6. Glob. Res. J. Pharm. Pharmacol.

- pharmacokinetics of artemether and lumefantrine in pregnant women with uncomplicated falciparum malaria. *Eur J Clin Pharmacol.* 62(12):1021-31
- Nakanjako D, Kiragga AN, Castelnuovo B, Kyabayinze DJ, Kanya MR (2011). Low prevalence of *Plasmodium falciparum* antigenaemia among asymptomatic HAART-treated adults in an urban cohort in Uganda. *Malar J* 10:66
- Piola P, Fogg C, Bajunirwe F, Biraro S, Grandesso F, Ruzagira E, Babigumira J, Kigozi I, Kiguli J, Kyomuhendo J, Ferradini L, Taylor W, Checchi F, Guthman JP (2005) Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated *Plasmodium falciparum* malaria in Mbarara, Uganda: a randomised trial. *Lancet* 365: 1467-1473
- Proietti C, Pettinato DD, Kanno BN, Ntege E, Cristani A, Riley EM, Egwang TG, Drakeley C, Bousema T (2011). Continuing intense malaria transmission in northern Uganda. *AM J Trop Med Hyg* 84(5): 830-7
- Rasheed A, Khan SM, Awan MY, Khurshid U, Ahmad K (2011). Efficacy and safety of artemether-lumefantrine in uncomplicated malaria in Liberia. *J Pak Med Assoc* (2): 131-4
- The Joint United Nations Programme on HIV/AIDS: (UNAIDS 2007) AIDS in Africa, Country by Country. African Development Forum
- Tshetu AK, Gaye O, Kayentao K, Thompson R, Bhatt KM, Sesay SS, Bustos DG, Tjitra E, Bedu-Addo G, Borghini-Fuhrer I, Duparc S, Shin CS, Fleckenstein L (2010). Efficacy and safety of a fixed-dose oral combination of pyronaridine-artesunate compared with artemether-lumefantrine in children and adults with uncomplicated *Plasmodium falciparum* malaria: a randomised non-inferiority trial. *Lancet* 375(9724):1457-67
- White NJ, van Vugt M, Ezzet F (1999). Clinical pharmacokinetics and pharmacodynamics and pharmacodynamics of artemether-lumefantrine. *Clin Pharmacokinet* 37:105-125
- Whitworth J, Morgan D, Quigley M, Smith A, Mayanja B, Eotu H, Omoding N, Okongo M, Malamba S and Ojwiya A (2000). Effect of HIV-1 and increasing immunosuppression on malaria parasitemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet* 356(9235): 1051-1056
- World Health Organisation (2010). Guidelines for the treatment of malaria. 2<sup>nd</sup> ed. World Health Organisation, Geneva, Switzerland.
- Zeng MY, Lu ZL, Yeng SC, Zhang M, Liao J, Lin SL, Teng XH(1996). Determination of benflumetol in human plasma by reversed phase high performance liquid chromatography. *J Chromatogr. B Biomed. Appl* (2): 299-306
- Zhou S, Chan SY, Goh BC, Chan E, Duan W, Huang M, McLeod HL (2005). Mechanism-based inhibition of cytochrome P450 3A4 by therapeutic drugs. *Clin Pharmacokinet* 44 (3): 279-304