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Short Report: Preliminary Study of Quinine Pharmacokinetics in Pregnant Women with Malaria-HIV Co-Infection

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Abstract.

Pregnant women bear the greatest burden of malaria–human immunodeficiency virus co-infection. Previous studies suggest that interaction with antiretroviral drugs may compromise antimalarial pharmacokinetics and treatment outcomes. We conducted a preliminary clinical study to assess quinine pharmacokinetics in Malian pregnant women with acute malaria who reported taking nevirapine-based antiretroviral therapy. Of seven women, six had stable concentrations of nevirapine in the plasma and one had none. Quinine concentrations were lower, and its metabolite 3-hydroxyquinine higher, in the six women with nevirapine than in the one without, and quinine concentrations were below the recommended therapeutic range in 50% of the women. This preliminary observation warrants further research to understand the impact of long-term antiretroviral therapy on the treatment of acute malaria.

Pregnant women bear the largest burden of malaria–human immunodeficiency virus (HIV) co-infection in sub-Saharan Africa.[1] The risks of malaria and related morbidity such as severe anemia and adverse pregnancy outcomes are significantly higher in pregnant women with HIV than in those without.[2,3] Limited data suggest that antimalarial treatment outcomes in pregnant women with HIV may be suboptimal,[4,5] and more frequent dosing of intermittent preventive malaria treatment is recommended for HIV-infected pregnant women.[6,7]

Quinine remains important in malaria treatment as an alternative to the first-line artemisinin-based combination therapy.[8] Quinine, with clindamycin, is recommended for uncomplicated malaria in pregnant women in the first trimester, whereas artemisinin-based combination therapies are recommended in the second or third trimester of pregnancy. Quinine is one of two antimalarial drugs available in an intravenous formulation, and intravenous quinine may be used for severe malaria when intravenous artesunate is not available. Despite its poor tolerability and complex dosing regimen, quinine maintains its place in malaria because of its safety, low cost, long shelf-life, and wide availability, and to its persistent efficacy against *P. falciparum*.

Quinine disposition in humans is relatively well studied, and pregnancy does not seem to alter its metabolism.[9] Quinine is predominantly metabolized by CYP3A enzymes to its major active metabolite 3-hydroxyquinine,[10] and subjected to clinically significant interactions with drugs that inhibit[11] or induce[12] this enzyme, including antiretroviral drugs.[13,14] Inadequate quinine concentrations increase the risk of malaria treatment failure, and it is recommended that the trough level of total quinine be kept within 5–15 mg/L.[12,15]

A prospective preliminary study to assess quinine pharmacokinetics in pregnant women with HIV was conducted in Sikasso, Mali, in 2010–2011. At the time of the study, quinine was the first-line treatment of malaria in pregnancy. The HIV testing was universal in pregnant women and antiretroviral therapy (ART) was provided to those with HIV clinical stage III or higher or CD4 counts below 350 cells/mm^3. Nevirapine in combination with stavudine lamivudine, or zidovudine was the ART regimen most commonly used.

The study was approved by the Institutional Review Boards of the University of Bamako and the Johns Hopkins University Bloomberg School of Public Health. Inclusion criteria were age 16–45 years; pregnancy gestation 12–34 weeks; documented HIV diagnosis and history of nevirapine-based ART for at least 14 days; smear-proven *Plasmodium falciparum* infection; axillary temperature > 37.5°C or history of fever in the last 24 hours or symptoms suggestive of malaria; ability to tolerate oral intake; provision of written informed consent; and agreement to comply with the study protocol. Provision of blood samples for pharmacokinetic analysis was not an eligibility criterion. Exclusion criteria included severe malaria[16]; history of hypersensitivity to quinine; hemoglobin < 8 g/dL; or reported use of drugs with antimalarial activity within 48 hours before enrollment, excepting trimethoprim-sulfamethoxazole for prevention of opportunistic infections and sulfadoxine-pyrimethamine for malaria prevention. The first day of quinine treatment was designated Day 0. Participants were hospitalized on study Days 0–6, and monitored as outpatients weekly until Day 28. Complete blood counts, CD4 count, hepatic alanine aminotransferase, and serum creatinine were assessed at baseline, at hospital discharge, during outpatient visits and when clinically indicated. Standard thrice-daily oral doses of quinine sulfate (600 mg quinine base), procured from the Thai Government Pharmaceutical Organization (Lot no. F530190; expiration September 24, 2013), were administered under observation on Days 0–6. Blood glucose was monitored every 12 hours on Days 0–2. Adverse events were assessed using standard criteria.[17] Treatment outcomes were classified following the World Health Organization (WHO)-recommended methods.[18] Smear-proven recurrent cases were retreated with a standard regimen of artemether-lumefantrine.

Parasite density was assessed every 12 hours until two consecutive negative readings, by two independent microscopists, on Giemsa-stained thick smear. Parasites were counted by dividing the number of asexual parasites by 200 white blood cells (WBCs) (500 for parasite density < 10/μL) and multiplying by an assumed WBC count of 6,000/μL. Smears were considered negative when no asexual parasites were found after counting 1,000 WBC.

Dried blood spots were collected on Whatman 3 MM filter paper along with smears and during follow-up. The DNA was extracted, amplified, and analyzed to distinguish new versus recrudescent infection,[18] targeting genes encoding merozoite surface protein-1 and -2 and glutamate-rich protein.[19] Blood was collected for drug assay analyses: immediately before and every12 hours after morning quinine doses on Days 0–6, and before the morning dose of nevirapine on Days 1, 3, and 6. Plasma was separated and stored in liquid nitrogen until analysis. Plasma quinine/3-hydroxyquinine and nevirapine were determined using a validated high-performance liquid chromatography method with fluorescence detection,[20] and liquid chromatographic-tandem mass spectroscopic,[21] respectively. Free quinine was obtained by removing plasma proteins by ultrafiltration using Millipore Centrifree Centrifugal Filter Units.[22] Because of the small sample size the analysis was exploratory and descriptive. The CD4 counts at enrollment and at the end of study follow-up were compared using a non-parametric Wilcoxon signed-rank matched test.

Of 15 screened candidates, 10 eligible participants were enrolled and completed the study (Table 1). All were multigravid with HIV diagnosis and oral nevirapine-based ART for months-years; five became pregnant while taking ART. None reported malaria illness or treatment in the last year. Four of 10 were taking trimethoprim-sulfamethoxazole prophylaxis for HIV-related opportunistic infections, and none were taking pyrimethamine-sulfadoxine for malaria prevention. Eight and two women reported taking nevirapine + lamivudine + stavudine, and nevirapine + lamivudine + zidovudine. Five had moderate anemia (hemoglobin 8–9.9 g/dL). A modest, but significant, increase in CD4 counts was observed from the median 364 (range 102–1,068) cells/mm^3 at enrollment to 419 (148–910) cells/mm^3 at the end of follow-up (Wilcoxon $P < 0.05$). A participant with no measurable concentrations of nevirapine in her plasma had the lowest CD4 count, 155 cells/mm^3.

Adverse events (tinnitus, headache, and epigastric pain) were mild-moderate in severity, and resolved in 2–7 days. There were no serious adverse events or clinically important changes in laboratory parameters. Concomitant drugs included dexchlorpheniramine for pruritis in one participant, acetaminophen for headache in five participants, and amoxicillin for urinary tract and respiratory tract infection in two participants, respectively.

Symptoms at enrollment included headache, nausea, fatigue, and fever, and parasite density was low (geometric mean [95% confidence interval] 477 [10–2,261] parasites/μL). All smear-positive infections were polymerase chain reaction (PCR) positive. Time to clearance of parasites was 24–57 hours. Two participants had recurrent *P. falciparum* on Day 28 by smear, confirmed by PCR as new infections, making the 28 days PCR-corrected cure rate 100%. Both were successfully treated with artemether-lumefantrine.

Seven participants provided plasma for drug assay analysis, and one who reported taking nevirapine-based ART had no measurable concentrations of nevirapine. The median (interquartile range) of plasma nevirapine concentration in the other six participants was 2.7 (2.0–3.7) mg/L. Table 2 summarizes plasma trough concentrations of total and free quinine and metabolite 3-hydroxyquinine in the six participants with measurable nevirapine (pooled and summarized as median and interquartile range) and one with no measurable nevirapine in her plasma . These values were separated for the first 3 and last 4 days of treatment, because quinine concentrations are most likely to be in a steady state after Day 2 or 50–72 hours (terminal half-life 8–12 hours) from treatment initiation. Figure 1 shows the plasma concentration of total and free quinine and 3-hydroxyquinine in all seven participants on study Days 0–6. Trough plasma concentrations of both total and free quinine appeared lower in those with than in the one participant without nevirapine (Figure 2A). A higher 3-hydroxyquinine concentration was seen in the one without than in those with nevirapine (Figure 2B). This finding is also reflected in the ratio of metabolite-to-parent quinine (Figure 3), almost 4-fold higher in the presence than absence of nevirapine.

This preliminary observation represents a potentially important signal suggesting that quinine concentrations may be lower in pregnant women taking nevirapine-based ART, and highlights a need to understand antimalarial drug disposition and treatment responses in individuals living with HIV and long-term ART. The low predose trough concentration of quinine likely reflects low total drug exposure.[23] The 4-fold higher ratio of metabolite/parent ratio in the presence of nevirapine indicates that induction of CYP3A4 metabolism by chronic use of nevirapine may explain this finding. Quinine is primarily biotransformed to 3-hydroxyquinine by CYP3A4,[10] and nevirapine is a potent inducer of this enzyme.[24] The activation of the CYP3A family has been

proposed for the interactions[12,14] but clear mechanisms need further elucidation. Interaction with one or more reported concomitant drugs (stavudine, lamivudine, or zidovudine) in this study is possible but unlikely because none of these drugs is involved in CYPP450 metabolism[25] or shares significant overlapping metabolic pathways with quinine. Our finding is consistent with previous reports of quinine–antiretroviral drug interaction in healthy volunteers,[13,14] and quinine–rifampin interaction in non-pregnant adults with acute falciparum malaria.[12] However, CYP3A4-mediated interactions between antimalarial and antiretroviral drugs may be deleterious or beneficial. It has been shown that CYP3A4 inhibition caused by ritonavir-boosted lopinavir (HIV protease inhibitors) results in a high concentration of lumefantrine that is associated with lower incidence of malaria and longer post-treatment prophylaxis in Uganda children.[26]

Despite sub-therapeutic quinine concentrations in one-half of participants, everyone achieved complete cure in our study. However, the study was underpowered to assess the impact of nevirapine on quinine treatment efficacy. The risk of treatment failure caused by inadequate drug exposure needs to be evaluated in a larger study.

Quinine continues to be important for the treatment of malaria, and may be increasingly relied upon if artemisinin-resistant *P. falciparum* that emerged recently in Southeast Asia[27–31] disseminates. Few previous studies have examined quinine pharmacokinetics in the presence of antiretroviral drugs. Data are especially scarce for pregnant women, and absent to our knowledge for pregnant women with HIV. Studies are needed to understand the pharmacokinetic interaction between quinine and antiretroviral drugs, particularly in pregnant women who are at higher risk of adverse outcomes of both malaria and HIV.

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FIGURE 1. Semi-log time-concentrations plot of quinine and its metabolite in pregnant women with malaria-human immunodeficiency virus (HIV) co-infection ($N = 7$). Solid line plot with closed circles represents total quinine concentrations. Dashed line plot with open circles represents free quinine concentrations. Solid line plot with closed triangles represents 3-hydroxyquinine (major active metabolite of quinine) concentrations. Error bars represent upper and lower bounds of the interquartile range around median values.

FIGURE 2. Trough concentration of quinine and its metabolite with and without nevirapine ($N = 7$). **Panel A** shows median trough concentration of total (solid line plots with closed symbols) and free (dashed line plots with open symbols) quinine in the presence (triangles) ($N = 6$) and absence (circles) ($N = 1$) of measurable nevirapine. **Panel B** shows median trough concentration of active metabolite 3-hydroxyquinine in the presence (triangles) and absence (circles) of measurable nevirapine. Error bars represent upper and lower bounds of the interquartile range around median values.

FIGURE 3. Ratio of metabolite 3-hydroxyquinine and quinine. Upper plot with triangles represents 3-hydroxyquinine/quinine ratio in the presence of nevirapine ($N = 6$), and lower plot with circles represents this ratio in the absence of measurable nevirapine ($N = 1$). Error bars represent upper and lower bounds of the interquartile range around median values.

TABLE 1

Baseline characteristics at enrollment*

Characteristics	Median (range) (laboratory reference)
Age (years)	29.0 (21–32)
Body weight (kg)	58.0 (49–77)
Gestation (weeks)	27 (16–32)
Parity/gravidity	4 (2–7)/5 (3–10)
Duration since HIV diagnosis (years)	2.9 (1.2–7.4)
Duration of antiretroviral treatment (years)	2.8 (0.84–6.0)
Number (%) taking trimethoprim-sulfamethoxazole	5 (50)
Hemoglobin (g/dL)	9.4 (8.0–13.2) (11.0–15.5)
Number with hemoglobin < 10 g/dL (%)	6 (60)
White blood cell count (cells × 10^3/mm^3)	4.0 (1.8–11.9) (3.5–10.5)
Number (%) neutropenic	5 (50)

CD4 count (cells/mm^3)	358 (102–1068) (500–1,500)
Number (%) with CD4 < 350/mm^3	5 (50)
Platelets (cells × 10^3/mm^3)	200 (96–337) (150–450)
Alanine aminotransferase (unit/l)	13.0 (11.8–16.1) (7.0–45)
Serum creatinine (mg/dL)	0.75 (0.5–1.3) (0.5–1.0)
Blood glucose (mg/dL)	90 (60–145) (60–100)

* HIV = human immunodeficiency virus.

TABLE 2

Trough concentrations of quinine and 3-hydroxyquinine

Day	Drug from	Quinine (mg/L)*		3-hydroxyquinine (mg/L)*	
		With NVP (*N* = 6)	No NVP (*N* = 1)	With NVP (*N* = 6)	No NVP (*N* = 1)
0–2	Total	5.3 (3.6–6.2)	7.0 (6.5–7.5)	1.3 (1.0–1.5)	0.24 (0.21–0.27)
	Free	0.69 (0.63–0.90)	1.7 (1.6–1.8)	0.78 (0.67–0.86)	0.13 (0.11–0.15)
3–6	Total	4.4 (3.6–6.2)	10.7 (10.0–11.0)	1.3 (1.1–1.5)	0.74 (0.67–0.76)
	Free	0.70 (0.60–1.0)	2.0 (1.7–2.1)	0.80 (0.72–0.87)	0.50 (0.40–0.50)

* Values expressed in median (interquartile range); NVP = nevirapine.

Figure 1

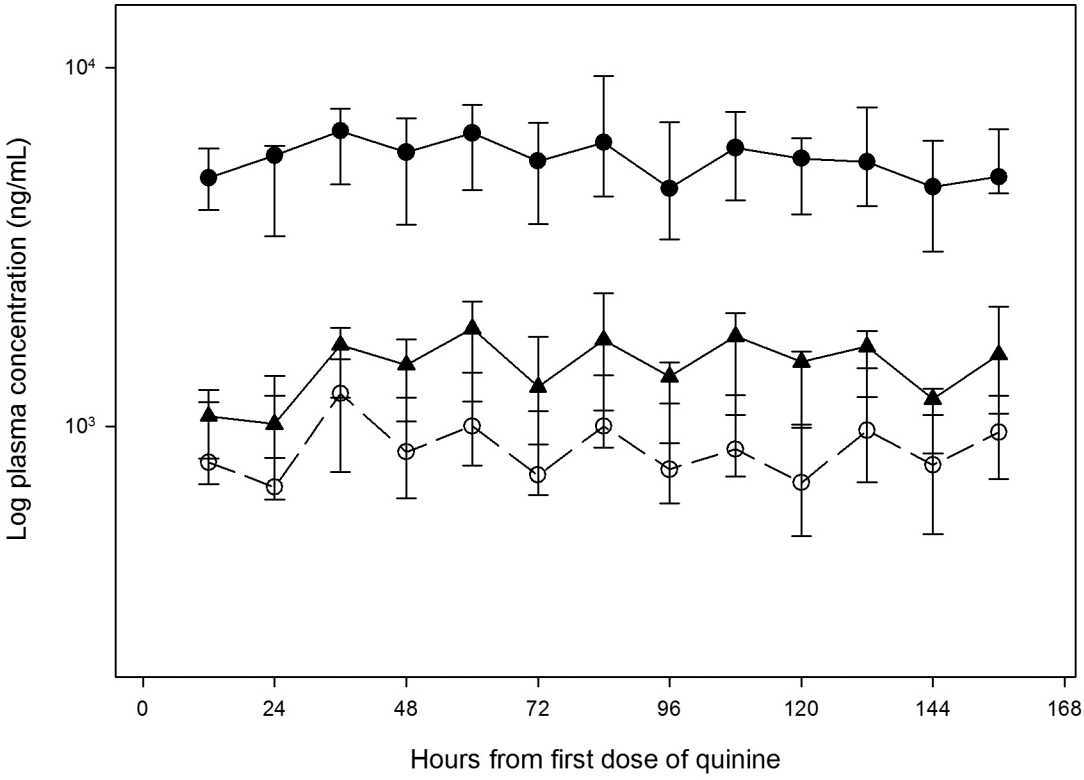

Log plasma concentration (ng/mL)
10⁴
10³
0
24
48
72
96
120
144
168
Hours from first dose of quinine

Figure 2

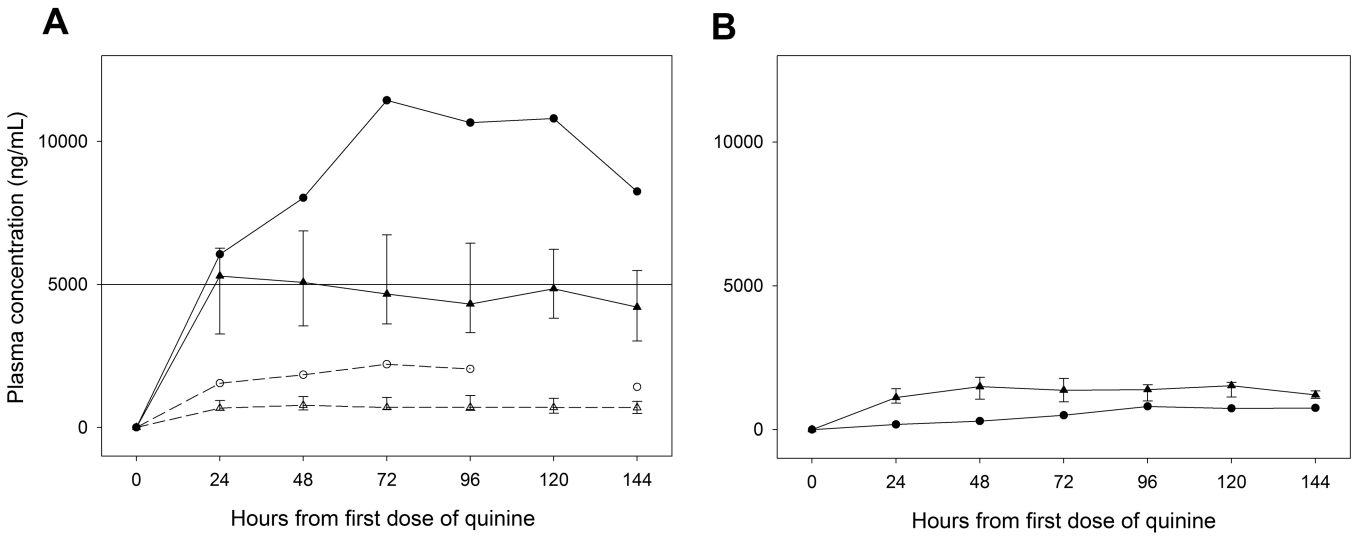
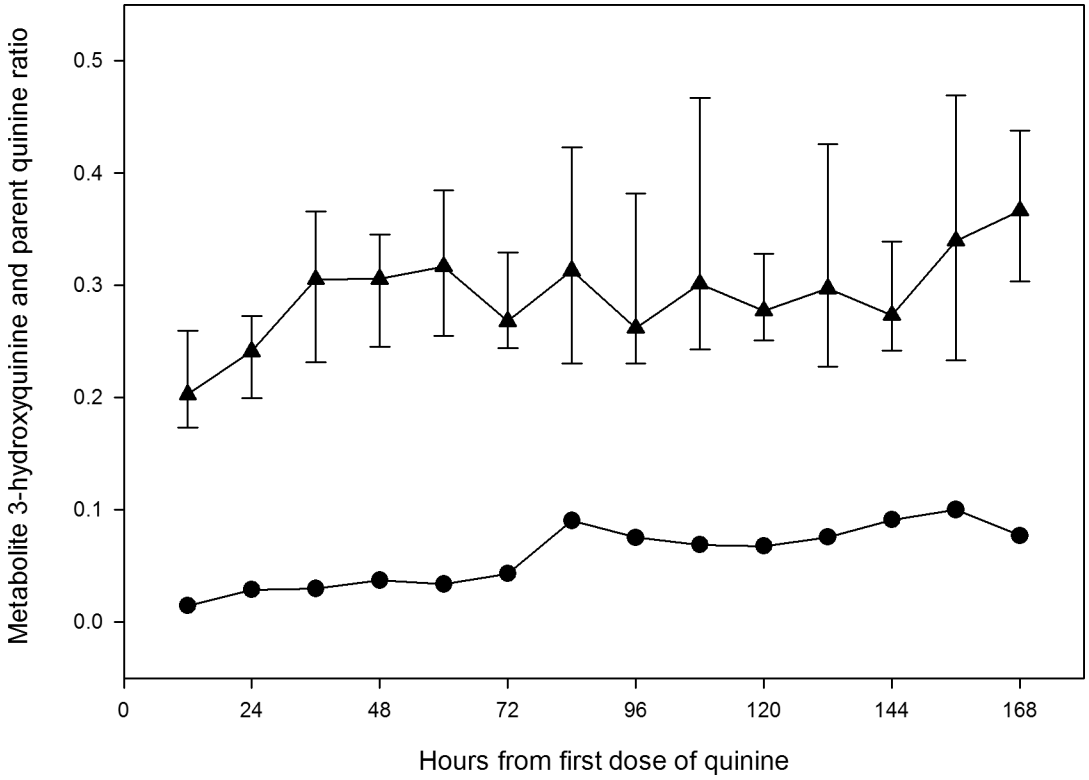

A
B
Plasma concentration (ng/mL)
10000
5000
0
0
24
48
72
96
120
144
Hours from first dose of quinine
Hours from first dose of quinine

Figure 3


Metabolite 3-hydroxyquinine and parent quinine ratio
0.5
0.4
0.3
0.2
0.1
0.0
0
24
48
72
96
120
144
168
Hours from first dose of quinine