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Halofantrine and primaquine for radical cure of malaria in Irian Jaya, Indonesia

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The combination of halofantrine and primaquine therapies was evaluated as a regimen for achieving radical cure of falciparum or vivax malaria in Irian Jaya, Indonesia, and compared with combined chloroquine and primaquine therapies. The patients who volunteered for the study {adult, male, Indonesian immigrants with no previous exposure to endemic malaria, normal glucose-6-phosphate dehydrogenase (G6PD) activity, uncomplicated malaria illness, no prior use of antimalarials, and parasitaemias of 0.001%–1.0%} were randomized to receive either halofantrine (24 mg base/kg bodyweight, in three equal doses over 12 h) or chloroquine (25 mg base/kg bodyweight over 48 h, in doses of 10, 10 and 5 mg base/kg at 24-h intervals). Each patient also received concurrent daily primaquine (0.5 mg base/kg bodyweight) for 14 days followed by the same dose on alternate days to day 28. A recurrent parasitaemia during the 28 days of follow-up constituted drug failure. Of the 40 cases of falciparum malaria and 26 cases of vivax malaria treated with halofantrine-primaquine, none had a recurrent parasitaemia (100% efficacy). In contrast, 20 of 30 patients with falciparum malaria and three of 27 with vivax malaria had recurrent parasitaemias after chloroquine-primaquine, giving efficacies of 33% and 89%, respectively. Halofantrine-primaquine was significantly more effective than chloroquine-primaquine against falciparum malaria ($P < 0.001$) but was similarly efficacious against vivax malaria ($P = 0.23$). On average, fever associated with falciparum or vivax malaria cleared 17 h faster with halofantrine-primaquine ($P < 0.01$) although there were no significant differences ($P > 0.4$) in parasite-clearance times between the two regimens. The halofantrine-primaquine regimen was also associated with a more rapid and significant decline in malaria-related physical complaints.

Radical cure of malaria, the elimination of both the blood and tissue stages of the parasites by chemotherapeutic agents, is desirable for prevention of recurrence of infection after returning from work or travel in places where relapsing malaria is endemic. In studies that measure attack rates of malaria, with or without chemoprophylactic intervention, radical cure is also necessary to eliminate interference and confounding by relapsing or recrudescing parasitaemias. There is currently no single drug with sufficient safety and dual blood and tissue schizonticidal properties to achieve this

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sterilizing cure. Most of our studies have used a combination of three drugs, quinine, doxycycline and primaquine, to achieve radical cures (Jones *et al.*, 1994; Fryauff *et al.*, 1995; C. J. Church, T. L. Richie, C. Ohrt, E. Tjitra, B. Subianto, B. Sandjaya, E. Gomez, J. K. Baird, D. J. Fryauff and A. L. Richards, unpubl. obs.; C. K. Ohrt, T. Richie, H. Widjaja, G. D. Shanks, D. J. Fryauff, E. Tjitra, B. Sandjaja, H. Basri, W. Widjaja, C. Church and G. Watt, unpubl. obs.). The frequent, prolonged dosing of quinine and the undesirable side effects of this drug compound the problem of full compliance with therapy. The drug-related illness which frequently occurs in otherwise healthy subjects discourages their voluntary participation and, even among symptomatic cases, rigid supervision and incentives are required to achieve completion of therapy. The doxycycline component is generally well-tolerated as long as it is not taken on an empty stomach but, due to its effect on bone growth and tooth development, use of this drug is contra-indicated in children under the age of 8 years and in females during pregnancy and nursing (Anon., 1995). Despite the effectiveness of the current, quinine-based radical cure, there is interest in developing a more broadly acceptable drug regimen for radical cure of chloroquine-resistant malaria.

Halofantrine is an effective and generally well-tolerated blood schizonticide for use against chloroquine-resistant *Plasmodium falciparum* in areas where mefloquine resistance has not also developed (Horton and Parr, 1989). Trials have also demonstrated this drug to be highly effective against *P. vivax*, including the chloroquine-resistant strains occurring in Irian Jaya, Indonesia (Parkinson *et al.*, 1989; Baird *et al.*, 1995*a*). The use of halofantrine as an alternative component for achieving radical cure of malaria was therefore explored; the use of three, well tolerated doses of halofantrine over 12 h may be substantially better than treatment with 12 poorly tolerated doses of quinine over 4 days given concurrently with 20 doses of doxycycline over 10 days. The aim of the present study was to see if falciparum and vivax malaria acquired in Irian Jaya could be cured radically by using combined halofantrine and primaquine therapies. A 'control' group, given simultaneous chloroquine and primaquine therapies, was included in order to estimate properly the effect of primaquine on patency of parasitaemia after chloroquine therapeutic failure.

PATIENTS AND METHODS

Study Site and Patients

The study was conducted in the new, transmigrant villages of Arso X and XI in north-eastern Irian Jaya, Indonesia (Baird *et al.*, 1995*b*; Fryauff *et al.*, 1995) between January and July 1993. Most of the approximately 2000 villagers had moved from Java, where the risk of malaria infection has been about 1 case/10 000 person-years since 1965 (Baird *et al.*, 1995*c*). Point prevalences of malaria at the time of enrolment were 24% in Arso X and 38% in Arso XI, despite the provision of bednets to all households and the availability of free chloroquine at the village health clinics.

Enrolment

Overall, 123 Javanese or Balinese males aged >15 years, with uncomplicated malaria and parasitaemias of 0.001%–1.0%, qualified for enrolment. Informed consent, a physical examination and a negative qualitative test for glucose-6-phosphate dehydrogenase (NADPH spot test; Sigma) preceded their random assignment to one of two treatment groups: halofantrine-primaquine (HF-PQ) or chloroquine-primaquine (CQ-PQ).

Treatment and Follow-up

Patients in the HF-PQ group received halofantrine (a total of 24 mg base/kg bodyweight, in three equal doses over 12 h) and primaquine (0.5 mg base/kg bodyweight daily for 14 days and thereafter on alternate days until day 28). Those in the CQ-PQ group were given chloroquine (a total of 25 mg base/kg bodyweight in three unequal doses over 48 h: 10 mg/kg on Day 0; 10 mg/kg on Day 1; and

5 mg/kg on Day 2) and primaquine (as above). Three drug formulations were used: Halfan® (halofantrine; 250 mg base hydrochloride salt in uncoated tablets, kindly provided by Dr J. Horton of SmithKline Beecham, Brentford, U.K.); primaquine (15 mg base as diphosphate salt in coated tablets; Sanofi-Winthrop, New York, NY); and Resochin® (chloroquine; 150 mg base as phosphate salt in uncoated tablets; P. T. Bayer Indonesia, Jakarta). Every dose was supervised by a member of the research team. Dry biscuits and bottled water were provided and patients were encouraged to eat immediately prior to or just after consuming the medication. Patients were visited in their homes daily for the first 2 weeks and then on alternate days until day 28. Visits consisted of administering medications, recording answers to a physical-complaint questionnaire, and making blood smears for parasitological examination. Patients suffering treatment failure were offered standard quinine therapy.

Parasitological Examination

Diagnosis of malaria was based upon microscopical examination of Giemsa-stained, thick and thin, blood films using oil-immersion optics ($\times 1000$). At least 300 ocular fields were examined before a slide was considered negative. The number of asexual parasites per 200 white blood cells (WBC) was counted and the number of parasites/μl blood was then estimated by multiplying this value by 40 (Shute, 1988).

Analysis of Data

The efficacy of combined HF-PQ therapies relative to that of combined CQ-PQ therapies was determined using Fisher's exact test. The number of hours from starting treatment to the point at which parasites became undetectable and remained so for at least 2 consecutive days constituted the parasite-clearance time (PCT). Axillary temperatures $\geq 37.5^{\circ}$C indicated fever and fever-clearance time (FCT) was the number of hours from starting treatment to the point at which a normal temperature of at least two consecutive days' duration began. One-way analysis of variance was used to compare age, weight, density of parasitaemia, PCT, frequency of fever and FCT between the two treatment groups. The incidence density (ID) of physical complaints **not** associated with parasitaemia was calculated from the number of complaints reported per person-month of observation after discounting day-0 complaints and those associated with unremitting or recurrent parasitaemias. The decline of **all** physical complaints, including those associated with the initial parasitaemias, was estimated from the proportion of patients reporting any complaint consistent with malaria (fever, chills, headache, malaise, abdominal pain, nausea, vomiting, diarrhoea, arthralgia, myalgia) and the incidence density per person-day of specific complaints reported on each of test days 0–7. Proportions and incidence densities were compared using Fisher's exact test or χ^2 with Yate's correction applied. Two-tailed P values are reported and the cut-off for statistical significance was a P value ≤ 0.05.

RESULTS

Baseline Characteristics

There were no statistically significant differences between treatment groups at enrolment in terms of mean age, weight or parasitaemia (Table 1). More than 92% of the study patients in each treatment group presented with malarial symptoms at enrolment and the two treatment groups were similar in the number and types of physical complaints reported (Fig. 1). Malaise, headache, abdominal pain and nausea were the most frequently reported physical complaints. Fever was observed in 50% (35/70) of the *P. falciparum* cases and in 49% (26/53) of the *P. vivax*.

Comparative Efficacy

HF-PQ was completely effective and no treatment failures (persistent or recurrent parasitaemias) occurred among the 40 *P. falciparum* and 26 *P. vivax* cases during 28 days of follow-up (100% efficacy). In contrast,

TABLE 1

Baseline characteristics of study patients randomized to halofantrine-primaquine (HF-PQ) or chloroquine-primaquine (CQ-PQ) treatment groups

	Plasmodium falciparum		Plasmodium vivax	
Characteristic	*HF-PQ*	*CQ-PQ*	*HF-PQ*	*CQ-PQ*
No. of patients	40	30	26	27
Mean (S.D.) age (years)	28 (8)	31 (10)	27 (8)	33 (9)
Mean (S.D.) weight (kg)	50 (7)	51 (7)	51 (7)	49 (6)
Geometric mean parasitaemia (asexual parasites/μl blood) and (95% confidence interval)	1318 (733–2382)	832 (371–1919)	933(479–1799)	457 (214–933)

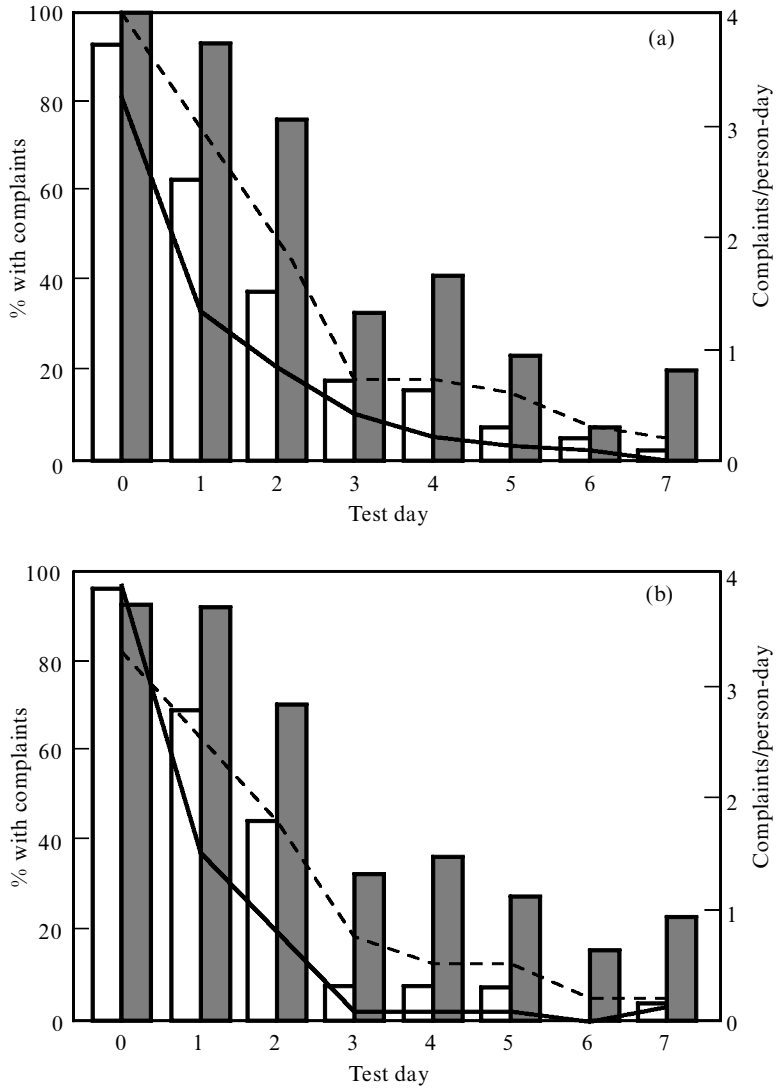

Fig. 1. Proportions of subjects with malaria-related physical complaints after treatment with halofantrine-primaquine (□) or chloroquine-primaquine (▨) and mean numbers of physical complaints after treatment with halofantrine-primaquine (—) or chloroquine-primaquine (– – –) amongst the *P. falciparum* (a) and *P. vivax* (b) cases.

failures of CQ-PQ therapy occurred within 28 days in 20 of the 30 patients infected with *P. falciparum* (33% efficacy) and in three of the 27 patients infected with *P. vivax* (89% efficacy). HF-PQ was significantly more efficacious than CQ-PQ against *P. falciparum* ($P < 0.001$) but similarly efficacious against *P. vivax* ($P = 0.23$). As expected, CQ-PQ was significantly more efficacious against *P. vivax* than against *P. falciparum* ($P < 0.001$).

TABLE 2
The means (and ranges) of the parasite- and fever-clearance times from the start of therapy with halofantrine-primaquine (HF-PQ) or chloroquine-primaquine (CQ-PQ)

	Parasite-clearance time (h)			*Fever-clearance time (h)*		
Infection	*HF-PQ*	*CQ-PQ*	P	*HF-PQ*	*CQ-PQ*	P
Plasmodium falciparum	42 (24–72)	51 (24–72)	0.61	28 (24–72)	45 (24–72)	0.003
P. vivax	58 (24–192)	53 (24–120)	0.44	24 (24)	42 (24–72)	0.008

Clearance of Parasitaemia and Fever

There was no difference in PCT between the two treatment regimens for either *P. falciparum* ($P = 0.61$) or *P. vivax* ($P = 0.44$). Under either regimen or infection, the mean PCT was about 50 h (Table 2). In contrast, FCT in malaria cases treated with HF-PQ was a mean of 17 h shorter than in those given CQ-PQ and the difference was significant for both *P. falciparum* ($P = 0.003$) and *P. vivax* ($P = 0.008$).

Physical Complaints

In the absence of a patent parasitaemia, physical complaints in both treatment groups were infrequent, but the ID per person-week of malaria-like complaints during the follow-up period was consistently lower among patients treated with HF-PQ and collectively were reported 3.7–4.0 times less often than by cases of falciparum and vivax malaria treated with CQ-PQ ($P < 0.005$; Fig. 2).

Figure 1 shows a comparison of the interval (daily) proportions of patients registering any physical complaint consistent with malaria and the ID/person-day of these specific malarial complaints during test days 0–7, between treatment groups for each malaria species. Day-0 physical complaints were similar in the two treatment groups and most complaints were registered during the first 48 h of evaluation, before and during the period of parasite clearance. Within 24 h of having received the last HF-PQ dose, there was a highly significant decline in the proportion of patients reporting any physical complaint ($P = 0.003$ for *P. falciparum*; $P = 0.02$ for *P. vivax*) and in the number of specific complaints reported by a patient ($P < 0.001$ for *P. falciparum*; $P = 0.005$ for *P. vivax*). In contrast, CQ-PQ treatment required 48–72 h to produce a statistically significant reduction in physical complaints.

DISCUSSION

The rationale for the primaquine dosing used in the present study was that cure of *P. vivax* of New Guinea-Irian Jaya origin requires 0.5 mg/kg rather than the standard regimen of 0.25 mg/kg (Clyde and McCarthy, 1977). The unconventional, alternate-day dosing of 0.5 mg/kg following the 14-day therapy period was applied as causal prophylaxis, to prevent re-infection and/or relapse while not interfering with recrudescence (Arnold *et al.*, 1954, 1955; Schmidt *et al.*, 1982; Wernsdorfer and Payne, 1988). It is recognized, however, that chloroquine and primaquine do apparently act synergistically against *P. vivax* (Baird *et al.*, 1995*a*). Alternate-day use of primaquine, alone, at 0.5 mg base/kg has been shown to be a well tolerated prophylactic regimen, affording protective efficacies of 74% against *P. falciparum* and 90% against *P. vivax* among non-immune children and adults living in Irian Jaya (Baird *et al.*, 1995*b*).

Combined HF-PQ therapy cleared parasitaemia from all of the study patients and no treatment failures occurred within 28 days of beginning treatment, in cases of uncomplicated falciparum or vivax malaria acquired in north-eastern Irian Jaya. This regimen apparently provided a 100% efficacious radical cure. The therapeutic failures seen among similar

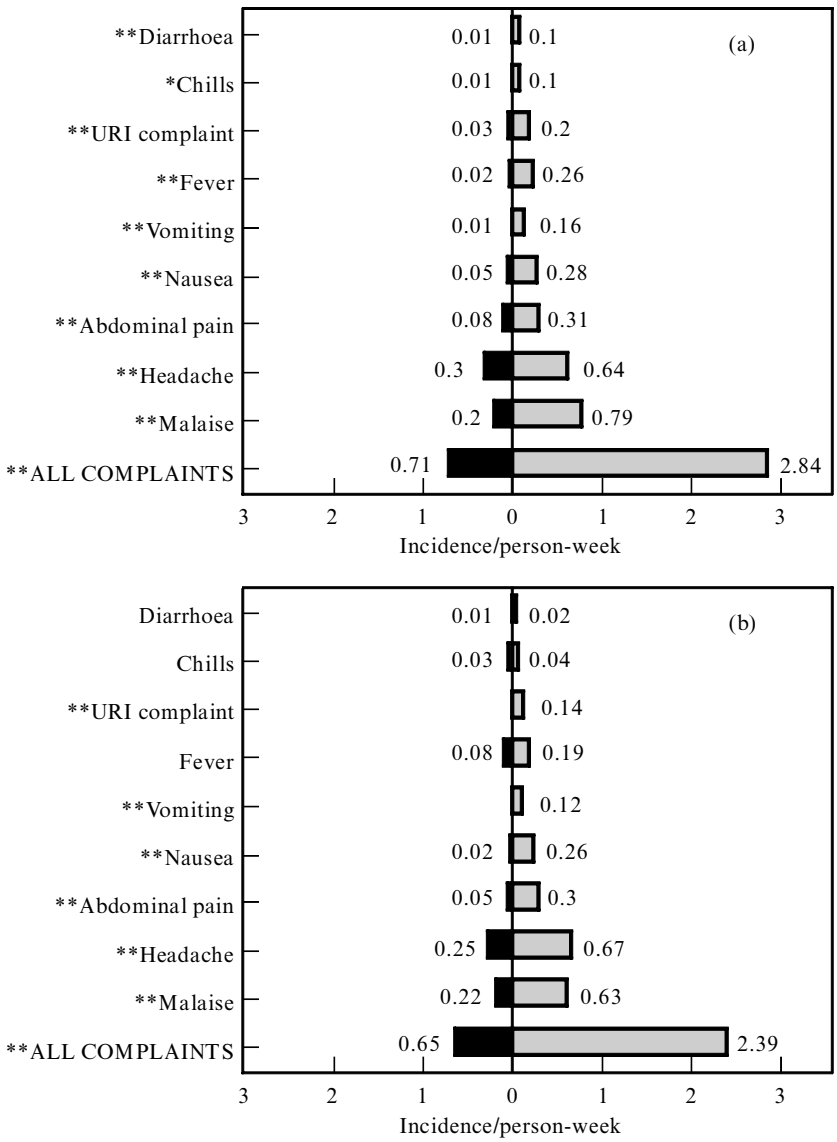

Fig. 2. Incidence densities of physical complaints not associated with patent parasitaemia amongst the *P. falciparum* (a) and *P. vivax* (b) cases treated with halofantrine-primaquine (■) or chloroquine-primaquine (▒). URI, Upper respiratory infection; (*), significant difference between treatment groups ($P < 0.05$); (**), very significant difference between treatment groups ($P < 0.005$).

patients treated with CQ-PQ prove this because it shows that primaquine, *per se*, was not sufficient to prevent the appearance of blood-stage parasites. The absence of recurrent parasitaemias among patients treated with HF-PQ therefore demonstrates complete clearance of the asexual blood stages of *P. falciparum* and *P. vivax*. These results accord with those of another study in which treatment of *P. vivax* with chloroquine or halofantrine, alone, was

compared in the same location in Irian Jaya (Baird *et al.*, 1995*a*). In that study, just one of 19 patients treated with halofantrine had a recurrence of parasitaemia and this single infection, which appeared 25 days post-therapy, was considered to have been a re-infection or relapse. Subsequent, more extensive use of halofantrine alone against *P. falciparum* or of halofantrine with primaquine against *P. vivax* in the Arso district of Irian Jaya has achieved comparably high success rates (A. Richards and T. Richie, unpubl. obs.). A clinical trial of halofantrine alone in East Kalimantan, Indonesia, achieved a cure rate for uncomplicated falciparum malaria of $>98\%$ (Tjitra *et al.*, 1992), with FCT and PCT similar to those seen in the present study when halofantrine and primaquine were used together.

Physical complaints reported in the absence of detectable parasitaemias were consistently higher among patients treated with CQ-PQ than in those given HF-PQ, but these complaints may not have been drug-related. Although there were no differences between treatment groups in PCT, the slower decline of malaria-like illness seen in cases treated with CQ-PQ, and certainly the high failure rate obtained with this combination against *P. falciparum*, indicate that the physical complaints were related more to subpatent parasitaemias in the non-immune population sampled than to side effects of the drugs.

Primaquine administered at a single daily dose of 0.5 mg base/kg for 14 days apparently clears the liver of the tissue stages of *P. falciparum* and *P. vivax*. Although the present results do not prove this, the results of other studies demonstrate this effect. The adult regimen of 30 mg daily for 14 days was completely effective against the Chesson strain of *P. vivax* from New Guinea, whereas the 15-mg regimen has been repeatedly unsuccessful (Clyde and McCarthy, 1977; Rombo *et al.*, 1987; Jelinek *et al.*, 1995). In a series of four trials conducted in the Arso region of Irian Jaya between 1993 and 1995, a total of 651 study volunteers, most of them non-immune to malaria, and $>25\%$ with patent malaria infections, were cured radically with a combination of quinine, doxycycline and primaquine (Q4D10P14) and no subsequent chemoprophylaxis. Not one of these subjects developed a patent parasitaemia within 2 weeks of the end of the 14-day therapy (Jones *et al.*, 1994; Fryauff *et al.*, 1995; C. J. Church, T. L. Richie, C. Ohrt, E. Tjitra, B. Subianto, B. Sandjaya, E. Gomez, J. K. Baird, D. J. Fryauff and A. L. Richards, unpubl. obs.; C. K.Ohrt, T. Richie, H. Widjaja, G. D. Shanks, D. J. Fryauff, E. Tjitra, B. Sandjaja, H. Basri, W. Widjaja, C. Church and G. Watt, unpubl. obs.). Had any parasitaemia appeared within the usual 8–14-day incubation period, this would have marked the failure of primaquine to clear the liver. Extrapolating from the results for the study populations involved ($N=651$) and assuming a conservative two malaria infections/person-year for the Arso region, an expected 50 parasitaemias would have appeared within the collective 50 person-years of post-radical-cure susceptibility which were contributed by these 651 volunteers if primaquine had not been an effective causal prophylactic. The absence of any such parasitaemia is a confirmation of primaquine's potent effect on the liver stages of falciparum and vivax malaria when dosed at 0.5 mg base/kg daily for 14 days. Parasitaemias following the 14-day primaquine regimen, as applied with halofantrine in the current study, could only have resulted from re-infections.

Reports of cardiotoxicity associated with the high-dose halofantrine regimen (Castot *et al.*, 1993; Nosten *et al.*, 1993) and changes in recommendations for its use (WHO, 1993) were only published after the completion of the present study. While the administration of halofantrine with food is now contra-indicated, the provision of food in this study was intended to protect against the stomach upsets associated with primaquine use (Clayman *et al.*, 1952; Clyde, 1981). It now seems clear that foods may have enhanced the bio-availability and perhaps the efficacy of halofantrine in the present study (Shanks *et al.*, 1992).

In summary, combined halofantrine and primaquine therapies achieved radical cure of falciparum and vivax malaria among non-immune, G6PD-normal, Indonesian men. The HF-PQ regimen was associated with

significantly fewer occasions of physical complaint and/or drug intolerance than were experienced by patients randomized to CQ-PQ therapy, and a more rapid decline of malaria symptoms. These results indicate that the HF-PQ regimen may be preferred over quinine-doxycycline-primaquine for radical cure of malaria among G6PD-normal men with no contra-indicating, cardiac risk factors.

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The opinions or assertions expressed herein are the private views of the authors and are not to be construed as representing those of the U.S. Navy, the Department of Defense, or the Indonesian Ministry of Health.

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