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Safety, Tolerability, and Compliance with Long-Term Antimalarial Chemoprophylaxis in American Soldiers in Afghanistan

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Abstract. Long-term antimalarial chemoprophylaxis is currently used by deployed U.S. military personnel. Previous small, short-term efficacy studies have shown variable rates of side effects among patients taking various forms of chemoprophylaxis, though reliable safety and tolerability data on long-term use are limited. We conducted a survey of troops returning to Fort Drum, NY following a 12-month deployment to Operation Enduring Freedom, Afghanistan from 2006 to 2007. Of the 2,351 respondents, 95% reported taking at least one form of prophylaxis during their deployment, and 90% were deployed for > 10 months. Compliance with daily doxycycline was poor (60%) compared with 80% with weekly mefloquine (MQ). Adverse events (AEs) were reported by approximately 30% with both MQ and doxycycline, with 10% discontinuing doxycycline compared with 4% of MQ users. Only 6% and 31% of soldiers reported use of bed nets and skin repellents, respectively. Compliance with long-term malaria prophylaxis was poor, and there were substantial tolerability issues based on these anonymous survey results, though fewer with MQ than doxycycline. Given few long-term antimalarial chemoprophylaxis options, there is an unmet medical need for new antimalarials safe for long-term use.

INTRODUCTION

Doxycycline is one of the three remaining effective drugs approved by the Food and Drug Administration (FDA) for the chemoprophylaxis of *Plasmodium falciparum* malaria. Daily oral doxycycline hyclate (DH) has been the malaria prophylaxis drug of choice for deploying U.S. military personnel, in part for its ability to protect against other tropical infections such as leptospirosis.[1] However, the safety and tolerability of long-term doxycycline use in a large population has not been well documented. Earlier literature reports the use of doxycycline as malaria prophylaxis among relatively small populations in clinical trials and field studies and describes an adverse event (AE) profile that is significant for gastrointestinal (GI) upset and phototoxicity.[2] In particular, the DH salt form has been reported to have significant tolerability issues related to a decline in the gastric pH on dissolution, causing GI side effects including nausea, emesis, epigastric pain, and occasionally, chemical esophagitis.[3] Alternate dosage forms of doxycycline such as doxycycline monohydrate (DM) and enteric coated doxycycline hyclate (DHEC) are purportedly better tolerated.[4,5] In a 2006 study, the respective costs of these dosage forms were 3.5 and 22 times more than the cost of immediate-release, generic DH.[6] In addition, these forms of doxycycline have never been directly compared with DH. Prior studies of deployed soldiers have demonstrated poor compliance with daily doxycycline prophylaxis.[7–12] Although most efficacy trials of DH and DM have shown comparable rates of GI toxicity, AE withdrawals, and noncompliance, it is important to realize that most of the safety and tolerability data are from trials powered for efficacy, not tolerability.[13] Differences in study design, end points, assessment methods, and length of follow-up complicate the comparison of the safety and tolerability of the different dosage forms of doxycycline (Table 1).

Among troops deploying to Afghanistan in 2006 as part of Operation Enduring Freedom VII, oral mefloquine (MQ) 250 mg per week was the primary alternative to DH. In spite of MQ's advantage of weekly dosing and good antimalarial efficacy, it was used as a second-line agent because of its well-documented neuropsychiatric toxicity. In some cases, MQ was chosen as the first-line therapy based on either perceived advantages in compliance, unit force protection, and/or operational concerns. Aversion to MQ use among military personnel has been documented and requires logistically challenging neuropsychiatric screening by regulation.[14] At the time of the study, atovaquone-proguanil (AP) was a third alternative for antimalarial chemoprophylaxis. Although AP is a safe and effective daily medication, it remains more costly than DH and MQ and was not routinely used by U.S. forces in 2006–2007.

To assess long-term compliance and tolerability of currently used antimalarial chemoprophylaxis, we conducted a survey between January and June 2007 at Fort Drum, NY among U.S. military personnel returning from a yearlong deployment to Afghanistan. Although the data were collected 8 years ago, this was the largest survey conducted of antimalarial chemoprophylaxis in soldiers returning from Operation Enduring Freedom. The results of the survey prompted policy changes including more liberal use of AP.

MATERIALS AND METHODS

A retrospective, anonymous survey was completed by soldiers returning to Fort Drum, NY from Afghanistan between January and June of 2007. Surveys were offered with written instructions requesting voluntary participation and assuring anonymity. No individually identifying information was collected on the survey instrument. Of the 2,601 surveys handed out, 2,351 (90%) surveys were returned and at least partially completed. General demographic data including respondent's gender, rank, and length of deployment were obtained. Questions measuring medication compliance were designed to evaluate the timing of doses, and the extent to which soldiers took

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TABLE 1
Summary of AEs reported in relevant antimalarial chemoprophylaxis studies

Treatment arms	Blinding	*n*	Time	Assessments	Key outcomes	Locations	References
DM vs. C-P	Geographic	522	4 months	Directed survey on days 7, 60, 120, 150	C-P 74% compliance vs. 90% for DM	Chad, Gabon	2
				Urine drug level	Higher rates of diarrhea, epigastralgia, urticaria, sun rash, mouth ulcers for C-P		
				Days 7 and 120	No difference in malaria rates		
MQ vs. 'Doxy'	Open label	1,358	6 months	AE questionnaire and interview at the end of the study	Doxy: 24% sleep disturbance, 18% headache, 25% fatigue, 21% nausea MQ: 9 SAEs	East Timor	16
MQ vs. DH	Open label	385	Variable	AE questionnaire mailed 2 weeks after returning home	Doxy: 14.9% nausea, 7.8% abdominal pain, 5.7% withdrew d/t abdominal pain; MQ: 20.7% nausea, 10.5% abdominal pain, 6.3% withdrew due to AEs	Travelers from Australia to malarious area	8
'Doxy' vs. MQ vs. placebo	Double dummy; DOT	204	3 months	Active AEs daily + exit survey, weekly smears	Doxy: lower rates nausea, neuro, HA, dizziness; higher rate of cough Cases: MQ 0, Doxy 1, placebo 53	Irian Jaya	11
Enteric DH vs. DM vs. placebo	Double dummy; crossover	111	3 days + 10 days	AEs	DM: 66% AE, enteric DH 40% AE, placebo: 30% AE	Finland, healthy volunteers	4
DH vs. MQ	Open label; deployed	499		Survey: switch DH to MQ	GI complaints: 17% DH vs. 10% MQ; four hospitalized for odynophagia	Somalia	19
DH vs. MQ	Open label; deployed	734	8 weeks 6 months f/u	Surveys at weeks 2 and 8	GI complaints: 51% DH vs. 11% MQ at week 2; 14% DH vs. 1% MQ Week 6; no malaria cases; only 50% completed questionnaires	Afghanistan	7
DM vs. MQ vs. C-P vs. A-P	Double dummy (no placebo arm)	623	1–3 weeks	Surveys at days 17 and 11 before travel; day 7 after travel	GI complaints: Moderate: 9% DM vs. 16% MQ vs. 16% A-P vs. 20% C-P; all events: 53% DM vs. 58% MQ vs. 54% A-P vs. 61% C-P	Sub-Saharan Africa	20
Doxy carageenate vs. DM (PK study)	Open label, crossover	24	2 days	PK, Aes	Nausea: 3 DM (1 loose stools) vs. 1 DC	Sweden, healthy	29
DM-CQ vs. DM-Placebo	Double blind	936	Variable	Self-report in standardized notebooks	Both groups reported at least one AE (~57%) and similar AEs (abdominal pain, diarrhea, headache, insomnia); DM-CQ group reported significantly more nausea or vomiting: 18.4% vs. 11.6%	Sub-Saharan Africa	12
Doxy vs. MQ vs. CQ	Observational	228	6 months	Self-report	Doxy AEs: 35% GI, 34% skin and vaginal, 30% neuropsychological; reports of GI, skin, and vaginal AEs greater in doxy group compared with MQ and CQ groups	Varies	28

AE = adverse event; DH = doxycycline hyclate; DM = doxycycline monohydrate; GI = gastrointestinal; MQ = mefloquine; DC = doxycycline carageenate; DOT = directly observed therapy; HA = headache; d/t = due to; SAEs = serious adverse events; PK = pharmacokinetics; CQ = chloroquine; C-P = chloroquine-proguanil.

the medications as prescribed. Questions related to AEs associated with doxycycline were phrased to capture the classification scheme of the Common Terminology Criteria v3.0. Questions related to MQ-associated AEs were phrased in a more abbreviated listing of commonly reported side effects given the far fewer number of anticipated MQ prescriptions. It is important to note that although no face-to-face interviews took place, the survey was distributed during redeployment medical screening so medical staff were available to answer respondents' questions as needed. The study protocol was reviewed and approved as a minimal risk study by the institutional review board at the Walter Reed Army Institute of Research. Questionnaire responses were scanned using TeleForm version 9.0 software (Cardiff; Vista, CA), and data were analyzed using Microsoft Excel 2003 (Microsoft, Redmond, WA), Epi Info v3.3.2, and SPSS 22.0 (SPSS Inc.; Chicago, IL).

RESULTS

Of the 2,351 survey respondents, 2,206 (93.8%) reported taking at least one form of antimalarial chemoprophylaxis for some of the deployment. Only 154 (6.5%) reported any prior use of antimalarial chemoprophylaxis. More than half (57%) were deployed in the southern, southeastern, or eastern provinces of Afghanistan where malaria risk is highest. Table 2 shows the demographic distribution of respondents by prophylaxis medication used. Of the respondents, 2011 (85.5%) reported taking doxycycline, 596 (25.3%) took MQ, and only 78 (3.3%) reported taking AP for at least some period during deployment. Overall, 16 (0.7% of all respondents) reported that they were diagnosed and treated for malaria during the deployment of whom 14 reported taking any chemoprophylaxis. All 14 reported taking doxycycline, though 5 of these reported using MQ as well, and 1 reported using AP. The timing of these events was not captured so it is unclear whether these represent "breakthrough" cases, subsequent treatment of malaria with MQ, or the result of noncompliance.

TABLE 2
Demographic characteristics of U.S. military personnel surveyed at Fort Drum, NY, by prophylaxis medication used, 2006–2007

	Doxycycline		MQ		AP	
Doxycycline						
Yes	2,011	(100.0%)	376	(100.0%)	63	(100.0%)
MQ						
Yes	376	(100.0%)	596	(100.0%)	25	(100.0%)
Months deployed						
10 or more	1,841	(91.5%)	561	(94.1%)	76	(97.4%)
6–9	85	(4.2%)	18	(3.0%)	2	(2.6%)
4–6	34	(1.7%)	7	(1.2%)	0	(0.0%)
0–3	23	(1.1%)	1	(0.2%)	0	(0.0%)
No response	28	(1.4%)	9	(1.5%)	0	(0.0%)
Area deployed						
Central	853	(42.4%)	110	(18.5%)	21	(26.9%)
Southeastern	586	(29.1%)	240	(40.3%)	28	(35.9%)
Eastern	271	(13.5%)	191	(32.0%)	13	(16.7%)
Southern	218	(10.8%)	20	(3.4%)	10	(12.8%)
Northern	17	(0.8%)	11	(1.8%)	0	(0.0%)
No response	66	(3.3%)	24	(4.0%)	6	(7.7%)
Sex						
Male	1,297	(64.5%)	406	(68.1%)	66	(84.6%)
Female	164	(8.2%)	41	(6.9%)	5	(6.4%)
No response	550	(27.3%)	149	(25.0%)	7	(9.0%)
Age group						
18–24	576	(28.6%)	196	(32.9%)	24	(30.8%)
25–29	380	(18.9%)	124	(20.8%)	19	(24.4%)
30–39	373	(18.5%)	101	(16.9%)	20	(25.6%)
Over 40	113	(5.6%)	21	(3.5%)	6	(7.7%)
No response	569	(28.3%)	154	(25.8%)	9	(11.5%)
Rank						
Field grade/ general	73	(3.6%)	16	(2.7%)	2	(2.6%)
Company grade	188	(9.3%)	59	(9.9%)	7	(9.0%)
Warrant officer	83	(4.1%)	4	(0.7%)	2	(2.6%)
NCO	830	(41.3%)	272	(45.6%)	35	(44.9%)
Enlisted	820	(40.8%)	241	(40.4%)	32	(41.0%)
No response	17	(0.8%)	4	(0.7%)	0	(0.0%)

AP = atovaquone-proguanil; MQ = mefloquine; NCO = non-commissioned officer.

There were 520 respondents (25.2%) reporting more than one medication used to prevent malaria over the course of the deployment. In most cases, respondents who took MQ had initially taken doxycycline. Among individuals taking more than one medication, 22 (4%) reported an interval of greater than 1 month duration between stopping the initial medication and starting the new one.

Although 1,951 (97%) of 2,011 respondents taking doxycycline reported receiving instructions from a medical provider on its safe use, only 1,495 (74.3%) reported regularly taking doxycycline with food, 870 (43.3%) reported drinking a full glass of water, and 474 (23.6%) reported waiting 30 minutes before lying down after taking the medication. Official policy required 100% compliance with prophylaxis regimens throughout the deployment period, starting 1–3 weeks prior to departure. The majority of respondents were initially deployed during the winter months when no malaria transmission occurs, and only 1,238 (61.6%) of doxycycline users began medication before arriving in theater as directed.

Among those taking doxycycline who also responded to the compliance question, only 60% (870/1,438) of respondents reported daily use, with 26% respondents on doxycycline leaving the question on compliance blank. Among those reporting compliance, 27% reported taking doxycycline 4–6 days per week, 7% reported taking it 1–3 days per week, and 6% reported taking it less than once per week. Of the respondents who provided reasons why they did not adhere to doxycycline, the two most frequently reported reasons for noncompliance were simply forgetting (70%) and side effects/safety concerns (18%), with 4% reporting that they did not believe doxycycline prophylaxis was important or effective.

Side effects were attributed to doxycycline by 623 of 1,898 respondents (32.8%) who completed the side effects questionnaire (Table 3). Among the respondents reporting side effects to doxycycline, 26% (164/623) indicated that the side effect limited their ability to perform their job, with 8% (51/623) reporting severe performance limiting side effects. Of those experiencing side effects, 30% (190/623) reported stopping doxycycline overall, with 9.7% (196/2,011) reporting that they stopped treatment due to side effects. Table 3 lists doxycycline-associated side effects by severity with a total of 172 severe AEs. GI effects predominated with nausea (17%), diarrhea (15.5%), heartburn (12.9%), and anorexia (10.2%) being most common. Although a large proportion of respondents revealed their gender on the survey (1,461/2,011), and females made up a relatively small minority (8%), they reported higher rates of nausea and vomiting than males (30% versus 15% and 19% versus 6.6%, respectively). Meaningful comparisons between AE rates based on length of

TABLE 3
Soldiers using long-term doxycycline antimalarial chemoprophylaxis reporting nine common AEs attributed to medication, by severity

Specific AEs reported	Total (N = 2,011)	Total (%)
Photosensitivity	115	5.7
Mild: painless rash in sun exposed areas	57	2.8
Moderate: painful rash in sun exposed areas	58	2.9
Severe: rash with peeling of the skin	26	1.3
Rash other than photosensitivity	85	4.2
Mild rash: no other symptoms	34	1.7
Moderate rash: pain, itching, slight desquamation	33	1.6
Severe rash: pain, itching, large desquamation	18	0.9
Loss of appetite	205	10.2
Mild: no change in diet	131	6.5
Moderate: change in diet; no weight loss	51	2.5
Severe: with weight loss or malnutrition	23	1.1
Diarrhea	311	15.5
Mild: 1–3 bowel movements/day	247	12.3
Moderate: 4–6 bowel movements/day	56	2.8
Severe: 7 + bowel movements/day; intravenous (IV) fluids/hospitalization	8	0.4
Heartburn/dyspepsia	259	12.9
Mild	136	6.8
Moderate	85	4.2
Severe	38	1.9
Nausea	341	17.0
Mild: no change in diet	217	10.8
Moderate: change in diet; no weight loss	100	5.0
Severe: above plus dehydration, malnutrition, IV fluids, or hospitalization	24	1.2
Vomiting	151	7.5
Mild: once in 24 hours	124	6.2
Moderate: 2–5 times in 24 hours; requiring IV fluids < 24 hours	24	1.2
Severe: > 6 times in 24 hours; IV fluids > 24 hours	3	0.1
Esophagitis "pain and/or difficulty swallowing"	41	2.0
Mild: no symptoms, told by physician of esophagitis	18	0.9
Moderate: pain on swallowing, altered diet	20	1.0
Severe: symptomatic, admitted to hospital, or required IV fluids	3	0.1
Vaginitis	28	1.4
Mild	16	0.8
Moderate	10	0.5
Severe	2	0.1
Reported only one AE	186	9.2
Reported two to three AEs	289	14.4
Reported more than three AEs	148	7.4
Reported severe AE	172	8.6
Total reporting at least one AE	623	31.0

AE = adverse event.

deployment were also difficult to make with only 7.1% of those on doxycycline deploying for fewer than 9 months. Similarly, comparison of AEs by age groups was limited by missing age data (28.3%).

There were 596 subjects who took MQ prophylaxis during deployment, including 25 subjects reported taking both MQ and AP. Self-reported compliance among soldiers taking MQ was higher than those taking doxycycline, with 80% (477/596) reporting regular weekly use (Table 4). Side effects were reported by 33% (187/564) of those taking MQ and completing the questions on MQ side effects (32/596 left these blank). The two most common side effects reported were vivid dreams (21%) and dyspepsia (9.2%). Approximately 4% of respondents experiencing MQ -related side effects reported having to stop the medication as a result.

Information about the use of personal protective measures against mosquito bites to prevent malaria, including bed nets, insecticide-treated uniforms, and mosquito repellants was also gathered. Only 1% (123/2,134) and 4% (75/2,121) of respondents reported consistent use of bed nets and repellant, respectively (Table 5). Similarly, only 31% (663/2,137) of respondents reported that all of their uniforms had been treated with permethrin. Significantly, 44% (934/2,134) and 20% (417/2,121) of respondents reported that bed nets and skin repellents, respectively, were not issued.

DISCUSSION

We conducted this survey in returning U.S. military personnel to gauge compliance, tolerability, and safety of DH and MQ, as well as use of personal protective measures (PPMs) to assess potential operational concerns. At the time of the study, deployed soldiers using long-term antimalarial prophylaxis were predominantly taking immediate release DH, with MQ used as the alternative. Compliance with therapy was poor, particularly for doxycycline. Fewer than half of respondents reported taking DH every day. These findings are consistent with observations from previous studies in both civilian and military populations, identifying daily dosing regimens as significant obstacles to compliance with doxycycline prophylaxis.[7,8] Similarly, long-term use of daily doxycycline for dermatological indications yield lower compliance owing to GI side effects.[15] Although the majority of those not taking DH daily reported simply forgetting to take it, one-third of

TABLE 4
Frequency of side effects among soldiers taking MQ as antimalarial chemoprophylaxis in Afghanistan

Side effect	Total (N = 596)	%
Vivid dreams	135	23
Dyspepsia	57	9.6
Dizziness	26	4.4
Insomnia	25	4.2
Lightheadedness	24	4.0
Headache	24	4.0
Diarrhea	22	3.7
Other	21	3.5
Nervousness	21	3.5
Ringing in ears	12	2.0
Depression	12	2.0
Vomiting	9	1.5
Chills	7	1.2
Adverse event?	198	33
Stopped due to adverse event?	23	3.9
Compliance		
Weekly	477	80
3 weeks per month	40	6.7
1–2 weeks/month	21	3.5
Rarely	83	12
Total noncompliant with therapy	144	24

MQ = mefloquine.

soldiers reported concerns with side effects as the primary reason for noncompliance. DH and MQ have been shown to have high rates of AEs and noncompliance in prior clinical studies.[2,3,7,8,16] Because of the poor compliance with doxycycline, theater policy changed during the deployment, and personnel were offered the option of using MQ (Mod 9 to US CENTCOM, Individual Protection and Individual-Unit Deployment Policy, 8 Sep 2008). Given their comparative expense, AP, DHEC, and DM were not routinely used, though AP was taken on a limited basis by aviators, accounting for the small proportion here.

Despite 97% reporting that they had received instruction from a medical provider, knowledge of proper use of doxycycline to reduce GI side effects was limited. Although three-quarters reported ingesting doxycycline with food, less than half reported taking with a full glass of water and only one quarter remained upright for 30 minutes after swallowing. At least one prior study identified an association between improper doxycycline administration and poor tolerability, which may explain the poor compliance and tolerability observed here.[10] Given the demands of a deployment, adhering to prescribed practices may not always be possible. In addition to poor individual compliance, nearly 40% of respondents did not begin chemoprophylaxis until after arriving in theater, increasing their chances for early breakthrough events prior to development of protective drug levels. It should be pointed out that the deployment began in January of 2006 and much of Afghanistan was snow covered for the first several months, particularly at higher elevations. Self-reported compliance was higher with weekly MQ prophylaxis than with daily DH prophylaxis, despite prior concerns related to neuropsychiatric AEs with MQ. This is consistent with findings from other studies measuring compliance with MQ and daily administered comparators.[7,8]

Despite these shortcomings, compliance with and appropriate use of antimalarial chemoprophylaxis observed here were significantly better than that seen with PPMs to prevent mosquito bites including treated uniforms and insect repellants. Studies have shown that permethrin-treated clothing and bed nets are protective against malaria infection when used correctly.[17,18] Wallace and others previously demonstrated that malaria occurred in those who were noncompliant with both chemoprophylaxis and PPMs, particularly failure to use bed nets and to keep sleeves rolled down.[19] The latter is now part of official uniform wear policy for the U.S. military, underscoring the overall importance of command discipline to vector-borne disease prevention. In addition, Army combat uniforms are now treated with permethrin prior to their issuing to soldiers. However, soldiers may not wear uniforms at all times, and thus, may have limited protection in their personal recreational clothing. Renewed command emphasis on disease prevention may lead to improvements in availability and correct use of PPMs.

Prior studies have shown a strong link between noncompliance and poor tolerability.[2,3,7–9,16] Overall rates of side effects were comparable between doxycycline and MQ,

TABLE 5
Reported use of personal protective measures

Use of personal protection	Total respondents (N)	n	%	Months in theater			
Bed net				0–9	%	10+	%
Total who used bed net	2,134	121	6	2	1	118	6
Always	2,134	23	1	0	0	23	1
Sometimes	2,134	98	5	2	1	95	5
Total who did not use bed net	2,134	2,013	94	140	99	1,830	94
Did not use despite issue	2,134	1,079	51	92	65	971	50
Not issued	2,134	934	44	48	34	859	44
Permethrin-treated uniforms							
Used treated uniforms	2,137	1,244	58	47	33	1,174	60
All uniforms treated	2,137	663	31	25	18	633	32
Some uniforms treated	2,137	581	27	22	15	541	28
Did not use treated uniforms	2,137	757	35	78	55	661	34
Did not know if uniforms were treated	2,137	136	6	17	12	116	6
Skin repellants							
Used skin repellant	2,121	649	31	30	21	606	31
Always	2,121	75	4	5	3	68	4
Sometimes	2,121	574	27	25	17	538	28
Did not use skin repellant	2,121	1,472	69	114	79	1,327	69
Did not use despite issue	2,121	1,055	50	81	56	955	49
Not issued	2,121	417	20	33	23	372	19

reported by roughly 30% of respondents to both drugs. Neuropsychiatric reactions, manifested largely as "vivid dreams," were the primary side effects seen here with MQ, reported by more than 20% of respondents. Overall, 4% of those taking MQ reported that side effects caused them to stop treatment. Because a significant number of respondents did not disclose gender, we could not determine here whether females were at higher risk for neuropsychiatric MQ effects seen in prior studies.[8,20] MQ use in military personnel has been a point of controversy given higher rates of contraindications to MQ use than the civilian population, particularly with respect to psychiatric diagnoses such as posttraumatic stress disorder.[14] In response to these concerns in 2009, the Assistant Secretary of Defense required individualized screening for MQ prescriptions and established an algorithm favoring DH as the first-line choice.[21] Compliance with the psychiatric screening policy for MQ use was not assessed in this study.

More than 8% of those taking doxycycline reported that side effects caused them to stop taking it, with GI effects predominating. A number of studies have recommended replacement of DH with alternative salt forms to reduce GI side effects, though it should be noted that the various forms of doxycycline have never been compared directly in a clinical trial for this purpose.[2,4,20] Because of the high incidence of AEs associated with DH, the French Armed Forces have replaced its use with DM, and two studies suggested though did not confirm that DHEC leads to even fewer AEs when compared with DM.[2,4] The large number of side effects reportedly associated with DH here suggest that cost considerations may reflect a "false economy" if use of the less expensive product leads to higher rates of AEs and noncompliance. Although the relatively small number of apparent "breakthrough" malaria cases (0.7%) seen here may seem reassuring, it is difficult to determine how well this rate reflects actual risk reduction. Although it has been suggested that antimalarial chemoprophylaxis compliance is higher in areas with greater malaria risk, malaria risk and transmission patterns have been known to shift rapidly in Afghanistan.[22,23] Given the wide geographic distribution of respondents, actual malaria exposure during the period was unknown, and varied widely ranging from no risk in the mountainous regions to substantial risks in some of the northern and southeastern regions.[24]

This study highlights issues with compliance and side effects experienced by U.S. Army soldiers taking long-term antimalarial chemoprophylaxis, which should be interpreted in light of the study's limitations. Comparison of side effect rates between MQ and doxycycline is challenging, as medication assignment was not random and MQ therapy was generally provided only to those intolerant of doxycycline. Sources of potential selection bias included self-selection, self-reporting, and a small proportion of females, all of which may limit generalizability. Failure to comply with command-directed force health protection measures such as antimalarial chemoprophylaxis may be a violation of the Uniform Code of Military Justice (UCMJ). Although the survey was anonymous and non-attributional, potential subject fears regarding legal repercussions of responses may have been significant given that 26% did not respond to questions on compliance. This was also evidenced in the large numbers of nonresponses to demographic variable questions. Recall bias over a yearlong deployment may also have been significant. Despite these limitations, the study provides useful information for future malaria prophylaxis policy.

The shortcomings in compliance and tolerability of currently available malaria prophylaxis highlighted here represent an unmet medical need for safer, better tolerated weekly or monthly dosed medications. Although malaria breakthrough rates were low, the high rates of AEs observed may have a significant impact on military readiness. There are few drugs currently being developed for use as antimalarial chemoprophylaxis, with the exception of tafenoquine, an 8-aminoquinoline intended to replace primaquine. Like primaquine, tafenoquine is known to cause hemolysis in G6PD-deficient persons and also requires CYP2D6 metabolic activation; however, because of its otherwise excellent efficacy and tolerability profile, it remains in clinical development by the U.S. Army.[25,26] As costs continue to decline for alternative safe and efficacious medications, such as DM, DHEC, and AP, it may be advantageous to incorporate these drugs as first-line agents. Within the Military Health System, encompassing 9.7 million soldiers and their families, the number of AP and doxycycline prescriptions were stable or increased from 2007 to 2011, whereas MQ prescriptions dropped from 36% to 2%.[27]

This study underscores the need for research on new malaria prevention tools to increase the range of safe options available for long-term use. In the meantime, AP has clearly emerged as an efficacious malaria chemoprophylaxis although it too requires more longitudinal safety data. Additional investigation into the reasons for noncompliance with PPMs may reveal ways in which vector-borne disease control strategy can be adapted. The need to have multiple chemoprophylaxis options available in theater is also apparent, given that 25% of the respondents took more than one medication over the course of their deployment. This finding echoes earlier reports of long-term prophylaxis tolerability in Peace Corps volunteers living in malaria-endemic regions who required more than one medication over the course of their stay due to AEs.[28] Future studies should consider tolerability, compliance, and cost-effectiveness of alternative medications for malaria chemoprophylaxis for U.S. military use.

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