

ADHERENCE TO ANTIMALARIAL COMBINATION THERAPY WITH SULFADOXINE-PYRIMETHAMINE AND ARTESUNATE IN RURAL TANZANIA

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Abstract. Artemisinin-containing antimalarial combination therapies are recommended to confront drug-resistant *Plasmodium falciparum* malaria. Among the questions surrounding whether these complex multidose treatments will be practical is to what extent patients complete the recommended doses. Combination therapy through coadministration of sulfadoxine-pyrimethamine plus artesunate was introduced as a first-line treatment for uncomplicated malaria in one district in Tanzania. Interventions to optimize correct use were also implemented. We observed 453 patient encounters at one health facility and recorded key practices as health workers dispensed the combination. A total of 253 patients were followed-up at 24 or 48 hours. Complete adherence measured at 48 hours reached 75.0%, based on self-report and tablet counts. This is substantially better than reported elsewhere and compares favorably with intervention studies to optimize adherence to chloroquine. Counseling about what to do if a patient vomits appears to have been an independent risk factor for nonadherence.

INTRODUCTION

Antimalarial drug resistance undermines efforts to reduce the public health burden nearly everywhere malaria transmission occurs. Chloroquine, once highly effective against the parasites that cause the disease, has become compromised as drug-resistant *Plasmodium falciparum* parasites have become increasingly prevalent in recent decades.¹ Resistance to other drugs, including sulfadoxine-pyrimethamine (SP), mefloquine, and quinine, has followed closely behind. In two refugee camps in Thailand, the use of an artemisinin-containing combination treatment (ACT) with artesunate (AS) and mefloquine has been linked to halting the progression of antimalarial drug resistance² and reducing malaria transmission.³ Advocates of this approach⁴ and international organizations⁵ have recently called for ACT strategies to be deployed without delay across Africa, where the greatest burden of malaria-related morbidity and mortality occurs. Although there are limited data and experience to guide the introduction of ACTs in Africa, there is consensus evolving that the threat of unchecked resistance to the currently used drugs is too urgent to delay their deployment. At least two large-scale evaluations are underway to document the effect of ACTs in African settings.⁶ However, these research outcomes may be years away and potential short-term advantages of ACTs are already evident from *in vivo* efficacy studies on the continent.^{7–9} So far, the cost of artemisinin-containing drugs,¹⁰ their limited global supply,¹¹ and some lingering concerns about safety¹² have slowed their wide-spread deployment. As unprecedented resources for malaria control start to become available,¹³ these barriers, too, are being lowered.

When chloroquine was efficacious, patterns of drug use evolved that were often far from ideal. Because it was relatively affordable and safe, health officials widely recommended chloroquine for anyone who might have malaria.¹⁴ Over decades the drug was pervasively used with or without diagnostic confirmation, easily obtained from formal health facilities as well as unregulated sources in the community, and taken with little or no attention to complete, appropriate dosing. As a result, a number of studies in Africa documented that health workers' and consumers' adherence to recommended indications and doses was poor,¹⁵ and may have

contributed to the intensification and spread of resistant parasites.¹⁶ More recently, efforts to improve the use of chloroquine have demonstrated promise. Providing the drug through trained community health workers,^{17,18} training shopkeepers¹⁹ and wholesalers,²⁰ and dispensing prepacked unit doses²¹ with improved labeling²² have all been shown to enhance the proportion of patients who receive and complete the recommended dose.

Before ACTs are widely deployed in Africa, it will be useful to revisit experiences gained with chloroquine and other monotherapies and carefully consider how the new treatments can be used judiciously. Health officials will have to balance the need to make ACTs widely accessible with concerns about minimizing their inappropriate use.¹² In particular, it may be possible to adapt approaches used to improve complete adherence with chloroquine to the more complex combination regimens. As part of a multidisciplinary evaluation of ACT, the Rufiji District Council Health Management Team (CHMT) introduced SP plus AS as first-line treatment for confirmed or suspected malaria at all registered health facilities in the district. Shortly after introducing the new treatment, we undertook a follow-up study to assess patient adherence.

MATERIALS AND METHODS

This study was completed as part of the Interdisciplinary Monitoring Project for Antimalarial Combination Therapy in Tanzania.* The objective of this study was to measure adher-

*The Interdisciplinary Monitoring Project for Antimalarial Combination Therapy in Tanzania (IMPACT-Tz) is a multiyear implementation research evaluation project that rests on a collaborative platform comprising the United States Centers for Disease Control and Prevention, the Ifakara Health Research and Development Centre, the National Institute for Medical Research, Muhimbili University College of Health Sciences, the London School of Hygiene and Tropical Medicine, and the Tanzanian Ministry of Health, including its National Malaria Control Programme, the Tanzania Essential Health Interventions Project, the Adult Morbidity and Mortality Project, and the Council Health Management Teams of Rufiji, Morogoro, Kilombero, and Ulanga Districts. IMPACT-Tz is primarily supported by funding from the United States Agency for International Development.

ence shortly after introduction of SP plus AS for routine treatment of malaria and to assess factors that might influence this proportion. Informed consent was obtained from all adult participants and from parents or legal guardians of minors. The study protocol was reviewed and approved by the institutional review boards of the Centers for Disease Control and Prevention (CDC) and the Ifakara Health Research and Development Center. In addition, this research has been approved by the National Medical Research Coordinating Committee of the Tanzania Commission on Science and Technology.

The study was conducted in the Rufiji District, a rural community in the Coast Region of Tanzania. *Plasmodium falciparum* malaria transmission is intense and perennial with some seasonal fluctuation.²³ The district population of 203,102²⁴ is served by 56 hospitals, health centers, and dispensaries operated by the government of Tanzania, or officially registered non-governmental organizations. One of these, the Ikwiriri Health Center was chosen for this evaluation because of its central location and high use.

Beginning in January 2003, 2–5 senior health workers from each of the 56 health facilities in the district were invited to participate in one-day training workshops conducted by the Rufiji District CHMT. These participatory training workshops introduced the principle of ACT and informed health workers to prescribe SP plus AS as first-line treatment of confirmed or suspected cases of uncomplicated malaria in all patients ≥ 2 months of age. The trainers adopted four age-stratified three-day dosing regimens that had been validated elsewhere⁹ and are shown in Table 1.

The training used simple job aids including a dosing guide, wall chart, and dispensing envelopes with age-appropriate dosing instructions written in Swahili and illustrated for illiterate clients. Participants were trained to administer the first dose of SP plus AS under direct observation and to counsel patients and their caretakers about how to take the remaining two days of AS to complete the course of therapy. They were also trained to counsel patients and caretakers on how to prevent malaria and when to return if treatment failed or the patient developed additional symptoms. The training methodology included lecture as well as participatory question and answer sessions and clinical case studies. Health workers left the training workshops with supplies of drugs and supporting materials and were directed to train the remaining workers at their respective facilities. This cascade training approach is commonly used to introduce new clinical guidelines and other health system innovations.

Following introduction of SP plus AS at all health facilities in the district, we enrolled patients treated with this combination at the Ikwiriri Health Center between February 4 and

March 27, 2003. Consecutive outpatients diagnosed with uncomplicated malaria and prescribed SP plus AS were approached for enrollment at the under 5 clinic and the general outpatient clinic before arriving at the dispensing unit to receive treatment. Patients residing in a catchment area of nine census-enumerated villages surrounding the health facility were considered eligible and provided consent for enrollment. Patients with severe or complicated infections, those requiring inpatient treatment, individuals with known sensitivity to sulfa drugs, pregnant women, and infants less than two months of age were excluded from receiving the combination and were ineligible for the study.

Two data collectors were recruited from the local community. These data collectors observed encounters between dispensing health workers and all study patients in the dispensing unit and recorded key health worker behaviors on a structured observation checklist. This included noting the exact number of tablets delivered under direct observation for the first dose and the number dispensed to the patient for follow-up doses on the second and third days. In addition, they noted what counseling advice dispensing health workers provided. Data collectors also recorded demographic data and any additional diagnoses other than malaria. Before being discharged home, detailed information about the household location was obtained from all enrolled patients.

Enrolled participants were randomly assigned to three study arms: observation of dispensing encounter with no follow-up; observation of dispensing encounter with follow-up at home after 24 hours; and observation of dispensing encounter with follow-up at home after 48 hours. This design was selected to minimize two sorts of bias that might be expected to affect the behavior of the participants. Including a no follow-up group introduced some uncertainty, so that patients and caretakers may have been less prone to social desirability bias. Including the follow-up at 24 hours, before the treatment should have been completed, allowed us to characterize practices such as completing the entire course ahead of time, which might be overlooked by assessing adherence only once, at or beyond 48 hours. Data collectors, patients, caretakers, and health workers were blinded to the study arm on the day of enrollment.

At the end of each enrollment day, data collectors reviewed the random assignment of patients, identified those selected for follow-up visits, and planned these visits for the following days. If one of the data collectors observed the dispensing encounter with a patient or caretaker, the other data collector was assigned to visit that household in follow-up. With the assistance of local leaders, they visited patients at home on the selected follow-up day and completed a standardized questionnaire. The follow-up questionnaire included questions about household education, construction, and ownership of specific assets. These were included to characterize each household's relative socioeconomic status. Knowledge of the recommended dose was determined by structured interviews with patients themselves or their primary caretaker for patients less than 12 years of age. Adherence with recommended follow-up doses was assessed by self report and corroborated by physically counting the remaining number of tablets available at the time of the visit.

Data entry forms were checked in the field by a single investigator (RAK). Forms were then sent to the central data processing unit. Data were double-entered using Microsoft

TABLE 1

Age-specific dosing schedule for sulfadoxine-pyrimethamine (SP) plus artesunate (AS) in the Rufiji District of Tanzania, 2003

Age group	SP tablets* at time 0	AS tablets† at time 0	AS tablets† at 24 hours	AS tablets† at 48 hours
2–11 months	0.5	0.5	0.5	0.5
1–5 years	1	1	1	1
6–13 years	2	2	2	2
≥ 14 years	3	4	4	4

* SP tablets contain 500 mg of sulfadoxine and 25 mg of pyrimethamine.

† AS tablets contain 50 mg of artesunate.

(Redmond, WA) FoxPro® software. Data managers developed automated routines to identify discrepancies and execute some simple consistency and range checks and these were resolved with reference to the original data forms. The investigators cleaned and analyzed data using Stata version 7 software (Stata Corp., College Station, TX).

We defined adherence by self report as any case where the patient stated they had taken all of the tablets as recommended by the time of the follow-up visit at either 24 or at 48 hours. Adherence based on tablet counts was defined as any case where the expected number of remaining tablets was physically counted. Cases in which the health worker dispensed an incorrect number of tablets to begin with were excluded. Finally, a composite assessment of adherence was made using information from both the self-report and tablet counts. Cases where tablet counts were correct but where the reported timing of doses was incorrect and cases where the reported timing of the doses was correct but did not match tablet counts were considered non-adherent using this composite measure. Complete adherence was assessed by this composite measure only for patients visited at 48 hours. Patients randomized to the 24-hour follow-up arm were not considered in calculating complete adherence, but are presented for comparison and were included in the analysis of factors associated with adherence (on the basis of the composite measure).

An index of socioeconomic status was derived from a list of 42 household asset variables using principal components analysis. This technique has been validated in a previous cross-sectional survey in the study area.²⁵ Statistical comparisons across two variables were made using the chi-square test or Fisher's exact test as appropriate. The chi-square test for linear trend was used to examine statistical associations between the asset index and outcome variables. Multivariate logistic regression analyses were performed to examine the simultaneous influence of multiple potential predictors on patient knowledge and adherence outcomes. Findings with a $P < 0.05$ were considered statistically significant.

RESULTS

Figure 1 illustrates the enrollment, randomization, and follow-up of study patients. A total of 453 consenting patients were enrolled: 222 from the under 5 clinic and 231 from the general outpatient clinic. Among these 20 (4%) were excluded from further analysis because the health worker dispensed an incorrect number of tablets. Seventeen of these patients were dispensed too few tablets and only three received more than the recommended number. Table 2 includes information on the patients assigned to each of the study groups. There were no statistically significant differences observed between the study groups with respect to age, sex, or the likelihood of receiving the correct number of tablets. Although additional diagnoses other than malaria were rare, participants enrolled in the 48-hour follow-up arm were significantly more likely than other participants to have been diagnosed with a respiratory infection.

Two hundred fifty-three (90.7%) of the participants randomized to receive a follow-up visit were successfully identified in the community and completed the study. There was no statistically significant difference in loss to follow-up between

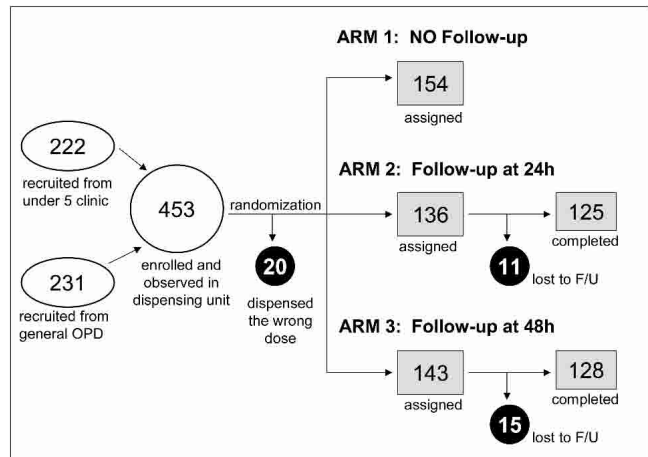


FIGURE 1. Enrollment, assignment, and follow-up (F/U) of patients in a sulfadoxine-pyrimethamine plus artesunate adherence study in the Rufiji District of Tanzania, 2003. h = hours.

the study arms. The 29 patients lost to follow-up did not differ significantly from those who completed follow-up visits with respect to age, sex, additional diagnoses, or village of residence.

Household asset index. Of the 42 household asset ownership questions asked, 15 were eliminated from further analysis because they were reported too frequently or too infrequently to adequately characterize variation in the sample. The analysis retained 27 principal components. The first principal component explained 21% of the variability in these variables and gave the greatest weight to households constructed with cement walls (0.30), using electric lighting (0.30), having a dirt floor (-0.29), or relying on locally made

TABLE 2

Characteristics of clients enrolled in an SP plus AS adherence study, by study arm in the Rufiji District of Tanzania, 2003*

	No visit (n = 162)	24-hour visit (n = 143)	48-hour visit (n = 148)
Point of recruitment			
Under 5 clinic	76 (46.9%)	74 (51.7%)	81 (54.7%)
General OPD	86 (53.1%)	69 (48.3%)	67 (45.3%)
Sex			
Male	64 (39.5%)	58 (39.2%)	57 (39.9%)
Female	98 (60.5%)	90 (60.8%)	86 (60.1%)
Additional diagnoses			
Respiratory infection	9 (5.6%)	10 (7.0%)	18† (12.6%)
Gastroenteritis	5 (3.1%)	7 (4.9%)	4 (2.7%)
Skin infection	0	3 (2.1%)	4 (2.7%)
Dispensed the correct number of SP and AS tablets for age	154 (95.1%)	136 (95.1%)	143 (96.6%)
Completed follow-up visit	Not applicable	125 (91.9%)	128 (89.5%)
Socioeconomic status by wealth quintile			
Most poor		22 (19.8%)	24 (21.8%)
Very poor		20 (18.0%)	23 (20.9%)
Poor		27 (24.3%)	17 (15.5%)
Less poor		23 (20.7%)	21 (19.1%)
Least poor	Not applicable‡	19 (17.1%)	25 (22.7%)

* SP = sulfadoxine-pyrimethamine; AS = artesunate; OPD = outpatient department.

† Differs significantly from no visit and 24-hour follow-up arms ($\chi^2 = 3.92$, degrees of freedom = 1, $P = 0.05$).

‡ Socioeconomic data were not collected from patients randomized to the no follow-up arm.

oil lamps (-0.29). An overall index of socioeconomic status was generated using these weights for each of the 27 principal components. One common way of using this information is to divide the participants into wealth quintiles based on their asset index scores. Comparing wealth quintiles between participants followed up at 24 hours and at 48 hours produced a chi-square test value for linear trend of 0.02, which demonstrates no statistically significant difference in socioeconomic status between participants assigned to the 24 and 48 hour follow-up study arms (Table 2).

Patient knowledge and adherence. Nearly all patients or caretakers in both study groups accurately reported knowledge of the correct dose (Table 3). Adherence was measured by self report, tablet counts, and a composite of the two, as defined earlier. In general, adherence was higher among patients visited at 24 hours compared with those in the 48-hour follow-up group. This difference was statistically significant. The most restrictive measure of complete adherence is that from the composite measure in the 48-hour group: 75.0%. Among the 45 patients who were non-adherent in either study arm, a reason for this could be assessed in 42 cases (Table 4). Finishing all the tablets in under 48 hours was the most common reason for non-adherence and 12 of the 16 cases to which this applied were children.

Predictors of adherence. In bivariate analyses, adherence was not associated with patient's age, sex, or home village. As noted earlier, adherence was slightly but significantly higher among patients visited at 24 hours. There was also a statistically significant association between adherence and knowledge of the correct dose. Adherence was not statistically associated with the education of the patient's head of household nor with socioeconomic status as defined by household wealth quintiles. All patients diagnosed with gastroenteritis were adherent, and those patients diagnosed with a skin infection were less likely to adhere to the recommended doses. There was no statistical association with adherence for those diagnosed with acute respiratory illness or for those with no diagnosis other than malaria.

During their training, health workers learned to use simple job aids for prescribing and dispensing SP plus AS and for counseling patients and their caretakers on how to complete the dose. As part of the study, data collectors observed the encounter between each patient and the dispensing health worker and recorded key behaviors (Table 5) to examine whether any were associated with patient adherence. At one

TABLE 3

Patient/caretaker knowledge and adherence to SP plus AS by self report, tablet counts, and composite measure at 24 and 48 hours in the Rufiji District of Tanzania, 2003 (n = 253)*

Parameter	At 24 hours	At 48 hours
Total number completing follow-up	125	128
Patient/caretaker knowledge of correct dose	118 (94.4%)	115 (89.8%)
Adherent by self report only	115 (92.0%)	98† (76.6%)
Adherent by tablet count only	113 (90.4%)	105 (82.0%)
Adherent by composite measure of self report and count	112 (89.6%)	96‡ (75.0%)

* SP = sulfadoxine-pyrimethamine; AS = artesunate.

† Differs significantly from the estimate at the 24-hour follow-up ($\chi^2 = 11.79$, degrees of freedom [df] = 1, $P = 0.001$).

‡ Complete adherence; This estimate differs significantly from the comparable estimate at the 24-hour follow-up ($\chi^2 = 9.48$, df = 1, $P = 0.002$).

TABLE 4

Reasons for non-adherence to sulfadoxine-pyrimethamine plus artesunate in the Rufiji District of Tanzania, 2003 (n = 45)

Reason for non-adherence	Frequency (percent)
Finished total course of doses in under 48 hours	16 (35.6%)
Discontinued prematurely because the patient's condition improved	12 (26.7%)
Skipped one dose	6 (13.3%)
Intended to take the dose later in the day	5 (11.1%)
Took too few tablets with one or more dose	3 (6.7%)
No reason identified	3 (6.7%)

extreme, none of the observed dispensing health workers mentioned that the treatment was for malaria, informed the patient about possible side effects, or advised the patient to sleep under an insecticide-treated net. On the other hand, in nearly all interactions, the health worker dispensed the correct number of tablets (96.5%), gave the first dose under direct observation (98.9%), and correctly advised the patient how to take the remaining AS tablets at 24 and 48 hours (98.9%). These behaviors occurred either too frequently or too infrequently to be evaluated effectively as predictors of adherence. Among the behaviors that were observed more intermittently, most were not statistically associated with adherence. Paradoxically, only health workers' advice about what to do if the patient vomited was associated with adherence ($\chi^2 = 5.28$, degrees of freedom [df] = 1, $P < 0.022$), and this association was negative.

We fitted logistic regression models to examine the influence of various predictive factors associated with knowledge of the correct dose and with adherence. Because patient knowledge and adherence were closely correlated ($\chi^2 = 86.08$, df = 1, $P < 0.001$), we modeled each outcome individually and did not include knowledge as a predictor of adherence. Models developed for patient or caretaker knowledge were similar to those developed for adherence outcomes and are not presented here. Independent variables included at the start of the stepwise logistic regression included demographic characteristics such as age and sex; the household asset index as a continuous variable; additional diagnoses of acute respiratory illness, skin infections, or none but malaria; and six of the dispensing health worker behaviors that occurred with enough frequency to be assessed as predictors of adherence. Diagnosis of acute respiratory infection was dropped for collinearity. The health worker behaviors included in the modeling process were counseling the patient about what to do if he or she vomited a dose, advising them to return if the condition worsened, asking if the patient had questions, recommending that the medications be taken with food or water, advising that the medications were for one person only, using the dosing wall chart, and dispensing the medicines in the age-appropriate dosing envelope. Most of these along with sex and the additional diagnosis variables were eliminated in fitting the multivariate model.

Because they were related to the study design, variables for an age less than five years and study follow-up arm were retained at each step. In the final fitted model, only being counseled about what to do if the patient vomited was an independent risk factor for nonadherence. Being randomized to the 48-hour follow-up arm was also statistically associated

TABLE 5
Potential factors associated with adherence to SP plus AS in the Rufiji District of Tanzania, 2003*

Potential factor	Adherent (n = 208)	Nonadherent (n = 45)	OR (95% CI)	Adjusted OR (95% CI)
Demographic factors				
Patient's age < 5 years old	110 (52.8%)	25 (55.6%)	0.90 (0.47, 1.72)	1.11 (0.54, 2.28)
Male patient	82 (39.4%)	18 (40.0%)	0.98 (0.50, 1.89)	Dropped
Assigned to the 48-hour study arm	96 (46.2%)	32 (71.1%)	0.35 (0.17, 0.70)	0.38 (0.18, 0.80)
Patient/caretaker knowledge of correct dose	207 (99.5%)	26 (57.8%)	151.27 (11.81, 1937.21)	Not included
Socioeconomic status				
Head of household has had formal education	119 (65.4%)	20 (51.3%)	1.79 (0.89, 3.63)	–
Household asset index in the poorest 2 quintiles	73 (35.2%)	16 (35.6%)	0.98 (0.50, 1.92)	–
Household asset index in the least poor 2 quintiles	75 (36.1%)	13 (28.9%)	1.39 (0.68, 2.81)	–
Household asset index as a continuous variable	–	–	–	1.05 (0.92, 1.20)
Additional diagnoses				
Acute respiratory illness	16 (7.7%)	6 (13.3%)	0.54 (0.20, 1.48)	Dropped
Gastroenteritis	11 (5.3%)	0	Undefined	Not included
Skin infections	3 (1.4%)	4 (8.9%)	0.15 (0.03, 0.71)	Dropped
None	179 (86.1%)	36 (80.0%)	1.54 (0.67, 3.55)	Dropped
Dispensing health worker behaviors				
Told the patient the drugs were intended to treat malaria	0	0	Undefined	Not included
Told the patient about possible side effects	0	0	Undefined	Not included
Advised the patient to sleep under an insecticide-treated net	0	0	Undefined	Not included
Told the patient the names of the drugs	1 (0.5%)	0	Undefined	Not included
Advised the patient to return if condition worsened	1 (0.5%)	3 (6.7%)	0.07 (0.01, 0.67)	Dropped
Asked if the patient had questions	1 (0.5%)	1 (2.2%)	0.21 (0.01, 3.51)	Dropped
Told the patient what to do if he/she vomits after a dose	9 (4.3%)	6 (13.3%)	0.29 (0.10, 0.87)	0.29 (0.09, 0.90)
Used the wall chart or dosing guide to explain dose	58 (27.8%)	13 (29.0%)	0.95 (0.47, 1.95)	Dropped
Told the patient the drugs were for one person only	79 (38.7%)	19 (42.2%)	0.84 (0.43, 1.61)	Dropped
Told the patient to take the medicines with food or water	88 (42.3%)	18 (40.0%)	1.10 (0.57, 2.12)	Dropped
Dispensed tablets with the age-appropriate dosing envelope	188 (90.4%)	39 (86.7%)	1.45 (0.54, 3.85)	Dropped
Told the patient to take 2 daily doses of artesunate at home	207 (99.5%)	45 (100.0%)	Undefined	Not included
Gave the first dose under direct observation	207 (99.5%)	45 (100.0%)	Undefined	Not included

* SP = sulfadoxine-pyrimethamine; AS = artesunate; OR = odds ratio; CI = confidence interval.

with nonadherence. Socioeconomic status as measured by the household asset index approached statistical significance in the multivariate model, despite no observable trend in bivariate analysis. Interaction terms between socioeconomic status, follow-up arm, an age less than five years, and being counseled about vomiting were tested but did not achieve significance nor improve the fit of the model.

DISCUSSION

This study provides useful information about how complex multidose combination therapy regimens for malaria may be delivered in ways that can optimize adherence and appropriate drug use. Because patients observed at 24 hours may not have gone on to complete their third dose, we estimated complete adherence only among the patients randomized to the 48-hour follow-up arm. Based on a composite of self reports and tablet counts, 75.0% of the patients were completely adherent to the recommended regimen. This is substantially higher than the only other published follow-up study of patients treated with SP plus AS, in which only 39% of patients were considered adherent based on a similar definition combining tablet counts and caretaker's history.²⁶ This estimate is also encouraging because it comes immediately after the intervention was introduced at health facilities and can be expected to improve as health workers and their clients become more familiar with and confident in the new treatment. It is equally possible, however, that after the new treatment becomes routine, health workers and consumers may eventually feel comfortable enough to stray from recommended practices and adherence could decrease.

While there is clearly room for improvement, this estimate also compares favorably with data from studies examining adherence to three-day regimens of chloroquine monotherapy in Africa. Without interventions to improve complete adherence, cross-sectional studies have demonstrated that only a small fraction of children received adequate doses of chloroquine. Estimates of the proportion of children who received complete treatment with chloroquine ranged from 30% in Togo²⁷ to 12% in western Kenya²⁸ and 7% in Malawi.²⁹ These cross-sectional estimates can be difficult to compare across studies and are quite dissimilar from the methodology used in our assessment. We found one published study of adherence to chloroquine that used a design similar to ours, with observation at the dispensing unit and follow-up at home. This study in Uganda showed that among children who were dispensed a correct dose of chloroquine, complete adherence after three days was only 38%.³⁰

Intervention studies to improve adherence with chloroquine are more numerous. In one Nigerian study, complete adherence reached 73.3% after introducing a combination of illustrated dosing instructions and health worker counseling.³¹ In Ghana, complete adherence reached 91% after an intervention promoting prepackaged tablets.³² Also, an intervention based on training shopkeepers in coastal Kenya improved the proportion of children treated with an adequate dose of chloroquine to 65.2%.¹⁹ We achieved comparable results after introducing counseling and packaging innovations alongside the new SP plus AS combination therapy. We have no estimate of what complete adherence might have been without these additional intervention elements in place.

It is disappointing that few of the observed health worker

behaviors could be evaluated as independent factors predicting adherence. In general, dispensing health workers provided recommended doses very accurately, but failed to adopt many of the other training elements related to counseling or advising patients. It is not possible from this data to say if this is a trend throughout the district or if it is limited to the small number of health workers observed at this one health facility. The senior health workers who took part in the training workshops of the CHMT are primarily responsible for diagnosis and prescribing, and their activities were not directly observed. By conducting the study at the dispensing unit, we were able to observe only the practices of more junior dispensing health workers. From their observed behavior, the training cascades appear to have been only partially effective at this site. Busy supervisors may have abbreviated the training or dispensing health workers may have interpreted their role narrowly and opted to leave discussion of diagnosis and potential side effects to their senior colleagues. The project team plans to reemphasize these elements in future training workshops that will include dispensing health workers as well as prescribers. Additional studies are planned to observe prescribers' encounters with patients and document dispensing health workers' behavior at other sites in the coming months.

The surprising association between counseling about what to do when a patient vomits and nonadherence is difficult to explain. Perhaps health workers only emphasized this issue to patients who appeared more ill or complained of vomiting and who were less likely to complete the follow-up doses for those reasons. Alternatively, in the absence of any information about side effects, patients and caretakers may have been less likely to complete the follow-up doses if they feared the medicine might cause them to vomit. None of the participants reported vomiting after taking SP plus AS. More information about community perceptions of SP plus AS is needed and qualitative assessments are currently underway in the Rufiji District to assess these.

One practice of particular concern was identified in 16 cases, 12 of them children. These patients took all their follow-up doses, but were considered non-adherent because they or their caretaker reported having taken the entire course of treatment in under 48 hours. In dose-finding studies for AS monotherapies, the same dose was more effectively delivered over five days compared with three days³³ and still more effectively delivered over seven days compared with five days.³⁴ Indeed, three-dose AS monotherapy has been considered insufficiently efficacious to recommend, and when used in combination with other antimalarial drugs, a minimum of 2.5 days has been demonstrated to be efficacious.³⁵ This is particularly important because the SP plus AS combination may be only partially effective if the total dose is compressed into less than 48 hours. Even if the immediate clinical outcome is unaffected, shortening the duration of therapy may increase the theoretical potential to select for SP-resistant parasites.

Our findings regarding socioeconomic status, as measured by the household asset index, as a predictor of adherence, are also equivocal. In a previous study that included parts of the same district, Armstrong-Schellenberg and others²⁵ demonstrated that children from relatively poorer households were taken to health facilities less promptly and were less likely to receive appropriate care than children from wealthier households. However, they also demonstrated that once the chil-

dren received treatment, adherence was not affected by socioeconomic status.

Our study has several other important limitations that should be considered. First of all, the study was completed at a single health facility over a relatively brief period. It may not be representative of the situation in the rest of the district or at other times of year. More importantly, simply enrolling patients in a follow-up study may alter their adherence to treatment. We attempted to minimize this by including an arm with no follow-up and by blinding the clients, data collectors, and health workers to the randomization on the day of enrollment. We also visited participants only once, so that a visit at 24 hours would not affect a participant's behavior at or before 48 hours. It is still possible that social desirability bias may have led us to overestimate adherence. It is equally possible that some patients would have taken their 24- and 48-hour follow-up doses later in the day but had not done so by the time the investigators arrived at their homes. Indeed 6 of 45 nonadherent patients indicated that they intended to complete the recommended dose later that same day. In this way, we may have underestimated adherence. In the future, we plan to assess adherence retrospectively through population-based studies that will provide more representative data that may be less prone to these biases.

Admittedly, self report and tablet counts are imperfect measures of adherence. A measure based on drug levels in biologic samples would be more robust. Unfortunately, such an approach would be more invasive as well. Because the first dose of SP plus AS was given under direct observation, there would be little point measuring blood levels of the sulfa component. Furthermore, blood levels of the artemisinin compounds would be difficult to interpret without accurate information about the timing of the follow-up doses and the samples, which would make such a study more difficult to execute in a rural African community, where timepieces are not commonplace. In addition, such assays require expensive equipment and reagents that may be unsuitable for field conditions.³⁶

Nonetheless, these findings were immediately useful to the project team and contributed to efforts to improve the coverage and delivery of SP plus AS combination therapy in the Rufiji District. They directly led to development of a health communication campaign in the district, which emphasizes the need to take the tablets once a day for three days in a row, even if patients feel better before then. These findings also prompted us to revise our training and supervision plans for health workers in facilities throughout the district. As the SP plus AS combination therapy becomes more widely used in the Rufiji District and experience with it accumulates, we are hopeful that adherence will improve further. Repeat assessments are planned in 2004.

The findings have relevance beyond our study site as well. At the very least, they reinforce some of the lessons learned about how to improve malaria treatment during the chloroquine era. Interventions such as health worker training, simple job aids, patient counseling, directly observed therapy, and unit-dose packaging with illustrated instructions can be easily adapted to combination therapies for malaria. By carefully introducing these elements along with SP plus AS, we were able to achieve reasonable levels of adherence right from the first weeks. This will be particularly important as other ACTs become more broadly used throughout the re-

gion. Public health officials, pharmaceutical regulatory bodies, and manufacturers should begin now to make sure these simple interventions are incorporated as new drugs are deployed in both the public and private sectors.

Artemisinin-containing combination therapy has yet to be shown to reduce transmission or stall resistance in African settings. It will be an expensive and ambitious undertaking to extend this approach where resources and infrastructure are badly constrained, but the strategy may represent the best hope for confronting the crisis facing malaria treatment in the region. Whether this hope has a chance of being realized will depend on optimizing the delivery of and adherence to these new treatments. Our findings demonstrate that it is possible to achieve reasonably high levels of adherence to a three-day treatment with SP plus AS delivered through existing health systems. More experience measuring adherence is needed so that practical, standardized approaches that will facilitate comparisons across different settings can be devised.

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