Can Rapid Diagnostic Testing for Malaria Increase Adherence to Artemether–Lumefantrine?: A Randomized Controlled Trial in Uganda

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Abstract.   Most patients with suspected malaria do not receive diagnostic confirmation before beginning antimalarial treatment. We investigated the extent to which uncertainty about malaria diagnosis contributes to patient nonadherence to artemether–lumefantrine (AL) treatment through a randomized controlled trial in central Uganda. Among 1,525 patients purchasing a course of AL at private drug shops, we randomly offered 37.6% a free malaria rapid diagnostic test (RDT) and then assessed adherence through home visits 3 days later. Of these subjects, 68.4% tested positive for malaria and 65.8% adhered overall. Patients who tested positive did not have significantly higher odds of adherence than those who were not offered the test (adjusted odds ratio [OR]: 1.07, 95% confidence interval [CI]: 0.734–1.57, $P = 0.719$). Patients who received a positive malaria test had 0.488 fewer pills remaining than those not offered the test (95% CI: −1.02 to 0.043, $P = 0.072$). We found that patients who felt relatively healthy by the second day of treatment had lower odds of completing treatment (adjusted OR: 0.532, 95% CI: 0.394–0.719, $P < 0.001$). Our results suggest that diagnostic testing may not improve artemisinin-based combination therapy adherence unless efforts are made to persuade patients to continue taking the full course of drugs even if symptoms have resolved.

INTRODUCTION

Over the past 15 years, malaria deaths have fallen by 47% and the number of total infections has declined by more than 25%.[1] This mortality decline has been driven in part by the increased availability of artemisinin-based combination therapies (ACTs), which are very effective in treating the disease and have a short treatment timeline of approximately 3 days.[2–5] However, many patients with suspected malaria fail to complete the full course of drugs, with some studies finding adherence rates as low as 39%.[6,7] Patients who obtain drugs from the private sector have been shown to have lower adherence rates.[7,8]

When patients with malaria do not finish their medications, they risk a recurrence of the infection. Clinical studies have found that the 28-day cure rates for artemether–lumefantrine (AL), a type of ACT, are 10–30% points lower when patients take only four doses instead of the recommended six doses.[9,10] Recurrent malaria infections are not only harmful for individuals but also place a burden on the health system in malaria-endemic countries, where the disease is responsible for up to 50% of outpatient visits and 30–50% of hospital admissions.[11] Failure to complete the full treatment course—defined as "nonadherence"—also increases the risk that the parasite will develop resistance to the drug.[12] Resistance to artemisinin has already been identified in parts of southeast Asia, and widespread resistance to the drug would pose a major threat to malaria control efforts.[13–16]

A variety of interventions have been tested to increase adherence rates to ACTs with moderate degrees of success across different contexts.[17–20] We hypothesized that an important driver of nonadherence is diagnostic uncertainty, as few patients with suspected malaria receive diagnostic confirmation of malaria via blood test.[1,21,22] At the time of the study, malaria diagnostic testing was available in 35% of public health facilities in Uganda (4% had rapid diagnostic tests [RDTs]), 47% of private facilities, and 4% of private drug shops.[23] Since the symptoms of malaria overlap with several common diseases such as pneumonia, as well as other bacterial and viral infections,[24–26] untested patients may face significant uncertainty over whether the illness they are suffering from is malaria, particularly in contexts where they have less confidence in the provider's ability to clinically diagnose the disease.[27–30] If the practice of stopping medication mid-treatment is related to this uncertainty, then a confirmed malaria diagnosis could encourage patients to complete the treatment.

Understanding the impact of diagnostic testing on adherence is also important because malaria diagnostic testing is a cornerstone of current malaria policy.[31] Confirmation of malaria cases in the African public health sector has increased from less than 10% to over 60% between 2000 and 2013,[1] and much of this increase has come from a scale-up of the availability and use of malaria RDTs. If diagnostic testing can improve ACT adherence, this could have implications for both the benefits and cost-effectiveness of this policy.[32,33]

We conducted a randomized controlled trial in Uganda with private drug shop patients to examine the effect of a confirmed diagnosis of malaria, using RDTs, on adherence to AL, the ACT with the largest market share worldwide.[1] A random subset of patients who purchased AL at one of nine participating private drug shops were offered a free RDT to test for malaria. After 3 days, patients received an unannounced visit at their household to record whether they had finished their medicines. We analyzed whether a positive test result increased adherence to AL compared with no testing and also explored other determinants of adherence to over-the-counter AL.

MATERIALS AND METHODS

Study context and population. The study took place between May and September 2011 in Luwero District, in central Uganda. The district is largely rural and poor and has a high level of malaria endemicity with an average of over 100 infective bites per person per year.[34] As is common in the rest of Uganda, Luwero residents frequently treat episodes

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of suspected malaria with over-the-counter medicines at formal or informal retail shops and pharmacies.[22,35] At the time, approximately 44% of drug shops in Uganda sold ACTs, though these drugs were expensive, costing roughly five times as much as the most popular antimalarial drug, sulfadoxine–pyrimethamine.[23] Consequently, at the time of study launch, only about 23% of suspected malaria episodes among children under the age of 5 years were being treated with ACTs in Uganda.[34] In response to this low level of ACT access, the Affordable Medicines Facility-malaria (AMFm) program, which heavily subsidized ACTs for sale, including in private sector establishments, was launched as a pilot program in seven African countries including Uganda in April 2011.[36,37] However, subsidized ACTs had not yet reached shops in this area before the study was completed.

The study location constitutes catchment areas surrounding nine private drug shops that were located in or around three small trading centers (Busiika, Zirobwe, and Wabitungu). The shops were all licensed by Uganda's National Drug Authority and were chosen because they were within the catchment area of the trading center, had well-qualified staff, had been open for at least a year, were open long hours and most days per week, and had substantial customer traffic. Every household within 1-hour walking distance (2.5 km) of any of the nine selected shops was targeted for enrollment in the study (2,641 households).

Intervention procedures. Enrolled households were given an AL purchase ID card, which enabled any member of the household to buy AL at a 95% subsidy (similar to target ACT prices for AMFm) from one of the nine selected drug shops. No restrictions were placed on the number of times the card could be used during the study and no expiration date was given to avoid "hoarding."

Every day, a member of our study team (an enumerator) traveled to each of the nine drug shops with a supply of AL and sat at a table adjacent to the shop. When a study household member came to the drug shop asking about malaria treatment, the shop vendors were instructed to act as they normally would in deciding on the appropriate medication. If the patient requested an ACT, or the shop vendor recommended it, the patient was instructed to speak with the enumerator, who checked whether the patient was eligible to purchase AL through the study and conducted the financial transaction. Shop vendors, however, were the ones responsible for prescribing AL and providing information on how to take the medications to patients, though the AL package also had some dosing instructions (e.g., the standard AL package has pills grouped by dose in the blister pack with "Day 1, 0 hrs," "Day 1, 8 hrs," "Day 2, Morning," "Day 2, Night," etc. next to each dose).

A simple random number draw—conducted by the principal investigator and generated by Stata/SE version 11.0 (StataCorp, College Station, TX)[38]—was used for ex ante assignment of households to the RDT offer arm. If the patient was a member of a household randomly assigned to receive a free RDT, the research team's enumerator, who was trained in RDT administration by a member of the Ugandan Ministry of Health, asked the patient if they were interested in being tested for malaria. In cases where the patient was not present at the drug shop, the enumerator asked the caregiver permission to visit the patient at their home to administer the test ($N = 78$, 15% of those tested). The test was offered immediately after AL purchase (rather than prior) to avoid the possibility that patients were only visiting the drug shop to receive a free diagnostic test, which could have introduced selection bias.[39,40] Patients who tested negative for malaria could return the medicines for a full refund. Institutional review board guidelines required that our enumerators also explain to patients that, while the tests are very accurate, there is a small possibility of error. RDT-negative patients were advised to seek further medical care to encourage appropriate diagnosis and treatment of their illness.

Data collection. The study included four instances of data collection. The baseline survey, administered at home with the female household head, created a household roster listing names and ages of each household member, and collected information on household demographics and previous malaria treatment-seeking behavior. Households were also given their AL purchase ID card at this time. The second point of data collection, which took place when patients came in to purchase AL at the participating drug shops, asked patients to estimate the severity of the symptoms they were experiencing, as well as to estimate the likelihood that they were suffering from malaria, using a visual analog scale ranging from 0 to 10.

The third point of data collection—the "follow-up survey"—occurred at the patient's household and was scheduled for 72 hours after the time of AL purchase, or the following morning if this time fell at night. The timing was designed to allow patients sufficient time to have completed their medication while minimizing the risk that they would have disposed of their AL blister packs. Surveyors asked to see the blister pack and recorded the number of pills remaining. The follow-up survey also included visual analog-based questions about symptom severity (on a 0–10 scale) on each day of AL treatment and about the day and approximate time (morning, afternoon, and evening) each dose was taken. Nonadherent patients were asked their reasons for not completing the medication. For both the drug shop and the follow-up surveys, caregivers were interviewed when the patient was under the age of 12 years. If the patient was between 12 and 17 years of age, he/she was interviewed in the presence of his/her caregiver.

Finally, an endline survey, conducted with all participating households in the last few weeks of the study period, elicited the female household head's knowledge and beliefs about malaria treatment. Participants were told that subsidized AL was now being made available nationwide through the AMFm program and were also informed about proper adherence to AL.

Data collection procedures were designed to limit Hawthorne effects and social desirability bias as much as possible. Only a subset (77%) of patients was randomly selected ex ante to be visited for a follow-up survey, and patients were not informed of the intent to follow-up in advance. In addition, patients were told that the blister packs were being inspected for lot numbers, expiration dates, and other quality control purposes, rather than to check adherence.

AL and RDTs. The brand of AL used was Lumartem, manufactured by Cipla (Mumbai, Maharashtra, India). Drug shop vendors attended a day-long training session led by a Uganda Ministry of Health official on storage and appropriate use of AL. Lumartem is a six-dose treatment, with 1–4 pills per dose depending on the patient's age (Supplemental Appendix Table 1). The first two doses are taken 8 hours

apart, and the remaining doses every 12 hours, generally in the morning and evening. The RDT used was CareStart Malaria HRP2 (Pf) test manufactured by Access Bio (Somerset, NJ). It has a panel detection score of 98.7%, a false-negative rate of < 1%, and a total false-positive rate of 2.4%.[41]

Outcome measure. Patients were defined as adherent if they were visited for a follow-up survey between 62 and 96 hours after ACT purchase and had no pills remaining in their blister pack (we excluded 47 patients who could not be reached for surveying until more than 96 hours after AL purchase). We also excluded patients who had all pills remaining ($N = 16$) as we define adherence conditional on patients having started taking the medication. In the 11% of cases where the blister pack was missing, patients were asked to recall the number of pills left. Since the likelihood of remaining parasites, and therefore recurrence of infection, is a function of how many doses are left,[42,43] we also explored the number of pills and doses left as secondary outcomes (the doses left variable is the number of pills left divided by the pills per dose according to the patient's AL dosage group). We used logistic regression analysis for the binary outcome of adherence and ordinary least squares (OLS) regression for the continuous outcomes of the number of doses and pills remaining.

Analytical approach. Our main independent variable of interest was whether a patient tested positive on the RDT. We focused particularly on patients who tested positive for two reasons: first, patients are only supposed to take ACTs if they test positive for malaria. If a malaria-negative patient chooses, nonetheless, to take ACTs, the implications of non-adherence from a public and private health perspective are unclear (though the World Health Organization does recommend that once the decision to treat is made, a patient should finish the full course of drugs regardless of diagnostic confirmation).[31] Second, as this is an area of high malaria endemicity, the majority of patients tested positive for malaria and, therefore, we had much greater power to detect impacts among this group. For completeness, we also present results on how a negative RDT affected AL adherence.

To control for location- and age-specific effects, in the fully adjusted model we included shop and AL age/dosage group fixed effects and also controlled for a cross-cutting randomized intervention that varied the packaging of the AL (described in more detail by J. Cohen, I. Saran, E. Yavuz, unpublished data). Standard errors were adjusted for clustering at the household level as this was the level of RDT randomization. We used the same logistic model to also examine the association of other household, patient, and illness characteristics with adherence. We assigned households to wealth quintiles using a principal component analysis of housing characteristics and household ownership of durable assets and farm animals.[44] All analyses were conducted using Stata/SE version 11.0.[38]

Trial registry and ethics approval. The trial was registered at https://www.socialscienceregistry.org with registry number AEARCTR-0000490. Ethical approval for this study was given by the Harvard School of Public Health (protocol no. CR-19527-02) and the Uganda National Council for Science and Technology (protocol no. HS-832).

RESULTS

Sampling, assignment, and inclusion in analysis. Of the 2,641 households who were administered a baseline survey

for the study, 2,629 (99.5%) of them were included in the RDT randomization (Figure 1); 1,045 households (39.7%) were randomly assigned to be offered an RDT if they purchased AL and the rest were assigned to the control group. There were 573 AL purchases among RDT households and 952 AL purchases among control households over the course of the intervention. We excluded eight patients in the treatment arm who were not offered an RDT and one person in the control arm who was mistakenly offered an RDT. Of the remaining 565 patients in the treatment arm and 951 patients in the control arm, 452 (80%) and 724 (76.1%), respectively, were randomly assigned ex ante to receive a follow-up survey. Loss to follow-up for this survey was roughly 5% in both arms. Finally, among 428 patients with a completed follow-up survey in the RDT arm, 67 were excluded from the analysis, either because they never started the medication ($N = 7$) or because they were visited for a follow-up survey more than 96 hours after ACT purchase ($N = 18$), or because they refused to be tested ($N = 42$), leaving an analysis sample of 361. In the control arm, 38 were excluded from the analysis ($N = 9$ never started taking the medication, $N = 29$ followed up with after 96 hours), leaving an analysis sample of 657.

Sample characteristics and balance. Table 1 presents descriptive characteristics of the analysis sample, both overall and separately by treatment or control arm. The female household head was interviewed about 92% of the time. Approximately 42% of them could read a simple letter in English, and of those who had some education, they had on average 7.4 years of schooling (Table 1, Panel A). Most households were relatively poor: while 79% had a mobile phone, only 18% had access to electricity (Table 1, Panel B). Malaria is highly endemic in this region: 72% of households reported having a suspected malaria episode in the 30 days before the baseline survey. Among these households, 31% of suspected malaria episodes were treated at a drug shop, 43% at a private clinic, and 19% at a public hospital or health center. Although 68% of patients had heard of any type of ACT, only 53% of patients who took any medicine for the last suspected malaria episode had taken an ACT. As in most regions of Uganda at this time, testing was not the norm: only 20% of the last suspected malaria episodes had received a confirmed diagnosis through microscopy or RDT (Table 1, Panel C).

Both patients assigned to treatment and those assigned to control purchased, on average, 1.43 courses of AL during the intervention, which suggests that patients in the treatment group were not visiting the drug shop to get the free RDT. The proportions of patients who received AL in each of the different pack types tested as part of the cross-cutting intervention were similar across treatment and control groups (Table 1, Panel D). For the malaria episodes analyzed in the study, approximately 12% of patients had sought treatment elsewhere before visiting the drug shop and, while 43% had taken other medications, only 5% had already taken ACTs (Table 1, Panel E). Overall, the differences between the treatment and control groups presented in Table 1 are small, and only one is statistically significant at the 5% level.

Uptake of ACTs and RDT positivity rates. Malaria positivity rates among patients analyzed in our study were 68.4% overall and 77.3% for children under 5 years of age. This positivity rate is higher than the malaria prevalence rate of 62%
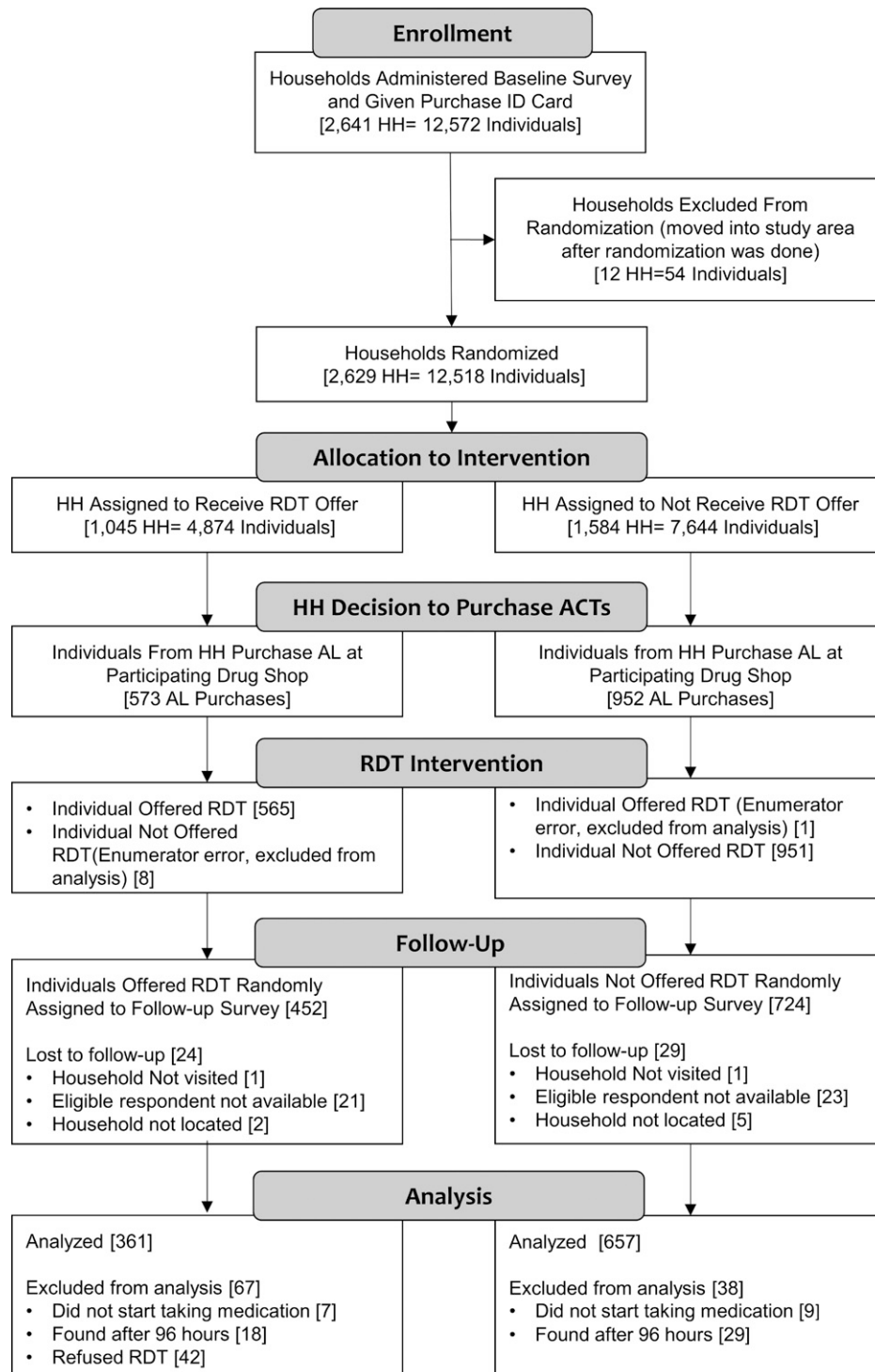
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┌─────────────────────────────────────┐
│              Enrollment              │
├─────────────────────────────────────┤
│  Households Administered Baseline Survey │
│   and Given Purchase ID Card         │
│   [2,641 HH= 12,572 Individuals]     │
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Enrollment

Households Administered Baseline Survey and Given Purchase ID Card
[2,641 HH= 12,572 Individuals]

Households Excluded From Randomization (moved into study area after randomization was done)
[12 HH=54 Individuals]

Households Randomized
[2,629 HH= 12,518 Individuals]

Allocation to Intervention

HH Assigned to Receive RDT Offer
[1,045 HH= 4,874 Individuals]

HH Assigned to Not Receive RDT Offer
[1,584 HH= 7,644 Individuals]

HH Decision to Purchase ACTs

Individuals From HH Purchase AL at Participating Drug Shop
[573 AL Purchases]

Individuals from HH Purchase AL at Participating Drug Shop
[952 AL Purchases]

RDT Intervention

- Individual Offered RDT [565]
- Individual Not Offered RDT(Enumerator error, excluded from analysis) [8]

- Individual Offered RDT (Enumerator error, excluded from analysis) [1]
- Individual Not Offered RDT [951]

Follow-Up

Individuals Offered RDT Randomly Assigned to Follow-up Survey [452]

Lost to follow-up [24]
- Household Not visited [1]
- Eligible respondent not available [21]
- Household not located [2]

Individuals Not Offered RDT Randomly Assigned to Follow-up Survey [724]

Lost to follow-up [29]
- Household Not visited [1]
- Eligible respondent not available [23]
- Household not located [5]

Analysis

Analyzed [361]

Excluded from analysis [67]
- Did not start taking medication [7]
- Found after 96 hours [18]
- Refused RDT [42]

Analyzed [657]

Excluded from analysis [38]
- Did not start taking medication [9]
- Found after 96 hours [29]

FIGURE 1.   Flow diagram showing households and individuals sampled, assigned, and analyzed.

found among children under 5 years of age in this region,[34] but this is to be expected since our sample consists of children for whom caregivers are actively seeking treatment of malaria. Among patients who tested negative for malaria, only four (2.30%) decided to return the AL that they had just bought, and 95% of RDT-negative patients who kept the medicines started taking them. One patient who tested positive for malaria also returned the drugs.

Testing and adherence to AL. We now turn to AL adherence rates. Overall, 65.8% of patients completed the full dose of AL (66.5% in the control group only). Figure 2 plots the unadjusted odds of adherence for those who tested positive on the RDT and those who tested negative, relative to those who were not offered the malaria test (the control group). Since adherence rates, and responsiveness to the test, might vary with the age of the patient, we also separated the

	Mean of sample (SD)	Mean RDT not offered (SD)	Mean RDT offered and accepted (SD)	Difference 2 − 3 [P value]
	N = 1,018	N = 657	N = 361	
	1	2	3	4
A. Characteristics of female household head				
Age (years)	32.43 (10.94)	32.61 (10.92)	32.11 (10.98)	0.50 [0.96]
Female	0.92 (0.27)	0.93 (0.25)	0.91 (0.29)	0.03 [0.42]
Reads English	0.42 (0.49)	0.41 (0.49)	0.45 (0.50)	−0.04 [0.37]
Years of education (among those who reported some education)	7.44 (2.93)	7.35 (2.73)	7.60 (3.26)	−0.25 [0.39]
Years of spouse/partner education (among those with some education)	8.66 (3.08)	8.65 (3.10)	8.67 (3.05)	−0.02 [0.84]
B. Household characteristics				
Household size	6.11 (2.64)	6.16 (2.58)	6.01 (2.75)	0.14 [0.94]
Has electricity	0.18 (0.38)	0.18 (0.38)	0.17 (0.38)	0.01 [0.96]
Owns mobile phone	0.79 (0.40)	0.80 (0.40)	0.77 (0.42)	0.03 [0.48]
C. Treatment-seeking for malaria episodes in 30 days before start of study				
Member of household had malaria in the last 30 days	0.72 (0.45)	0.72 (0.45)	0.71 (0.45)	0.01 [0.84]
Sought treatment at drug shop	0.31 (0.46)	0.27 (0.44)	0.37 (0.49)	−0.11 [0.08]
Sought treatment at private hospital or clinic	0.43 (0.50)	0.47 (0.50)	0.36 (0.48)	0.11 [0.08]
Sought treatment at public hospital or health center	0.19 (0.39)	0.17 (0.37)	0.22 (0.42)	−0.06 [0.25]
Heard of ACTs (Coartem/Lumartem/Lonart/AL)	0.68 (0.47)	0.67 (0.47)	0.69 (0.46)	−0.02 [0.30]
Used ACT (among those taking medicine)	0.53 (0.50)	0.58 (0.49)	0.46 (0.50)	0.12 [0.64]
Received confirmed diagnosis (microscopy or RDT)	0.20 (0.40)	0.19 (0.40)	0.22 (0.41)	−0.02 [0.37]
Slept under bed net previous night	0.65 (0.48)	0.63 (0.48)	0.68 (0.47)	−0.05 [0.24]
D. AL purchases at study drug shops during intervention period				
No. of AL purchases per individual	1.43 (0.65)	1.43 (0.66)	1.44 (0.64)	−0.01 [0.75]
% Dosage group 2 (3–6 years)	0.25 (0.43)	0.26 (0.44)	0.22 (0.41)	0.04 [0.08]
% Dosage group 3 (7–11 years)	0.14 (0.35)	0.14 (0.35)	0.14 (0.34)	0.01 [0.77]
% Dosage group 4 (aged ≥ 12 years)	0.35 (0.48)	0.35 (0.48)	0.35 (0.48)	0 [0.70]
% Received intervention pack 1	0.17 (0.38)	0.17 (0.37)	0.18 (0.38)	−0.01 [0.56]
% Received intervention pack 2	0.04 (0.19)	0.03 (0.18)	0.05 (0.22)	−0.02 [0.13]
% Received intervention pack 3	0.17 (0.38)	0.19 (0.39)	0.14 (0.35)	0.05 [0.03]
% Received intervention pack 4	0.16 (0.37)	0.16 (0.37)	0.15 (0.36)	0.01 [0.55]
% Received intervention pack 5	0.17 (0.38)	0.18 (0.38)	0.17 (0.38)	0.01 [0.96]
E. Treatment-seeking for malaria episodes analyzed in study (before visiting drug shop)				
Sought treatment elsewhere first	0.12 (0.32)	0.11 (0.32)	0.13 (0.33)	−0.01 [0.67]
Took other medication	0.43 (0.50)	0.42 (0.49)	0.45 (0.50)	−0.03 [0.55]
Took antimalarial drugs	0.08 (0.28)	0.08 (0.27)	0.09 (0.29)	−0.02 [0.56]
Took ACTs	0.05 (0.21)	0.05 (0.21)	0.05 (0.22)	−0.00 [0.97]

ACT = artemisinin-based combination therapy; AL = artemether–lumefantrine; RDT = rapid diagnostic test; SD = standard deviation. The sample is restricted to patients who purchased AL after the RDT intervention began, who were reached for follow-up within 96 hours of buying AL, and who started taking the medication. "Intervention pack types" 1–5 refer to a cross-cutting randomized intervention that varied by the packaging of the AL. SDs are in parentheses, P values in square brackets. The P values are from an OLS regression that includes fixed effects for the shop attended and for the pack type received and has standard errors adjusted for clustering at the household level.
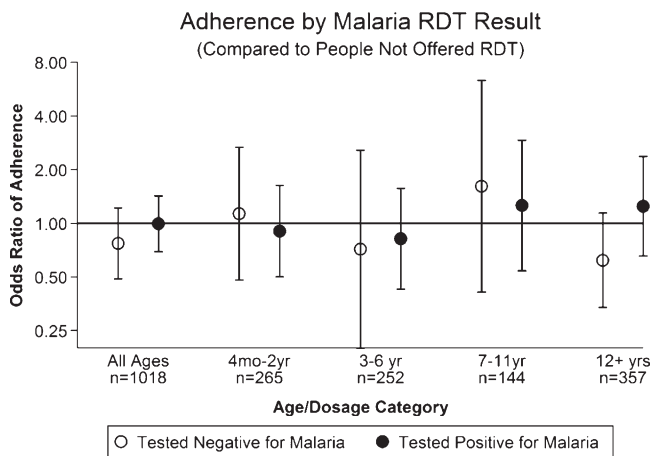

FIGURE 2. Unadjusted odds ratio of adherence for patients who tested negative or who tested positive for malaria compared with patients who were not offered the rapid diagnostic test (RDT). The error bars indicate 95% confidence intervals. The sample is limited to patients who started taking the medication and who were visited for a follow-up survey within 96 hours of purchasing artemether–lumefantrine (AL). The age groups correspond to the AL dosage categories.

results by age groups that correspond to the four AL dosage groups. For all age/dosage groups, the odds of adherence for patients who tested positive and those who tested negative, are similar to the odds of adherence for patients who were not offered the test, and none of the odds ratios are statistically different from one.

The data presented in Table 2 confirm the graphical results. Patients who tested positive did not have significantly higher odds of completing the medication than those who were not offered the test (adjusted odds ratio [OR]: 1.07, 95% confidence interval [CI]: 0.734–1.57, P = 0.719) and patients who tested negative had lower, though statistically insignificant, odds of completing treatment than those who were not offered the test (adjusted OR: 0.860, 95% CI: 0.535–1.38, P = 0.534). Table 2, columns 2–5, displays the results of OLS regressions with either the number of doses, or the number of pills, remaining as an outcome. On average, patients had 0.734 doses (1.89 pills) remaining at the follow-up visit. Patients who tested positive had 0.161 fewer doses remaining (95% CI: −0.357 to 0.035, P = 0.108) and 0.488 fewer pills remaining (95% CI: −1.02 to 0.043, P = 0.072) at the follow-up survey compared with those who were not offered the test. Nonadherent

Table 2

The impact of testing positive or negative for malaria on the odds of adherence (using logistic regression) and on the number of doses and pills remaining (using OLS regression)

	Full sample			Nonadherents only	
	Odds of adherence	No. of doses left	No. of pills left	No. of doses left	No. of pills left
	1	2	3	4	5
Coefficient on					
Tested positive for malaria (N = 247, 83)	1.072	−0.161	−0.488*	−0.272*	−0.624
	(0.207)	(0.100)	(0.270)	(0.159)	(0.440)
	[0.719]	[0.108]	[0.072]	[0.088]	[0.157]
Tested negative for malaria (N = 114, 45)	0.860	0.066	0.348	−0.038	−0.120
	(0.208)	(0.154)	(0.473)	(0.216)	(0.673)
	[0.534]	[0.669]	[0.462]	[0.861]	[0.859]
Mean of dependent variable	0.658	0.734	1.893	2.161	5.568
R-squared	0.044	0.057	0.117	0.083	0.428
No. of observations	1,018	1,015	1,015	345	345

OLS = ordinary least squares. Columns 4 and 5 limit the sample to patients who did not finish their medication. The reference group in all cases is patients who were not offered a rapid diagnostic test. All regressions include shop fixed effects and control for artemether–lumefantrine (AL) pack type received and for medication dosage group. Sample is limited to patients who were followed up within 96 hours of the AL purchase and who started taking the medication. Standard errors are in parentheses and are adjusted for clustering at the household level. P values are in square brackets.
*$P < 0.10$.

patients had, on average, 2.16 doses (5.57 pills) remaining at the follow-up visit. Among this group, those who received a positive test had, on average, 0.272 fewer doses (95% CI: −0.585 to 0.041, $P = 0.088$) and 0.624 fewer pills remaining (95% CI: −1.49 to 0.243, $P = 0.157$) at the follow-up visit than those who were not offered the test. Though most of these effects are only borderline statistically significant, they suggest that receiving a positive test may have encouraged some patients to take a few additional pills even if it did not increase full adherence compared with those not tested.

Figure 3 plots the distribution of pills remaining among those who did not finish their medication. Among these patients, those who tested positive were more likely to have five or fewer pills remaining at the follow-up survey compared with patients who were not offered the test. A Kolmogorov–Smirnov equality-of-distributions test confirms that the distribution of pills remaining for nonadherent patients who tested

Distribution of Number of Remaining Pills
Non-Adherents Only

FIGURE 3. Distribution of number of pills remaining among non-adherents at the time of the follow-up survey for those who tested positive and those who tested negative compared with those who were not offered the rapid diagnostic test (RDT). The sample is limited to patients who started taking the medication and who were visited for a follow-up survey within 96 hours of purchasing artemether–lumefantrine.

positive is statistically different from that of nonadherent patients who were not offered the test ($P = 0.006$).

We find suggestive evidence (Supplemental Appendix Table 2) that the effect of a positive test on reducing the number of doses/pills remaining (relative to the control group that was not offered the test) is stronger among dosage groups 2 (3–6 years) and 3 (7–11 years), however our study was not powered to detect impacts among these subgroups.

Factors associated with adherence. We also explored other factors that might influence adherence and present the full list of variables in Table 3. Figure 4 highlights some of the factors hypothesized to be particularly important for adherence. We plotted the coefficient and 95% CIs on each variable from a separate logistic regression, using the fully adjusted model. We found no evidence that demographic characteristics such as age, education, or wealth affect the odds of adherence. Prevention behavior (having slept under a bed net the night before the baseline survey) is also not correlated with adherence rates. However, patients who had heard of ACTs at baseline were more likely to finish their medications compared with those who had not heard of it (adjusted OR: 2.13, 95% CI: 1.52–2.98, $P < 0.001$). Patients who felt relatively healthy by the second day of treatment (27% of patients who gave a rating between 0 and 2 on a scale of 0 [perfect health] to 10 [worst feeling of illness]) had lower odds of finishing their medication compared with those who still felt unwell on the second day of treatment (adjusted OR: 0.532, 95% CI: 0.394–0.719, $P < 0.001$).

DISCUSSION

The increased availability of ACTs has contributed to large declines in the morbidity and mortality burden of malaria.[1] However, nonadherence to the recommended dosage dampens the effectiveness and cost-effectiveness of ACT distribution programs. This is one of the few studies that provides evidence on ACT adherence rates in the private retail sector as well as evidence on whether malaria RDTs can influence adherence behavior.[19] We found that adherence rates to AL are modest in this context (65.8%), though similar to ACT adherence rates found in comparable studies conducted in the
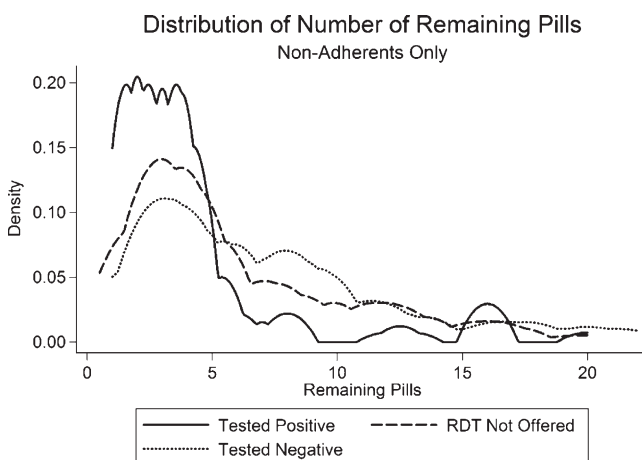
TABLE 3
Correlations between household/patient/illness characteristics and adherence

	OR	SE	P value	Corrected P value
	1	2	3	4
Characteristics of household head				
Age (years)	1.003	0.008	0.726	1.000
Female	0.927	0.289	0.808	1.000
Reads English	1.214	0.195	0.227	1.000
Married	0.908	0.143	0.539	1.000
Years of education (among those who reported some education)	0.994	0.027	0.832	1.000
Years of spouse/partner education (among those with some education)	1.048	0.032	0.122	1.000
Household characteristics				
Household size	1.035	0.033	0.280	1.000
Has electricity	1.044	0.214	0.833	1.000
Owns mobile phone	1.350	0.264	0.124	1.000
Wealth quintile	1.111*	0.070	0.097	1.000
Characteristics of patient				
Age of patient (years)	0.994	0.004	0.175	1.000
Patient is 4 months to 2 years	0.970	0.150	0.845	1.000
Patient is 3–6 years	1.081	0.179	0.639	1.000
Patient is 7–11 years	1.120	0.233	0.586	1.000
Patient is ≥ 12 years	0.911	0.128	0.505	1.000
No. of ACT purchases per person	1.241*	0.148	0.070	1.000
Health behaviors and knowledge				
Patient had malaria in the past 30 days	1.163	0.179	0.326	1.000
Member of household had malaria in the past 30 days	1.396**	0.227	0.040	1.000
Slept under bed net last night	1.146	0.178	0.381	1.000
No. of mosquito nets hanging in household	1.083	0.068	0.206	1.000
Heard of ACTs (Coartem/Lumartem/Lonart/AL)	2.128***	0.365	0.000	0.000
Prefer taking ACTs (conditional on knowing about ACTs)	1.610**	0.344	0.026	1.000
Believe ACT is most effective antimalarial drug (conditional on knowing about ACTs)	1.209	0.279	0.411	1.000
Treatment-seeking behavior for previous malaria episode				
Sought treatment at drug shop	0.726	0.200	0.245	1.000
Sought treatment at private hospital or clinic	0.805	0.209	0.404	1.000
Sought treatment at public health facility	2.263**	0.760	0.015	0.644
Received confirmed diagnosis (microscopy or RDT)	1.010	0.309	0.973	1.000
Used ACT (among those taking medicine)	2.107**	0.679	0.021	0.887
Took partial dose	0.902	0.159	0.558	1.000
Beliefs and symptoms at time of ACT purchase (current illness episode)				
Level of fever (on a 0–10 scale)	1.057	0.037	0.113	1.000
Level of pain (on a 0–10 scale)	1.040	0.039	0.287	1.000
Level of fatigue (on a 0–10 scale)	1.003	0.036	0.928	1.000
Overall level of illness (on a 0–10 scale)	1.089*	0.050	0.065	1.000
Perceived likelihood of malaria (on a 0–10 scale)	1.058	0.039	0.125	1.000
Low perceived likelihood that have malaria	0.695	0.157	0.107	1.000
Treatment-seeking for current illness episode (before drug shop visit)				
Days before sought treatment	0.788***	0.045	0.000	0.001
Sought treatment elsewhere first	0.952	0.194	0.809	1.000
Took medicines before visiting shop	0.895	0.130	0.445	1.000
Experiences during current illness episode				
Symptom severity on first day of treatment (on a 0–10 scale)	1.103***	0.038	0.005	0.198
Symptom severity on second day of treatment (on a 0–10 scale)	1.115***	0.040	0.002	0.097
Symptom severity on third day of treatment (on a 0–10 scale)	0.986	0.039	0.724	1.000
Symptom severity on fourth day of treatment (on a 0–10 scale)	0.885***	0.040	0.006	0.271
Felt better by second day of treatment (symptom severity in lowest quartile)	0.532***	0.082	0.000	0.002

ACT = artemisinin-based combination therapy; AL = artemether–lumefantrine; OR = odds ratio; RDT = rapid diagnostic test; SE = standard error. All regressions include shop and AL package fixed effects and control for the randomized RDT offer. The sample is limited to people who started taking the medication and who were visited for a follow-up survey within 96 hours of AL purchase. Column 4 presents Bonferroni-corrected P values adjusted for multiple comparisons. SEs are adjusted for clustering at the household level.
*,**,***P < 0.10, 0.05, and 0.01, respectively.

private retail sector.[8,18,45] (There was no evidence that adherence increased over the course of the study, which suggests that Hawthorne effects were relatively minor in this sample.) We also found that a positive result on the RDT did not significantly increase adherence to AL, not even among young children for whom the risk of malaria mortality is highest. There is, however, weak evidence that a positive result leads to an increase in the total number of pills taken, which may still be beneficial both in treating the disease and in minimizing the likelihood of the development of resistance.

There are several aspects of this study that may limit the generalizability of these results. First, the characteristics of patients who visit drug shops and the care they receive, are likely to differ from those visiting the public sector, and this may affect their response to diagnostic testing.[8,46] Though we did not record the specific dosing instructions given to patients, they are likely to have been more thorough than usual as drug shop vendors had been recently trained in AL administration, and may also have been influenced by the presence of study staff posted just outside the shop.

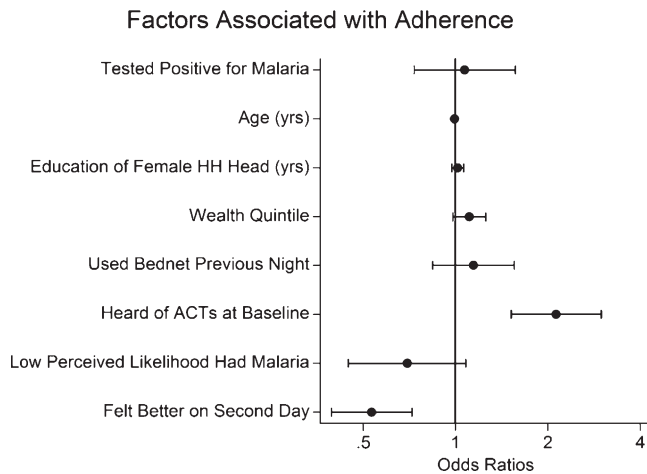## Factors Associated with Adherence

FIGURE 4. The relative impact of a positive malaria test, demographic variables, prevention behavior, knowledge of artemisinin-based combination therapies, uncertainty about the malaria diagnosis, and whether the patient felt better by the second day of treatment on the odds of finishing medication. The graph plots odds ratios and 95% confidence intervals from separate logistic regressions of adherence on each of the variables. Each regression also includes shop and artemether–lumefantrine (AL) pack type fixed effects with standard errors adjusted for clustering at the household level. The regression on "Tested Positive for Malaria" also controls for those who tested negative, and all other regressions control for the randomized offer of the rapid diagnostic test. The sample is limited to patients who started taking the medication and who were visited for a follow-up survey within 96 hours of purchasing AL.

Another important limitation of our study is that patients were tested after they purchased AL, whereas usually the test would be performed before the drug purchase. Although this was done to minimize selection bias (and patients could return the drugs for a full refund), the timing of the test, relative to drug purchase, may have influenced the adherence rates. Testing after AL purchase may also have inclined RDT-negative patients toward keeping and taking the drugs.

A third limitation of the study is that the RDTs were performed by members of our study team not by the drug shop vendors or by health workers. It is possible that RDTs performed in the public health sector, or by trusted drug shop vendors, would have a greater impact on adherence behavior. On the other hand, to the extent that the information from the test serves as a substitute for advice from well-qualified staff, diagnostic testing may have a greater impact on behavior when patients are less trusting of the clinical advice of the drug shop attendant or the health worker.

There are several potential explanations for why a confirmed malaria diagnosis did not increase AL adherence. The first possibility is that patients did not fully trust the RDT result, since RDTs were a relatively new technology at the time.[27,30,47] In our baseline survey, only 21% of households reported having a member who had been tested with an RDT for a previous suspected malaria episode. We found that patients who had previous experience with RDTs had a higher adherence rate when testing positive by the RDT (77.8%) than patients who tested positive but did not have previous experience with RDTs (64.1%), though the sample size was very small (only 18 patients who tested positive had previous RDT experience) and the difference is not statistically significant ($P = 0.27$). The fact that most people who tested negative on the RDT decided to still take AL also

suggests that patients may have lacked confidence in the RDT result. Though our study design is likely to have biased RDT-negative patients toward taking the medicines, several other studies, across different contexts, have also found high prescription and purchase rates of ACTs despite a negative test result,[28,48–50] likely because there is a tendency in malaria-endemic areas for both health workers and patients to treat all fever episodes as malaria.[51–53] It may be that over time, as patients learn about the accuracy of the test, RDTs will have a greater impact on adherence.[54,55]

It is also possible that a confirmed diagnosis did not affect AL adherence because diagnostic uncertainty is unrelated to ACT adherence rates. Figure 4, however, provides some suggestive evidence that this is not the case: patients who believed that it was less likely that they had malaria when they came to purchase AL had lower odds of completing treatment than those who were more certain that they had malaria, though the difference is not statistically significant (OR: 0.695, 95% CI: 0.447–1.08, $P = 0.107$).

Finally, though diagnostic uncertainty is important, there may be other factors that have a greater impact on adherence. For example, patients may not understand how to correctly take the medication,[45,56–60] they may forget to take their pills,[18,56,58,59] they may be saving some pills for a future malaria episode,[45,56] or they may stop taking the medication once they feel better.[61,62] In our study, we found no relationship between literacy or education and adherence, and we also found that 91% of patients took the first two doses of AL with the correct number of pills at approximately the correct time (data not shown). This suggests that noncomprehension of dosing may not be the major driver of nonadherence. In addition, less than 1% of patients in this study reported "forgetting" and only 3.7% of respondents reported "saving pills for future malaria episode" as reasons for nonadherence (Table 4). We did find that patients whose illness had largely resolved on the second day of treatment had approximately 50% lower odds of completing treatment than those still suffering from moderate or severe symptoms. This suggests that nonadherence may be partly influenced by the belief that malaria is cured before the full treatment is taken, a hypothesis that is explored in more detail by J. Cohen, I. Saran, E. Yavuz, unpublished data. The effect of symptom resolution on adherence is of particular concern for ACTs because the artemisinin component of the drugs works quickly to bring down the parasite load and relieve symptoms.[63] If this is a major factor affecting nonadherence, we might not expect diagnostic testing to substantially improve adherence rates.

In sum, we found that diagnostic testing is unlikely to significantly improve AL adherence among drug shop customers in

TABLE 4
Self-reported reasons for not completing the medication

Reasons for nonadherence	Percentage of nonadherents
Still continuing treatment	55.81
Felt better	23.72
No longer ill with malaria	11.16
Saving pills for next malaria episode	3.72
Felt worse/did not get better	0.47
Too many side effects	0.93
Forgot to finish them	0.93
Other	3.26

Only people who were nonadherent were asked why they did not finish. Responses were not prompted but were precoded in the questionnaire.

the short run, although it does seem to get patients somewhat closer to the full treatment course. We found suggestive evidence that a positive test does not increase adherence because adherence decisions are influenced by symptom resolution. However, RDTs were a fairly new medical device in Uganda at this time. Further research is needed to determine whether adherence behavior responds more strongly to testing as RDTs are scaled up and people become more familiar with the technology.

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