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How Patients Take Malaria Treatment: A Systematic Review of the Literature on Adherence to Antimalarial Drugs

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Abstract

Background: High levels of patient adherence to antimalarial treatment are important in ensuring drug effectiveness. To achieve this goal, it is important to understand levels of patient adherence, and the range of study designs and methodological challenges involved in measuring adherence and interpreting results. Since antimalarial adherence was reviewed in 2004, there has been a major expansion in the use of artemisinin-based combination therapies (ACTs) in the public sector, as well as initiatives to make them more widely accessible through community health workers and private retailers. These changes and the large number of recent adherence studies raise the need for an updated review on this topic.

Objective: We conducted a systematic review of studies reporting quantitative results on patient adherence to antimalarials obtained for treatment.

Results: The 55 studies identified reported extensive variation in patient adherence to antimalarials, with many studies reporting very high adherence (90–100%) and others finding adherence of less than 50%. We identified five overarching approaches to assessing adherence based on the definition of adherence and the methods used to measure it. Overall, there was no clear pattern in adherence results by approach. However, adherence tended to be higher among studies where informed consent was collected at the time of obtaining the drug, where patient consultations were directly observed by research staff, and where a diagnostic test was obtained.

Conclusion: Variations in reported adherence may reflect factors related to patient characteristics and the nature of their consultation with the provider, as well as methodological variations such as interaction between the research team and patients before and during the treatment. Future studies can benefit from an awareness of the impact of study procedures on adherence outcomes, and the identification of improved measurement methods less dependent on self-report.

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Introduction

While considerable progress has been made in the last decade to reduce malaria morbidity and mortality, malaria continues to cause more than 200 million cases and more than 600,000 deaths per year [1]. The vast majority of deaths occur among children under five in Africa, though many other parts of the world are also affected. Malaria is entirely preventable and treatable, but if treatment is delayed or ineffective, the parasite burden may rapidly increase and cause severe malaria, which has a case fatality rate of 10–20% even among those receiving treatment [2]. Resistance of parasites to antimalarials, exacerbated by their widespread and indiscriminate use, threatens the effectiveness of malaria treatment.

In order for antimalarial treatment to be effective, multiple steps must occur [3–4]. The patient must promptly seek care, the correct diagnosis must be made; the correct drug and dose must be recommended; the drug must be efficacious, of good quality and in stock; the patient must receive or purchase the correct dose; and the correct dose must be taken with correct timing until all doses are complete. Not only can incomplete dosage result in treatment failure, but it may arguably contribute to the spread of resistance [5–6]. Sub-therapeutic treatment can result in recrudescence and select for resistant parasites [7]. Patient adherence, defined as correctly taking the full therapeutic course of treatment, is thus a critical step in ensuring antimalarial effectiveness and reducing malaria mortality.

To achieve this goal, it is important for policymakers to understand levels of patient adherence to antimalarials, how they
vary by context, and how adherence can be improved. However, studies measuring patient adherence encounter substantial methodological challenges, such as selection of appropriate definitions of adherence and appropriate measurement methods. This results in a broad diversity of study designs which, along with the wide range of study contexts and different antimalarial drugs, can challenge interpretation of adherence results.

The use of antimalarial drugs was last reviewed by Yeung and White in 2004 [8]. Of the 22 studies they identified in Africa, Asia and South America that reported quantitative data on patient adherence, only five assessed adherence to artemisinin-based combination therapies (ACTs), and only eight studies, mostly household surveys, measured adherence to antimalarials obtained through community health workers or drug retailers. Since publication of this review, there has been a major expansion of the availability of ACTs, which have been shown to be efficacious and may reduce the spread of resistance in low transmission settings [9–12]. Due to the development of resistance to older antimalarials, such as chloroquine and sulfadoxine pyrimethamine (SP), ACTs have become the first-line treatment for *Plasmodium falciparum* malaria in the public sector in most malaria-endemic countries. In addition, a growing number of initiatives to increase ACT use through community health workers and private sector providers have been implemented [13]. Furthermore, a large number of new studies assessing adherence to antimalarials, particularly to ACTs, have been conducted in the last nine years, raising the need for an update on this topic.

Here, previously reviewed and recent studies providing quantitative results on adherence to antimalarials obtained for treatment are analysed. We examine how results vary by definition of adherence and key methodological characteristics, and we present the studies’ own findings on factors associated with adherence. We emphasize challenges in measuring adherence, avoiding bias, and implications for future research.

**Methods**

Studies included in this review were identified by three methods. First, a systematic literature search was conducted on PubMed using MeSH and free text terms as follows: (Medication Adherence (MeSH) or Patient Compliance (MeSH) or compliance or adhere*) and (Antimalarials (MeSH) or antimalarial*). Second, reference lists from studies and reviews identified were searched manually for relevant studies. Finally, researchers known to be currently active in the field were contacted.

Studies that were clearly irrelevant were immediately discarded, and abstracts and manuscripts of the remaining studies were examined in detail to determine relevance. Published studies that provided quantitative data on patient adherence to antimalarials obtained for treatment of malaria were included in this review. Where papers employed both quantitative and qualitative methods, only the quantitative results are reported here. Studies were included from all parts of the world in any language utilizing various study designs, including household surveys and clinical trials examining the effectiveness of supervised versus unsupervised treatment that specifically reported data on adherence in the unsupervised arm. Studies assessing adherence to antimalarials obtained for prophylaxis, and effectiveness studies that did not report data on adherence were excluded. Manuscripts of studies meeting inclusion criteria were read in detail and data on study settings, objectives, study design, definitions of adherence, methods of assessing adherence and results were systematically reviewed and abstracted into a database.

**Results**

The initial literature search using PubMed identified 1340 studies (Figure 1). In total, 49 studies were retained from the initial search. Many of the excluded studies referred to antimalarials obtained for prophylaxis or treatment of conditions other than malaria. Manual examination of reference lists and personal communication with other researchers in the field identified six additional studies, making a total of 55 studies.

**Characteristics of studies included**

Three main types of studies were identified: descriptive studies, interventions to improve adherence, and studies with clinical outcomes as a primary endpoint (Tables 1–3). While there is clearly some overlap between types, studies were categorised as descriptive except for those that described an intervention to improve adherence or simultaneously measured clinical outcomes and patient adherence. Distinguishing studies with clinical outcomes is helpful, as they were often conducted under relatively controlled conditions, or with relatively intensive follow-up, which may have influenced adherence results.

More than half of the 55 studies were descriptive (30 studies) [4,14–42]. The majority of these (21 studies) were observational follow-up studies [14–34], where patients obtaining a drug were visited at their home or returned to the drug outlet after a specified number of days, at which time adherence data were collected. While most follow-up studies were prospective, two studies retrospectively identified patients to follow-up for adherence assessments [21,25]. Several of these studies were part of larger studies that included an intervention (e.g. use of community health workers [15,24] or subsidization of ACTs in private retail outlets [16]), but did not provide information on the impact on adherence through pre and post or control group comparisons, so the studies were categorised as “descriptive” in terms of their assessment of adherence. Eight studies used household surveys to collect descriptive data [35–42], and one study used both household survey and follow-up methods [4]. In these household surveys, households in selected areas were visited without prior knowledge of who had obtained antimalarial drugs, and interviews were conducted about episodes of illness occurring in the weeks prior to the survey, treatment obtained, and adherence.

**Figure 1. Literature search results.**

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| Study, (Country), Source(s) of drugs | Drug regimen(s) | Method(s) of assessing adherence | Approach(es) to assessing adherence | Day of follow-up visit (Day 1 = drug dispensed) | Level of adherence (N = denominator) |
|-------------------------------------|-----------------|---------------------------------|------------------------------------|-----------------------------------------------|-------------------------------------|
| Abuaku et al. 2004 [35], (Ghana), Multiple sources | SP, chloroquine (CQ), & amodiaquine (AQ) | Household survey questionnaire | Completed treatment | n/a | SP - 100% (N = 4); CQ - 11.1% site 1 (N = 171); CQ - 36.4% site 2 (N = 195); AQ - 12.9% site 1 (N = 9); AQ - 50% site 2 (N = 2) |
| Ajayi et al. 2008 [36], (Ghana, Nigeria, Uganda), Community health workers | AL in Nigeria and Uganda & artesunate-amodiaquine in Ghana | Household survey questionnaire | Completed treatment | n/a | Ghana - 97% (N = 153); Nigeria - 93% (N = 60); Uganda - 81% (N = 31); Overall - 94% (N = 244) |
| Amin et al. 2004 [37], (Kenya) | SP & amodiaquine | Household survey questionnaire | Unique approach = patients who took a higher dose than recommended or an adequate dose | n/a | SP - 66.7% (N = 78); AQ - 13.8% (N = 94) |
| Barnes et al. 2005 [38], (South Africa), Health facilities | AL | Household survey questionnaire | Completed treatment | n/a | 96% (N = 235) |
| Beer et al. 2009 [14], (Zanzibar), Health facilities | Artesunate-amodiaquine (3 days) | Self-report, pill count | Verified completed treatment & Unique approach = Verified completed treatment, plus child did not vomit dose, or another dose was administered if child vomited first dose | Day 4 | Verified completed treatment - 77% (N = 174); Unique approach - 63% (N = 174) |
| Chinbuah et al. 2006 [15], (Ghana), Community health workers | AL (3 days) | Self report | Timely completion | Day 4 | 100% (N = 334) |
| Cohen et al. 2012 [16], (Uganda), Private drug shop | AL (3 days) | Self-report, pill count | Verified completed treatment | Day 4 | 65.8% (N = 152) |
| Deming et al. 1989 [39], (Togo), Multiple sources | Chloroquine | Household survey questionnaire | Completed treatment | n/a | 29% (N = 370) |
| Depoortere et al. 2004 [17], (Zambia), Health facility | SP + artesunate (3 days) | Self-report, pill count | Verified timely completion | Day 4 | 39.4% (N = 162) |
| Depoortere et al. 2004 [18], (So. Sudan), Health facility | AL (3 days) | Self-report, pill count | Verified timely completion | Day 4 | 59.1% (N = 93) |
| Fogg et al. 2004 [19], (Uganda), Health facilities | AL (3 days) | Self-report, pill count, lumefantrine assay | Verified timely completion | Day 4 | 90% (N = 210) |
| Gerstl et al. 2010 [20], (Sierra Leone), Health facilities | Artesunate-amodiaquine (3 days) | Self-report, pill count | Verified timely completion | Day 4 | 48% (N = 118) |
| Kabanywanyi et al. 2010 [22], (Tanzania), Health facility | AL (3 days) | Self-report | Timely completion & Completed treatment | Randomized to follow-up visit close to time of one of the five doses to be taken at home | Timely completion - 90% (N = 552); Completed treatment - 98% (N = 552) |
| Kachur et al. 2004 [23], (Tanzania), Health facility | SP + artesunate (3 days) | Self-report, pill count | Timely completion & Verified timely completion | After 48 hours | Timely completion - 76.6% (N = 128); Verified timely completion - 75% (N = 128) |
| Kalyango et al. 2013 [24], (Uganda), Community health workers | AL (3 days) | Self-report, pill count | Verified completed treatment & Unique approach = took as prescribed with fatty meals at each dose and no vomiting within 30 minutes | Day 4 | Verified completed treatment - 86% (N = 667); Unique approach - 16.9% (N = 667) |
Table 1. Cont.

| Study, (Country), Source(s) of drugs | Drug regimen(s) | Method(s) of assessing adherence | Approach(es) to assessing adherence | Day of follow-up visit (Day 1 = drug dispensed) | Level of adherence (N = denominator) |
|-------------------------------------|-----------------|---------------------------------|-----------------------------------|-----------------------------------------------|-------------------------------------|
| Khantikul et al. 2009 [25], (Thailand), Health facilities | Chloroquine + primaquine (14 days) | Self-report | Completed treatment | Up to one year | 24.8% (N = 206) |
| Kolaczinski et al. 2006 [26], (Uganda), Health facilities | Chloroquine + SP (3 days) | Self-report, pill count | Verified completed treatment | Day 4 | 96.3% (N = 241) |
| Krause & Saurenbom 2000 [4], (Burkina Faso), Multiple sources | Antimalarial drugs (mostly chloroquine & quinine) | Pill count | Unique approach = drugs taken correctly according to count of pills in the middle of the treatment course | Middle of the treatment course | 68% (N = 47) |
| Lawford et al. 2011 [27], (Kenya), Health facilities | AL (3 days) | Self-report, pill count | Verified completed treatment | Day 4 | 64.1% (N = 918) |
| Lemma et al. 2011 [28], (Ethiopia), Community health workers | AL (3 days) | Self-report, pill count | Verified timely completion & Completed treatment | Day 4 | Verified timely completion - 38.7% (N = 155); Completed treatment - 73.5% (N = 155) |
| Mace et al. 2011 [29], (Malawi), Health facilities | AL (3 days) | Self-report, pill count | Verified timely completion & Verified completed treatment | Day 4 | Verified timely completion - 65% (N = 386); Verified completed treatment - 75% (N = 386) |
| Nshakira et al. 2002 [30], (Uganda), Multiple sources | Chloroquine (3 days) | Self-report | Completed treatment | Day 4 | 37.8% (N = 463) |
| Niungwa-Sabiti et al. 2005 [40], (Uganda), Multiple sources | Chloroquine & chloroquine + SP | Household survey questionnaire | Completed treatment | n/a | 25% (N = 65) |
| Onyango et al. 2012 [41], (Kenya), Multiple sources | AL | Household survey questionnaire | Completed treatment | n/a | 47% (N = 287) |
| Peeters Grietens et al. 2010 [21], (Peru), Health facilities | Primaquine (7 days) | Self-report, triangulation with health centre records | Completed treatment & Unique approach = self-reported adherence plus health centre records verifying that patients returned to receive the last four doses of primaquine | Up to one year | Completed treatment - 71.9% (N = 185); Unique approach - 62.2% (N = 185) |
| Pereira et al. 2011 [31], (Brazil), Health facilities | Chloroquine + primaquine (7 days) | Self-report, pill count | Verified timely completion | Day 7 | 86.4% (N = 280) |
| Reilly et al. 2002 [32], (Sri Lanka), Health facility | Chloroquine + primaquine (5 days) | Self-report | Completed treatment | Day 6 | 74% (N = 132) |
| Simba et al. 2012 [33], (Tanzania), Health facilities | AL (3 days) | Self-report, lumefantrine assay | Timely completion | Day 7 | 88.3% (N = 444) |
| Thea et al. 2000 [42], (Mali), Multiple sources | Chloroquine | Household survey questionnaire | Completed treatment | n/a | 37.8% (N = 152) |
| Tivagirumukiza et al. 2010 [34], (Rwanda), Health facility | Quinine tablets (7 days, last 4 unsupervised) | Self-report, pill count, electronic pill boxes | Verified timely completion & Unique approach = percentage of doses taken according to electronic pill box | Day 8 | Verified timely completion - 100% (N = 56); Unique approach - 82.7% (N = 56) |

1 | Duration of drug regimen in days not given for household surveys; 
2 | See Table 4 for definitions of approaches; 
3 | Not incorporated into approach to assessing adherence. 

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Table 2. Characteristics of studies included in the review (by author) for studies assessing interventions to improve adherence.

| Study, (Country), Source(s) of drugs | Drug regimen(s) | Intervention | Method(s) of assessing adherence | Approach(es) to assessing adherence | Day of follow-up visit (Day 1 = drug dispensed) | Level of adherence without intervention (N = denominator) | Level of adherence with intervention (N = denominator) |
|-------------------------------------|-----------------|--------------|----------------------------------|-------------------------------------|-----------------------------------------------|------------------------------------------------------|------------------------------------------------------|
| Agyepong et al. 2002 [43], (Ghana), Health facility | Chloroquine (3 days) | Drug labels & verbal instructions | Self-report | Timely completion & Unique approach = at least the minimum dose or higher taken once per day | Day 4 | Timely completion - 24% (N = 205); Unique approach - 45% (N = 205) | Timely completion (control) - 27% (N = 78); Timely completion (intervention) - 39% (N = 121); Unique approach (control) - 44% (N = 78); Unique approach (intervention) - 78% (N = 121) |
| Ansah et al. 2001 [44], (Ghana), Health facility | Chloroquine (3 days) | Introduction of tablets to replace syrup | Self-report, pill count or measurement of remaining syrup | Timely completion | Day 4 | 45% (N = 144) | 91% (N = 155) |
| Denis et al. 1998 [45], (Cambodia), Multiple sources | Quinine + tetracycline (7 days) | Posters & video | Self-report, pill count | Completed treatment | Day 7 (Day 4 if doses were purchased for only 3 days) | Group 1 - 1% (N = 95); Group 2 - 10% (N = 82) | Group 1 (posters and video) - 39% (N = 88); Group 2 (posters only) - 15% (N = 120) |
| Kangwana et al. 2011 [46], (Kenya), Multiple sources | AL (3 days) | Subsidised AL, shopkeeper training, & community awareness activities | Self-report | Completed treatment | n/a | Group 1 - 40.5% (N = 26); Group 2 - 53.1% (N = 30) | Group 1 (control) - 24.8% (N = 89); Group 2 (intervention) - 67% (N = 221) |
| Lauwo et al. 2006 [47], (Papua New Guinea), Health facility | Chloroquine + SP (3 days) | Packaging & counselling | Self-report | Timely completion | Day 4 | 76.5% (N = 119) | Counselling - 92.9% (N = 112); Counselling & packaging - 95.9% (N = 91) |
| Marsh et al. 1999 [48], (Kenya), Private drug shops | Chloroquine | Shopkeeper training | Household survey questionnaire; laboratory assay in a subset of children given a full dose | Completed treatment | Day 4 | 7.3% (N = 105) | 7.3% (N = 105) |
| Marsh et al. 2004 [49], (Kenya), Private drug shops | Chloroquine & SP | Shopkeeper training | Household survey questionnaire | Completed treatment | n/a | Chloroquine - 8% (N = 160); SP - 64% (N = 441) | |
| Okonkwo et al. 2001 [50], (Nigeria), Health facilities | Chloroquine | Pictorial insert & verbal instructions | Self-report, measurement of remaining syrup | Verified timely completion | 48 hours after start of treatment | 84.5% (N = 190) | Pictorial insert - 51.9% (N = 225); Pictorial insert & verbal instructions - 73.3% (N = 217) |
| Qingjun et al. 1998 [51], (China), Health facilities | Chloroquine + primaquine (8 days) | Packaging | Self-report, laboratory assay | Timely completion & Biological assay (by phenobarbital markers) | Day 4 or Day 9 | Timely completion - 83% (N = 163); Biological assay - 80.5% (N = 134) | Timely completion - 97% (N = 161); Biological assay - 97% (N = 138) |
| Shwe et al. 1998 [52], (Myanmar), Health facilities | Artesunate + mefloquine (3 days) | Packaging & training | Laboratory assay | Biological assay (by chloroquine & quinine markers) | Day 7 | 99.5% (N = 380) | |
| Sirima et al. 2003 [53], (Burkina Faso), Community health workers | Chloroquine | Packaging & availability through community health workers | Household survey questionnaire | Completed treatment | n/a | n/a | 52% (N = 1806) |
| Winch et al. 2003 [54], (Malawi), Community health workers | Chloroquine (3 days) | Community health worker training | Self-report, pill count or measurement of remaining syrup | Timely completion & Unique approach = Timely completion or higher dose than recommended | Day 4 | Timely completion - 1.5% (N = 131); Unique approach - 21.6% (N = 131) | Timely completion - 42.1% (N = 151); Unique approach - 71.7% (N = 151) |
Table 2. Cont.

| Study (Country), (Source) of drugs | Drug regimen(s) | Intervention | Approach(es) to assessing adherence1 | Method(s) of assessing adherence2 | Day of follow-up visit (Day 1 = drug dispensed) | Level of adherence with intervention (N = denominator) | Level of adherence without intervention (N = denominator) |
|----------------------------------|-----------------|-------------|-------------------------------------|----------------------------------|-----------------------------------------------|--------------------------------------------------------|---------------------------------------------------------|
| Yeboah-Antwi et al. 2001          | Chloroquine     | Age-based packaging of syrup & tablets | Self-report, pill count          | Timely completion Day 4 Tablets - 60.5% (N = 152); Syrup - 32.6% (N = 95); Overall - 49.8% (N = 247) | Tablets - 62.3% (N = 157) | Tablets - 54.7% (N = 95) | Tablets - 49% (N = 247) |
|                                 |                 |             | or measurement of remaining syrup | Assessing effectiveness and adherence2 | Day 4 Tablets - 60.5% (N = 152); Syrup - 32.6% (N = 95); Overall - 49.8% (N = 247) | Tablets - 54.7% (N = 95) | Tablets - 49% (N = 247) |

1Duration of drug regimen in days not given for household surveys; 2See Table 4 for definitions; 3Not incorporated into adherence definition; 4Weighted results for three control and three intervention clinics.

Thirteen studies evaluated interventions to improve adherence [43–53]. Of these, seven were randomized controlled trials (RCTs) [44,46–47,50–51,54–55], two were controlled pre- and post-intervention studies [43,45], two were uncontrolled pre- and post-intervention studies [48–49], and two were post-intervention only adherence assessments [52–53]. Follow-up methods were used by eight of the thirteen intervention studies, while the remaining four used household surveys. The interventions included new packaging with and without training, including pre-packaging of two component drugs together and pictorial inserts to packaging [47,50–53,55], as well as dispenser training of shopkeepers [48–49] or community health workers [54]. Ansah et al. [44] conducted an RCT of chloroquine tablets for children compared to chloroquine syrup, while Denis et al. [45] evaluated videos and posters as community health education strategies to improve adherence to a 7-day regimen of quinine + tetracycline.

The third type of studies, those assessing clinical outcomes as a primary endpoint in addition to reporting patient adherence, included seven RCTs comparing effectiveness and adherence of different drug regimens [56–60] or supervised versus non-supervised treatment [61–62], and four uncontrolled studies also assessing effectiveness and adherence [63–66], all of which employed follow-up methods. In addition, a prospective open cohort study examined the association of previous compliance with antimalarials for malaria caused by P. falciparum or P. vivax and occurrence of malaria during follow-up [67].

Of the 55 studies, 40 took place in Africa, 11 in Asia, and four in Latin America. Subjects included all age groups in 25 studies, only children under five in 19 studies, both children under five and older children in an additional seven studies, and only adults in four studies. Most studies assessed adherence to antimalarials taken to treat infection with P. falciparum, with five studies focusing on treatment for P. vivax [21,25,31,51,62], and three studies on treatment for both species [32,66–67]. Most studies assessed adherence to treatment obtained in health facilities or malaria clinics. Four follow-up studies evaluated adherence to drugs obtained from community agents [15,24,28,54] three took place in the context of complex humanitarian emergencies [17–18,26], and three were conducted from private drug shops [16,30,45]. Most household surveys reported adherence to antimalarials obtained from both public and private sectors, except for four that focused on interventions to improve adherence to antimalarials obtained from drug shops [48–49] or community health workers [36,53].

Patient adherence to more than one drug regimen was assessed in 12 studies, while 43 studies reported adherence to a single drug (Tables 1–3). Adherence to ACTs was assessed in 26 studies. Artemether-lumefantrine (AL) was the ACT in 18 of these studies, with two of these 18 also reporting adherence to artesunate-amodiaquine [36,60]. Other ACTs evaluated included two additional studies of artesunate-amodiaquine [14,20], as well as SP + artesunate [17,23] and artesunate + mefloquine [52,63–64]. Non-artemisinin-based combinations featured in 13 studies (chlorproguanil-dapsone (CPD) [57–58], quinine + doxycycline or tetracycline [45,59,67], chloroquine + SP [26,40,47], SP + amodiaquine [65] and, for treatment of P. vivax malaria, chloroquine + primaquine [25,31–32,51,62,66–67]). Adherence to chloroquine and other monotherapies was assessed in 20 studies.

Definitions of adherence and measurement methods

The 55 studies reviewed here employed a wide range of definitions and methodologies. Adherence was measured by questionnaires containing varying detail about how and when drugs were taken (self-report); physical counts of tablets remaining...
| Study, (Country), Source(s) of drugs | Drug regimen(s) | Approach(es) to assessing adherence | Approach(es) to assessing adherence | Day of follow-up visit (Day 1 = drug dispensed) | Level of adherence with intervention (N = denominator) |
|-----------------------------------|-----------------|------------------------------------|------------------------------------|-----------------------------------------------|---------------------------------------------------|
| Achan et al. 2009 [56], (Uganda), Health facility | AL (3 days) & quinine (7 days) | Self-report, pill count | Unique approach = percentage of pills taken | Day 4 | AL - 94.5% (N = 85); Quinine - 85.4% (N = 75) |
| Bell et al. 2009 [57], (Malawi), Health facility | AL (3 days) & chloroproguanil-dapsone (CPD, 3 days) | Self-report, electronic pill boxes, laboratory assays | Completed treatment & Unique approach = electronic pill bottle opened once on Day 1 & two times each on Days 2 & 3 | Day 8 | Completed treatment (AL) - 100% (N = 185); Completed treatment (CPD) - 99.2% (N = 371); Unique approach (AL) - 92% (N = 87); Unique approach (CPD) - 90.6% (N = 181) |
| Congpuong et al. 2010 [63], (Thailand), Health facilities | Artesunate + mefloquine + primaquine (3 days) | Self-report, drug assays | Completed treatment & Biological assay | Day 4 | Completed treatment - 100% (N = 240); Biological assay (mefloquine marker) - 96.3% (N = 215); Biological assay (quinine marker) - 98.5% (N = 214) |
| Duarte et al. 2003 [67], (Brazil), Health facilities | Quinine + doxycycline (7 days) & primaquine + chloroquine (14 days) | Self-report | Completed treatment | Up to 4 months | 83.8% (N = 488) |
| Dunyo et al. 2010 [58], (The Gambia), Health facilities | AL (3 days) & chloroproguanil-dapsone (CPD, 3 days) | Self-report (pill count for some 3) | Completed treatment | Day 4 | AL - 67% (N = 600); CPD - 94% (N = 599) |
| Faucher et al. 2009 [60], (Benin), Health facility | AL (3 days) & artesunate-amodiaquine (ASAQ) (3 days) | Self-report, pill count | Verified completed treatment | Day 4 | AL - 83% (N = 96); ASAQ - 91% (N = 96) |
| Fungladda et al. 1998 [59], (Thailand), Health facility | Artesunate (4 days) & quinine + tetracycline (7 days) | Self-report, pill count | Verified completed treatment | Day 5 or Day 8 | Artesunate - 98.4% (N = 61); Quinine + tetracycline - 71.7% (N = 53) |
| Na-Bangchang et al. 1997 [64], (Thailand), Health facilities | Artemether + mefloquine (2 days) | Laboratory assays | Biological assay | Day 3 | 86.8% (N = 106) |
| Rahman et al. 2008 [61], (Bangladesh), Health facility | AL (3 days) | Self-report, pill count, lumefantrine assay 3 | Verified timely completion | Day 4 | 93% (N = 160) |
| Souares et al. 2008 [65], (Senegal), Health facilities | SP + amodiaquine (3 days) | Self-report, laboratory assays 3 | Timely completion & Unique approach = at least 80% of the prescribed dose of each of the two drugs was taken | Day 4 | Timely completion - 37.7% (N = 289); Unique approach - 64.7% (N = 289) |
| Takeuchi et al. 2010 [62], (Thailand), Health facility | Chloroquine + primaquine (14 days) | Self-report | Completed treatment | Day 8 & Day 15 | 85% (N = 101) |
| Yepez et al. 2000 [66], (Ecuador), Health facilities | Chloroquine + primaquine (3 days for Pf & 7 days for Pv) | Self-report | Timely completion | Day 4 or Day 8 | PF - 79.2% (N = 120); Pv - 58.5% (N = 129); Overall - 68.3% (N = 249) |

1Duration of drug regimen in days not given for household surveys;
2See Table 4 for definitions;
3Not incorporated into adherence definition

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Adherence results

The studies reported a very wide range of results for the percentage of patients adherent, ranging from 1.5% to 100% across different studies and settings. Below we explore how the results varied firstly by the approach to assessing adherence and data collection, secondly by antimalarial and outlet type, and thirdly by the nature of the interaction between patients and dispensers or researchers during the study. Scatter plots are used to facilitate the identification of general patterns in these results. Finally we present the studies’ own findings on factors found to be associated with adherence in multivariate models.

(i) Variation by approach and data collection method

Figure 2 shows a comparison of adherence results by the five approaches. The plot includes multiple points from studies which used more than one approach to report adherence. Studies that did not use any of the five approaches were not plotted [4,37,56]. In addition, when results of adherence to the same drug were reported from more than one study site within the same country, the weighted average of these sites was plotted [35,45]. For intervention studies, only baseline results were plotted in order to represent standard practice; thus, two studies were not plotted since they provided adherence results post-intervention only [52–53]. When multiple non-overlapping degrees of adherence were used (such as definitely non-adherent, probably non-adherent, probably adherent), the most adherent level was considered the proportion adherent for the purpose of Figure 2.

Overall, it does not appear that using stricter approaches involving correct dose timing (“timely completion” and “verified timely completion”) or requiring pill counts in addition to self-reported histories (“verified completed treatment” and “verified timely completion”) are associated with lower adherence, but this does not account for differences in contexts and methodologies. However, among studies of AL, adherence by “verified timely completion” (38.7%–65%) [18,28–29] was lower compared to

![Figure 2. Percentage of patients classified as adherent, by Approach to assessing adherence.](https://doi.org/10.1371/journal.pone.0084555.g002)
“timely completion” (88.3%–100%) [15,22,33], except in studies where the research team enrolled patients at the time the drug was obtained and likely had a more significant research presence than in other studies (90% and 93%) [19,61]. Similarly, adherence to AL by “verified completed treatment” (64.1%–83%) [16,24,27,29,60] tended to be lower than for “completed treatment” (67%–100%) [22,28,36,38,57–58], with the exception of two household surveys without pill counts with adherence of 47% [41,46]. Household surveys, which all used the “completed treatment” approach and assessed adherence from both public and private community sources, tended to have lower adherence results than studies with other designs, particularly studies with primary clinical outcomes (Tables 1–3). In addition, studies plotted before implementation of an intervention had lower adherence for all approaches, as is particularly evident in the community-based interventions by Marsh et al. (1999, 2004) and Winch et al. (2003) and the private-sector follow-up study by Denis et al. (2008); this may be because most of the interventions included in the review are older studies and the interventions (e.g. pre-packaging of drugs) have become a standard part of antimalarial treatment used in the newer studies.

Among studies using unique approaches, two studies used electronic pill boxes (Medication Events Monitoring Systems – MEMSTM) to measure adherence [34,57]. In the study by Bell et al. (2009) adherence by self-report (“completed treatment”) was 100% for AL and 99.2% for CPD, but by the electronic pill boxes, adherence was 92% for AL and 91% for CPD. Similarly, in the study by Twagirumukiza et al. (2010), adherence to quinine tablets was 100% by both self-report (“verified timely completion”) and pill count (no pill boxes had pills remaining), but only 78% of patients took at least 80% of the doses based on the electronic pill box data [34].

Results using biological assays to assess adherence were high (above 90%), but this accounted for only a few studies [15,51,64]. Qingjun et al. (1998) evaluated a packaging intervention to improve adherence to chloroquine + primaquine marked with phenobarbital to detect concentrations in plasma, while Na-Bangchang et al. (1997) measured adherence to artesunate + mefloquine by whole blood mefloquine concentrations based on a reference interval [64]. Similarly, Congpuong et al. (2010) used both whole blood mefloquine concentrations and plasma concentrations of primaquine [63] to detect adherence to artemether + mefloquine + primaquine. One additional study (Shwe et al., 1998) also found high adherence of 99.5%, but was not included in the plots because adherence to artesunate + mefloquine was only reported after implementation of a co-packaging and training intervention; in this study, tablets of quinine and chloroquine were added to the regimen as markers for detection by urine assays. Five other studies measured plasma levels of lumefantrine using HPLC with mass spectrometry or UV detection [19,33,57,60–61], but adherence was not reported on the basis of these assays. Median lumefantrine concentrations were not significantly different between patients who were or were not considered adherent by self-report (“completed treatment” and “timely completion”) or self-report with pill count (“verified timely completion”).

(ii) Variation by antimalarial type and outlet type

The pattern of adherence results between antimalarials was not clear. Across all approaches and by “completed treatment” adherence to AL (47%–100%) [22,28,36,38,41,46,57–58] was higher than both adherence to monotherapies estimated from
household surveys (3.7%–34%) [35,39–40,42,46–49] and adherence to longer primaquine regimens for the treatment of vivax malaria (25%–85%) [21,25,31–32,51,62,66–67]. Adherence to AL by “verified completed treatment” (64.1%–83%) [16,24,27,29,60] was lower than adherence to artesunate-amodiaquine (77%–91%) [14,60] and chloroquine+SP (96%) [26]. However, adherence to AL by “timely completion” was high in three studies (88.3%–100%) [15,22,33] in contrast with studies of SP + amodiaquine (37.7%) [65] and SP + artesunate (76.6%) [23].

Table 5. Factors associated with adherence in multivariate models (p<0.05 or 95% confidence interval crosses the null).

| Factors                                      | Studies                              |
|----------------------------------------------|--------------------------------------|
| Demographics                                 |                                      |
| Education                                    |                                      |
| - Caretaker education at least 7 years       | Beer et al. 2009 [14]                |
| - Attending some secondary school or beyond  | Cohen et al. 2012 [16]               |
| - Higher education                           | Onyango et al. 2012 [41]             |
| Residence in one of two areas in study location | Duarte et al. 2003 [67]             |
| Age                                          |                                      |
| - Respondent age 25-50 years versus less than 25 years | Lawford et al. 2011 [27]          |
| - Patient age 15 years or more versus less than 15 years | Lawford et al. 2011 [27]          |
| - Patient age less than 13 years             | Onyango et al. 2012 [41]             |
| Ownership of radio                           | Lemma et al. 2011 [28]               |
| Higher household income                       | Ongango et al. 2012 [41]             |

| Treatment-seeking behaviour                  |                                      |
|----------------------------------------------|                                      |
| Not having sought treatment at a public health facility | Cohen et al. 2012 [16]          |
| Respondent sought within 24 hrs of symptom onset versus waiting longer | Lawford et al. 2011 [27]          |
| Delay of more than 1 day in seeking treatment after the onset of fever | Lemma et al. 2011 [28]           |
| Previous care sought                         | Souares et al. 2008 [65]             |

| Factors related to the consultation          |                                      |
|----------------------------------------------|                                      |
| Having received exact number of pills to complete treatment | Beer et al. 2009 [14]                |
| Reporting having been given instructions at the shop | Cohen et al. 2012 [16]               |
| Reporting that instructions given were clear | Cohen et al. 2012 [16]               |
| Attended Migowi HC (one of three study outlets) | Mace et al. 2011 [29]                |
| Package used as visual aid by dispenser to explain how to take the drug | Mace et al. 2011 [29]                |
| Received written instructions                | Pereira et al. 2011 [31]             |
| Quality of history taking (i.e. nurses at the consultation asked questions about history, symptoms, and previous care) | Souares et al. 2008 [65]             |

| Behaviour                                    |                                      |
|----------------------------------------------|                                      |
| Took first AL dose at HC                     | Mace et al. 2011 [29]                |
| Taking AL with food or oil                   | Simba et al. 2012 [33]               |

| Knowledge and perceptions                    |                                      |
|----------------------------------------------|                                      |
| Knowledge that only mosquitoes cause malaria | Gerstl et al. 2010 [20]               |
| Knowledge of malaria aetiology               | Khantikul et al. 2009 [25]           |
| Respondent had seen the drug before          | Lawford et al. 2011 [27]             |
| Being able to cite at least one correct instruction on how to take AL | Lawford et al. 2011 [27]             |
| Belief that malaria cannot be treated traditionally | Lemma et al. 2011 [28]              |
| Access to information about antimalarials    | Khantikul et al. 2009 [25]           |
| Knowledge of the seriousness of the infection/knowing the species in mixed transmission areas | Yepez et al. 2000 [66]               |

| Satisfaction                                 |                                      |
|----------------------------------------------|                                      |
| Having an improved condition at follow-up    | Cohen et al. 2012 [16]               |
| Lower expectation of getting malaria in the next 30 days | Cohen et al. 2012 [16]               |
| Did not report dislikes/side-effects to medication | Lawford et al. 2011 [27]             |
| Preference for AL                            | Mace et al. 2011 [29]                |
| Satisfaction with received information       | Souares et al. 2008 [65]             |
to adherence to other ACTs (39.4%–75%) [17,20,23] and higher in two other studies (90%–93%) [19,61].

Although most studies evaluated adherence to antimalarials obtained in the public sector, the two descriptive private sector follow-up studies had low adherence, with Nshakira et al. (2002) reporting adherence of 37.8% to chloroquine by “completed treatment”, and Cohen et al. (2012) describing adherence of 65.8% to AL. Three household surveys [46,48–49] and one follow-up study [45] assessing interventions in private drug stores and surrounding communities also all reported adherence of less than 50%. Adherence where antimalarials were obtained from CHWs in four studies using follow-up methods ranged widely from 1.5%–100% [15,24,28,54], with a study of AL by Lemma et al. (2011) in Ethiopia finding adherence of 38.7% by “verified timely completion” and 75.5% by “completed treatment”. In addition, a study evaluating adherence to ACTs dispensed by CHWs reported high adherence of 83%–97% by “completed treatment” in household surveys in three countries [36].

(iii) Variation by nature of interaction of patients with dispensers and research personnel

We explored how adherence results varied depending on the nature of the interaction reported between patients and their dispensers, and between patients and research personnel. Figure 3a–d shows how patient adherence (as assessed by any of the five approaches) varied with four aspects of patient interaction that we hypothesised might influence adherence results. As shown in the first plot, patients in some studies were asked for informed consent to participate in the study at the outlet upon obtaining the drug, while patients in other studies were not asked for informed consent until a later follow-up visit, having had several days to take the drug (Figure 3a). Secondly, research staff in some studies observed the consultation of the patient with the dispenser or conducted the consultation themselves, while other studies did not (Figure 3b). Studies where most patients obtained a malaria diagnostic test prior to treatment were plotted in comparison to studies where patients were not tested (Figure 3c). The fourth plot compares studies where dispensers did and did not observe the patient swallowing the first dose of the drug (Figure 3d). Results of all studies that used one of the five approaches are plotted, as described previously for Figure 2, except that for studies using multiple approaches to assess adherence, only the most inclusive approach reported was plotted (i.e. “completed treatment”). Studies could not be plotted if the nature of the patient interaction for each of the four plots was not reported.

Table 6. Factors associated with non-adherence in multivariate models (p<0.05 or 95% confidence interval crosses the null).

| Factors                                      | Studies                                      |
|----------------------------------------------|----------------------------------------------|
| Demographics                                 |                                             |
| Being male                                   | Achan et al. 2009 [56]                       |
| Caretaker having different mother tongue to pharmacist | Pereira et al. 2011 [31]                  |
| Education                                    |                                             |
| - Caretaker education (none versus some)     | Depoortere et al. 2004 [17]                |
| - Lack of formal education                   | Depoortere et al. 2004 [17]                |
| Age                                          |                                             |
| - Being a child under 5                      | Mace et al. 2011 [29]                      |
| - Being a child age 8–10 years versus 2–4 years | Souares et al. 2008 [65]                 |
| Head of household profession (retailer/employee vs. farmer) | Souares et al. 2008 [65]                 |
| Treatment-seeking behaviour                  |                                             |
| No fever reported                            | Kalyango et al. 2013¹ [24]                 |
| Seeking care after 2 or more days            | Kalyango et al. 2013¹ [24]                 |
| Treatment with oral quinine versus AL        | Achan et al. 2009 [56]                     |
| Being counselled about what to do in case of vomiting | Kachur et al. 2004 [23]             |
| Not understanding instructions               | Kalyango et al. 2013¹ [24]                 |
| Knowledge and perceptions                    |                                             |
| Caregiver’s perception that illness is not severe | Kalyango et al. 2013¹ [24]             |
| Satisfaction                                 |                                             |
| Vomiting                                     | Achan et al. 2009 [56]                     |

¹Includes patients receiving AL only and AL plus antibiotics (treatment group not significant in multivariate analysis); ²Associated with non-adherence in the second week of primaquine treatment for P. vivax infection.
rapid diagnostic test (RDT) or blood smear prior to being 
dispensed antimalarials, adherence was higher than among those 
not tested (Figure 3c). There is also some indication that studies 
where dispensers observed patients’ first dose had higher 
adherence than those where the first dose was not observed, 
although the pattern is less clear (Figure 3d).

(iv) Factors associated with adherence in multivariate models

Understanding the characteristics and behaviours associated 
with patient adherence to antimalarials is vital to designing 
treatments to improve appropriate use of ACTs. Twenty-four 
studies used multivariate analysis to examine factors associated 
with adherence: of these, 13 studies reported 30 factors 
significantly associated with adherence in multivariate models, 
nine studies found 12 factors associated with non-adherence, and 
five studies reported not finding any factors significantly associated 
with adherence or non-adherence [32,44,50,55,61]. While many of 
the twenty-four studies tested similar factors, such as demo- 
graphics, instructions given and patient knowledge, there was 
substantial diversity in which factors were found significant.

Tables 5–6 show factors significantly associated with adherence 
(Table 3) and non-adherence (Table 6), including demographics, 
treatment-seeking behaviour, factors related to the consultation, 
behaviour, knowledge and perceptions, and satisfaction. Factors 
significantly associated with adherence in more than one study 
included higher education [14,16,41], higher household income 
[33,41], provision of better information on how to take drugs 
[16,29,31], and knowledge about malaria and antimalarials 
[20,25,27–28,66]. Factors significantly associated with non-adherence 
in more than one study included being male [31,56], lack of 
education [17,19], and vomiting [24,36]. There were contrasting 
results for the effects on adherence of patient age and the number 
of days after onset of symptoms that treatment was sought. Older 
age of the patient was associated with adherence in one study [27] 
and non-adherence in another [65], while two other studies found 
younger age associated with adherence [41] and non-adherence 
[29]. Similarly, Lemma et al. (2011) found that patients who waited 
more than one day to seek care after onset of fever were more 
likely to be adherent, but other studies showed that seeking care 
within 24 hours of symptom onset was associated with adherence 
[27], and waiting two or more days was associated with non- 
adherence [24,62].

Discussion

Extensive variation was observed in patient adherence to 
antimalarials, with many studies reporting very high adherence 
(90–100%) and others finding clearly suboptimal adherence, 
sometimes of less than 50%. This may be an important problem, 
both in terms of clinical outcomes and also in the context of the 
development of resistance to artemisinin in South-East Asia [68]. 
However, it is unclear how good adherence must be for ACTs to 
be efficacious, and which features of adherence (such as correct 
timing of dose intervals or taking each dose with a fatty meal) 
matter most.

We identified five overarching approaches to assessing adher- 
ence based on recall (“completed treatment” and “timely 
completion”), recall and pill counts (“verified completed treat- 
ment” and “verified timely completion”) and on biological assays. 
By “completed treatment” and “verified completed treatment”, 
adherent patients were defined as completing the full course of 
treatment though not necessarily following a specific schedule. 
Whether these are appropriate approaches to assess adherence 
should be considered in light of the pharmacology of the specific

drug if the safety or efficacy of the drug is critically dependent on 
the timing of the doses then it will be important to assess this when 
evaluating adherence. As these approaches do not include the 
spacing of the doses, it is possible for patients to have taken some 
doses too close together or even to have taken all doses at one time 
and still be considered “adherent”, though such practices could be 
of concern for drug safety and efficacy. Furthermore, there is 
potential variation within each approach in what was considered 
correct treatment, with some studies taking into account national 
guidelines on the correct dose-for-weight that the patient should 
have consumed and other studies assuming the correct amount 
was obtained.

By “timely completion” and “verified timely completion”, 
adherent patients were defined as exactly following instructions 
in terms of dose, frequency and duration according to their responses 
to interview questions. As noted above, there was considerable 
variation in definitions of “correct” timing, which may have 
affected comparability within these approaches. More information 
is needed on how precise time intervals between doses must be in 
order for drugs to be efficacious. For example, the packaging of 
various brands of AL states that the second dose should be taken 
eight hours after the first dose, which would fall in the middle of 
the night if the drug is obtained in the evening. In this situation it 
is unclear whether a patient should still be considered adherent if 
they take the drugs first thing the next morning instead.

The majority of the adherence studies used one or more of these 
approaches relying primarily on self-reported drug histories, which 
may be susceptible to recall and social desirability bias. Studies in 
Tanzania and Cambodia found high levels of antimalarials 
circulating in the blood among patients stating they had not 
taken any drugs in the previous 28 days [69–70]. Patients may not 
accurately recall information about the quantity of drugs taken. 
Moreover, even if the precise time of obtaining the drug from the 
provider is known, asking patients when each dose was taken is 
problematic as they may not have had clocks available or may not 
know or remember the exact time. Recall bias is likely to be higher 
in data obtained from household surveys, where interviewers 
frequently ask about drugs taken in the previous 14 days, 
compared to follow-up studies, where recall time is usually 4–7 
days. Even with short recall periods, patients may not correctly 
remember details related to each dose. Cultural and demographic 
factors may also affect the reliability of self-reported data [71]. For 
extample, in a study of the impact of the length of recall periods for 
health surveys, different recall periods gave different results, and 
these differences were shown to vary by income group [72].

To avoid being seen as ignorant or negligent, patients who are 
aware of the expected behaviour may say they were adherent even 
if they actually were not. A study by Peeters Grietens et al. (2010) 
found that while 72% of patients reported taking the full course of 
primaquine, only 49% claiming to take the full course had actually 
received the full course according to records [21]. Likewise, Bell 
and colleagues stated that self-reported data, which resulted in 
100% adherence to AL and CPD in Malawi, was unreliable 
compared to MEMSTM containers [57].

In order to reduce recall and social desirability bias, some 
studies incorporated manual examination of drug packaging into 
their definitions of adherence (“verified completed treatment” and 
“verified timely completion”). For studies of AL, these approaches 
yielded lower adherence results than the equivalent approaches 
without the pill counts (“completed treatment” and “timely 
completion”). However, even results including pill counts may 
over-estimate true adherence as removing pills from blister packs 
does not guarantee that the pills were consumed. Similarly, 
opening electronic pill boxes does not guarantee a dose was
consumed. Patients may have “played” with their pill boxes, opening them without removing pills, or alternatively, they may also have removed multiple doses at one opening, either to discard, consume, or save until the appropriate time.

Despite the limitations of self-reported and pill count approaches, Souares et al. (2008) suggested that self-reported data may be more reliable and feasible than assays for drug levels, which require invasive sample collection and complicated field logistics [68]. Drug assays were rarely used for measuring adherence, and their utility and appropriate role remains unclear. Adherence evaluated by the detection of drugs in biological assays was very high (90–100%) in four studies, but these studies assessed adherence to drugs other than AL and involved close interaction of the research staff with patients and in some cases extended follow-up periods. The five studies that reported measuring lumefantrine concentrations, but did not incorporate these assays into adherence results, did not find significant differences in lumefantrine concentrations between patients adherent and non-adherent by self-report. This may have been due to the metabolic variability of the study population, including age, pregnancy, concomitant fat intake and other factors affecting drug absorption, limiting the value of quantitative assessments of patient adherence [73–74]. Methods of collecting blood samples, sample preservation under field conditions, and details of the assays themselves are also likely to affect results.

Regardless of the approach used for assessing adherence, Hawthorne bias may occur if a patient’s awareness of being studied positively influences medication-taking behaviour. Similarly, if researchers observe patient consultations with the dispenser, this may positively influence the care and advice provided by the dispenser and/or patients’ attentiveness and adherence to the treatment. In the studies reviewed here, adherence was higher when informed consent was collected at the time of obtaining the drug and to some degree when patient consultations were directly observed (Figures 3a and 3b). While it is reasonable to assume that medication-taking behaviour of patients who are not aware they are being studied more accurately reflects behaviour in real life contexts, these concerns must be balanced by practical constraints, such as fulfilling other study objectives and the need to obtain the patient’s consent and address for follow-up visits.

Some specific patient-dispenser interactions might also be expected to improve adherence. For example, confirmation of diagnosis of malaria by an RDT or blood smear might increase adherence if patients are more aware that they are suffering from malaria, and if patients with confirmed malaria see a better response to treatment than those who have other conditions. Observing the first dose of treatment is another commonly recommended practice and was found to be significantly associated with adherence to AL in one study [29]. We found some indication that malaria diagnosis was associated with higher adherence in the reviewed studies, although the effect was less marked for observing the first dose on adherence overall.

In addition to the approach to measurement and the nature of the patients’ consultations, other factors often hypothesised to influence adherence include patient characteristics, antimalarial type and outlet type. However, it was not possible to discern clear patterns across the studies reviewed. There was some evidence from multivariate studies that patients who had higher socioeconomic status and were better educated or informed had higher adherence. While there is some concern that the greater number of tablets required for treatment with ACTs (i.e., 24 for an adult) contributes to lower adherence compared to antimalarials requiring fewer tablets, this was not clear in the studies reviewed here. One potential explanation for this is that ACTs often come in co-formulated or co-packaged blister packs, with different coloured packages for each age or weight group. This is in contrast to loose tablets dispensed into paper envelopes, which was often the case for older antimalarials. Not only can the dispenser give the patient the incorrect number of tablets, but the tablets may need to be cut in half to achieve the appropriate doses, and it may be more difficult for the patient to remember how many to take. Secondly, more effective antimalarials such as ACTs may encourage higher patient adherence; if drugs are perceived to be ineffective, patients may use a drug briefly or not at all before looking for a more effective alternative [8]. Finally, perceptions of side-effects may cause variation in adherence across antimalarials, with drugs such as chloroquine and quinine known to have more common minor adverse effects than ACTs such as AL.

It was hard to assess variation across outlet types as of the 55 studies included, only five specifically evaluated adherence to antimalarials from private drug shops [16,30,45,48–49] and five from community health workers [15,24,28,36,54]. However, there were some indications that adherence was relatively low from private sector outlets, highlighting the need for more studies to evaluate adherence to ACTs obtained in this sector and to design interventions to ensure drugs are used appropriately. Interventions to improve adherence that are currently being tested in the private sector include the introduction of RDTs [75–76], new packaging, SMS reminders to patients [77], and SMS reminders to drug shop dispensers to encourage them to advise patients on the importance of adherence [78].

Conclusion

The literature reports extensive variation in patient adherence to antimalarials. The unsatisfactory patient adherence sometimes reported to ACTs obtained in the public sector, and the current dearth of data from the private sector, represent significant challenges for maximising the impact of ACTs. Variations in adherence may reflect factors related to patient characteristics and knowledge, their treatment-seeking behaviour, and the nature of their consultation with the provider. However, methodological variations between studies are also likely to be an important source of variability in results, including the methods used for collecting data, and any interaction between the research team and patients before and during the treatment course. Future studies could be strengthened by a greater awareness of the impact of study procedures on adherence outcomes, and the identification of improved measurement methods that are less dependent on self-report.

Supporting Information

Checklist S1 PRISMA checklist.
(DOC)

Flow Diagram S1 PRISMA flow diagram.
(DOC)

Author Contributions

Conceived and designed the experiments: KB CG SPK DS. Performed the experiments: KB. Analyzed the data: KB. Contributed reagents/materials/analysis tools: KB CG SPK DS. Wrote the paper: KB CG SPK DS. Conceived and designed the review: KB CG SPK DS. Performed the literature search: KB. Abstracted the data: KB. Analyzed results: KB. Wrote the first draft of the paper, with inputs from all authors: KB. Read and approved the final paper: KB CG SPK DS.
References

1. World Health Organization (2012) World Malaria Report.
2. World Health Organization (2010) Guidelines for the treatment of malaria.
3. Bloland PB (2003) A contrarian view of malaria therapy policy in Africa. Am J Trop Med Hyg 68: 125–126.
4. Krause G, Sauerborn R (2000) Comprehensive community effectiveness of health care. A study of malaria treatment in children and adults in rural Burkina Faso. Ann Trop Med Parasitol 20: 273–282.
5. White NJ, Pongavprinpo W (2003) The de novo selection of drug-resistant malaria parasites. Proc Biol Sci 270: 354–359.
6. Korialangha V, Green MM, Nyangong L, Fernandez FM, Mayxay M, et al. (2008) Impaired clinical response in a patient with uncomplicated falciparum malaria who received poor-quality and underdosed intramuscular artesether. Am J Trop Med Hyg 78: 532–555.
7. White NJ, Pongavprinpo W, Mwaaidu R, Sardamalaha S, Agaya R, et al. (2009) Pyrponxaspirinaxemia and low dosing are an important source of anti-malarial drug resistance. Malar J 8: 253.
8. Yeung S, White NJ (2009) How do patients use antimalarial drugs? A review of the evidence. Trop Med Int Health 10: 121–138.
9. Nosten F, van Vugt M, Price R, Luxemburger C, Thway KL, et al. (2000) Factors associated with non-adherence to Artemisinin-based combination therapy (ACT) to malaria in a rural population from holoendemic region of western Kenya. BMC Infect Dis 12: 143.
10. World Health Organization (2012) World Malaria Report.
11. World Health Organization (2010) Guidelines for the treatment of malaria.
12. Dorsey G, Vlahos J, Kamya MR, Staedke SG, Rosenthal PJ (2003) Prevention of chloroquine-resistant Plasmodium falciparum malaria in Uganda. Am J Trop Med Hyg 71: 525–530.
13. Rao VB, Schellenberg D, Ghani AC (2013) Overcoming health system barriers to antimalarial treatment: evidence from a rural community in Tanzania. Trop Med Int Health 10: 1003–1016.
14. Cohen J, Yauvu M, Morris A, Arkel J, Sabot O (2012) Do patients adhere to over-the-counter artemisinin combination therapy? Evidence from an intervention study in Uganda. Malar J 11: 83.
15. Depoortere F, Goumas JP, Nsudando E, Sekunda E, Fermon F, et al. (2004) Adherence to antimalarial treatment in children under five in Kenya: a cluster randomized experiment in the context of integrated primary health care delivery in Ghana. Malar J 3: 96.
16. Deming MS, Gayibor A, Murphy K, Jones TS, Karsa T (1989) Home treatment of febrile children with antimalarial drugs in Togo. Bull World Health Organ 67: 695–700.
17. Thera MA, D’Alessandro U, Thiero M, Ouedraogo A, Packou J, et al. (2000) Efficacy of artesunate-amodiaquine combination therapy for uncomplicated malaria in children in Zouaoua, Northern Niger. Trop Med Int Health 5: 49–54.
18. Kalyango JN, Rutebemberwa E, Karamagi C, Mworozi E, Ssali S, et al. (2013) Adherence to prescribed artemisinin-based combination therapy (ACT) to malaria in a rural population from holoendemic region of western Kenya. BMC Infect Dis 12: 143.
19. Thera MA, D’Alessandro U, Thiero M, Ouedraogo A, Packou J, et al. (2000) Efficacy of artemisinin-based combination therapy for uncomplicated malaria in children in Zouaoua, Northern Niger. Trop Med Int Health 5: 49–54.
non-severe falciparum malaria in Myanmar. Bull World Health Organ 76 Suppl 1: 35–41.
53. Sirima SB, Konate A, Tiono AB, Convelbo N, Cousens S, et al. (2003) Early treatment of childhood fevers with pre-packaged antimalarial drugs in the home and referral of sick children to health facilities through a community-based intervention in Bougouni District, Mali. Trans R Soc Trop Med Hyg 97: 481–490.
54. Achan J, Tibenderana JK, Kyabazinga D, Walumbu R, Kamya MR, et al. (1998) Compliance with artesunate and quinine for uncomplicated falciparum malaria in Ugandan children: randomised trial. BMJ 317: 1276.
55. Bell DJ, Wootton D, Mukaka M, Montgomery J, Kayange N, et al. (2009) Impact of prepackaging antimalarial drugs on cost to patients and compliance with treatment. Bull World Health Organ 87: 394–399.
56. Rahman MM, Dondorp AM, Day NP, Lindegardh N, Imwong M, et al. (2008) Comparison of sulfadoxine-pyrimethamine, unsupervised artemether-lumefantrine and unsupervised artesunate-amodiaquine fixed-dose formulation for uncomplicated malaria in children in the Gambia. PLoS One 3(4): e2377.
57. Winch PJ, Bagayoko A, Diasara A, Kane M, Thierno F, et al. (2003) Increases in multidrug resistant falciparum malaria. Malar J 9: 308.
58. Duarte EC, Gyorkos TW (2003) Self-reported compliance with last malaria treatment and occurrence of malaria during follow-up in a Brazilian Amazon population. Trop Med Int Health 8: 133–139.
59. Clark S, Lal S, Mbonye A (2011) Study protocol: Introducing rapid diagnostic tests on adherence rates to artemether lumefantrine. Clinton Health Access Initiative.
60. Fink G, Goldberg J (2011) Preserving ACTs: PACT Pilot Report Cape Coast, Ghana.
61. Souares A, Lalou R, Sene I, Sow D, Le Hesran JY (2008) Adherence and baseline anti-malarial treatment in an area of Thailand with highly multidrug resistant falciparum malaria. Malar J 9: 43.
62. Takeuchi R, Lawpoolsri S, Imwong M, Kobayashi J, Kaewkungwal J, et al. (2003) Compliance with a three-day course of artesunate-mefloquine in an area of highly multi-drug resistant Plasmodium falciparum malaria. Br J Clin Pharmacol 43: 639–642.
63. Na-Bangchang K, Congpoung K, Sirichaisinthop J, Suprakorb K, Karbwang J (1997) Compliance with a 2 day course of artesether-mefloquine in an area of highly multi-drug resistant Plasmodium falciparum malaria. Br J Clin Pharmacol 43: 639–642.
64. Yepez MC, Zambrano D, Carrasco F, Yepez RF (2000) [The factors associated with noncompliance with antimalarial treatment in Ecuadorian patients]. Rev Cubana Med Trop 52: 81–89.
65. Yepez MC, Zambrano D, Carrasco F, Yepez RF (2000) [The factors associated with noncompliance with antimalarial treatment in Ecuadorian patients]. Rev Cubana Med Trop 52: 81–89.
66. Dondorp AM, Fanello CI, Hendriksen IC, Gomes E, Seni A, et al. (2010) Aqueous versus quinine in the treatment of severe falciparum malaria in African children [AQUAMAT]: an open-label, randomised trial. Lancet 376: 1647–1657.
67. Hoel EM, Genton B, Zanolari B, Mercier T, Duong S, et al. (2010) Residual antimalarial concentrations before treatment in patients with malaria from Cambodia: indication of drug pressure. J Infect Dis 202: 1083–1089.
68. Hoel EM, Wiesner L, Barnes K, Diawara A, Kane M, Thiero F, et al. (2011) Residual antimalarials in malaria patients from Tanzania-implications on drug efficacy assessment and spread of parasite resistance. PLoS One 6: e17377.
69. Blomstreh Y, Souares A, Na-Bangchang K, Le Hesran JY, et al. (2012) Measuring self-reported health in low-income countries: piloting three instruments in semi-rural Burkina Faso. Glob Health Action 5.
70. Das J, Hammer J, Sanchez-Paramo C (2011) The impact of recall periods on reported morbidity and health-seeking behavior. World Bank.
71. Clark S, Lal S, Mbonye A (2011) Study protocol: Introducing rapid diagnostic tests into the private health sector in Uganda- a randomised trial among registered drug shops to evaluate impact on antimalarial drug use. 43: 639–642.
72. Cohen JL (2011) Study protocol: Determining the impact of packaging and rapid diagnostic tests on adherence rates to artesether-lumefantrine. Clinton Health Access Initiative.
73. Fink G, Goldberg J (2011) Preserving ACTs: PACT Pilot Report Cape Coast, Ghana.
74. Bruevoort K, Festo C, Kalodella A, Cairns M, Kaachur P, et al. (2012) Study protocol: Cluster-randomized trial of text message reminders to retail staff of appropriate practices for dispensing artesether-lumefantrine in drug shops in Tanzania: effect on dispenser knowledge and patient adherence.