

## **Systematization of Studies of Adherence to Antimalarial Treatment Conducted from 2004 to 2009 in Countries of the Amazon Basin**

---



---

Strengthening Pharmaceutical Systems  
Center for Pharmaceutical Management  
Management Sciences for Health  
4301 North Fairfax Drive, Suite 400  
Arlington, VA 22203 USA  
Telephone: 703.524.6575  
Fax: 703.524.7898  
E-mail: [sps@msh.org](mailto:sps@msh.org)

This report is made possible by the generous support of the American people through the U.S. Agency for International Development (USAID), under the terms of cooperative agreement number GHN-A-00-07-00002-00. The contents are the responsibility of Management Sciences for Health and do not necessarily reflect the views of USAID or the United States Government.

## **About SPS**

The Strengthening Pharmaceutical Systems (SPS) Program strives to build capacity within developing countries to effectively manage all aspects of pharmaceutical systems and services. SPS focuses on improving governance in the pharmaceutical sector, strengthening pharmaceutical management systems and financing mechanisms, containing antimicrobial resistance, and enhancing access to and appropriate use of medicines.

## **Summary**

The results of the studies presented during the workshop on *improving prescription and dispensing practices and adherence to antimalarial treatment* held in Rio de Janeiro, Brazil, July 28–30, 2009, formed the basis for preparing, in a single document, a compilation and systematization of the studies conducted on adherence to antimalarial medicines available in countries participating in the Amazon Malaria Initiative between 2004 and 2009.

## **Acknowledgments**

This compilation was prepared by Edgar Barillas and Claudia Valdez, based on studies identified and compiled by José Pablo Escobar. The information provided has been taken from the original studies. The authors and institutions that provided technical and financial assistance are cited in the annex section of this report.

## **Recommended Citation**

This report may be reproduced if credit is given to SPS. Please use the following citation.

Management Sciences for Health/Amazon Malaria Initiative. 2010. *Systematization of Studies of Adherence to Antimalarial Treatment Conducted from 2004 to 2009 in Countries of the Amazon Basin*. Submitted to the U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

Strengthening Pharmaceutical Systems  
Center for Pharmaceutical Management  
Management Sciences for Health  
4301 North Fairfax Drive, Suite 400  
Arlington, VA 22203 USA  
Telephone: 703.524.6575  
Fax: 703.524.7898  
E-mail: [sps@msh.org](mailto:sps@msh.org)  
Website: [www.msh.org/sps](http://www.msh.org/sps)

## CONTENTS

Acronyms and Abbreviations .....	v
Introduction.....	1
Objective.....	3
Methodology.....	5
Adherence Studies Conducted in the region (AMI Member Countries) .....	7
Initial Adherence Studies Conducted in 2004 .....	7
Adherence Studies Conducted in 2005 .....	11
Adherence Studies Conducted in 2009 .....	15
Analysis.....	19
Annex 1: Analysis of the Results of Adherence Studies in the Latin American Region.....	23
Annex 2: Analysis of the Results of International Interventions .....	33



## ACRONYMS AND ABBREVIATIONS

ACT	artemisinin-based combination therapy
AMI	Amazon Malaria Initiative
AQ	amodiaquine
AS	artesunate
CIDEIM	Centro Internacional de Entrenamiento e Investigaciones Médicas (International Center for Medical Training and Research)
CQ	chloroquine
FDC	fixed-dose combination
IEC	information, education and communication
MQ	mefloquine
MSH	Management Sciences for Health
PAHO	Pan American Health Organization
PQ	primaquine
RAVREDA	Red Amazónica de Vigilancia de la Resistencia a los Antimaláricos (Amazon Network for the Surveillance of Antimalarial Medicine Resistance)
SNEM	Servicio Nacional de Erradicación de la Malaria (National Malaria Eradication Service)
SP	sulfadoxine/pyrimethamine
SPS	Strengthening Pharmaceutical Systems Program
USAID	U.S. Agency for International Development
WHO	World Health Organization



## INTRODUCTION

In 2001, the Amazon Network for the Surveillance of Antimalarial Medicine Resistance (RAVREDA) was created in collaboration with the Pan American Health Organization (PAHO). In that same year, the U.S. Agency for International Development (USAID) launched its Amazon Malaria Initiative (AMI). The purpose of both these endeavors was to improve malaria control and treatment in most of the countries sharing the Amazon Basin: Bolivia, Brazil, Colombia, Ecuador, Guyana, Peru, and Suriname. Since that time, with support provided by AMI, these countries have modified their treatment policies to include more effective therapeutic combinations in response to the challenge posed by resistance to antimalarial medicines in the Amazon region, a situation identified in the late 1990s (in Colombia, *P. falciparum* resistance to chloroquine, or CQ, was identified as early as the 1980s). This prompted RAVREDA-AMI to promote efforts focusing on improving the availability of antimalarial medicines, together with their proper use by both prescribers and patients. Pharmaceutical management surfaced rapidly as one of the most important of such efforts.<sup>1</sup>

By late 2001, Peru had become the first country to introduce artemisinin-based combination therapy (ACT) in its therapeutic regimens.<sup>2</sup> In early 2002, Bolivia also changed its first-line treatment in the Bolivian Amazon to mefloquine (MQ) plus artesunate (AS). By 2004, three countries (Suriname, Ecuador, and Guyana) had introduced ACTs into their regimens for treating *P. falciparum* malaria.<sup>3</sup> Between 2005 and 2009, all AMI member countries modified their first-line medicine regimens for treating *P. falciparum* to include ACTs, as recommended by the World Health Organization (WHO) and the Roll Back Malaria Partnership.<sup>4</sup> Many AMI member countries have conducted evaluations of the use of the new therapies, including patient acceptance, adherence to treatment regimens, and adverse drug reactions.

By 2004, treatment of *P. vivax* malaria with primaquine (PQ) continued to involve a 14-day course of PQ therapy in most countries. In that same year, the initial studies of adherence were conducted in Colombia, Bolivia, and Ecuador.

In 2005, a meeting was held in Caracas, Venezuela, to discuss and define a standard methodology for analyzing adherence to treatment within the RAVREDA framework. One result of this meeting was agreement on a strategy for improving adherence by promoting best practices and implementing guidelines for prescribing and dispensing malaria treatment. Following the Caracas meeting, studies in addition to those conducted in 2004 were carried out in Brazil, Colombia, and Ecuador. Although not all of these subsequent studies followed strictly

---

<sup>1</sup> USAID. Drug-Resistant Malaria. Amazon Malaria Initiative.

[http://www.usaid.gov/our\\_work/global\\_health/id/malaria/techareas/amazon\\_resistant.html#top](http://www.usaid.gov/our_work/global_health/id/malaria/techareas/amazon_resistant.html#top).

<sup>2</sup> RAVREDA/AMI-PAHO. 2003. *Practical Guide for in vivo Antimalarial Drug-Efficacy Studies in the Americas*. <http://www.paho.org/english/ad/dpc/cd/guia-practica.pdf>.

<sup>3</sup> Barillas, E., C. Valdez, and S. Holland. 2008. *Situación de la gestión del suministro de medicamentos para el tratamiento de la malaria en países que comparten la Cuenca Amazónica*. Submitted to the United States Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington VA: Management Sciences for Health.

<sup>4</sup> Ibid.

the Caracas recommendation regarding prescription control, all did use the agreed-upon classification for degrees of adherence.

During the Caracas meeting, it was proposed that a strategy be developed to promote the adoption of guidelines and practices for prescribing and dispensing antimalarials that would in turn lead to an increased likelihood of proper patient adherence to treatment. Accordingly, it was proposed that this approach be used in three study areas: (a) measurement of the adherence problem; (b) analysis of the determinants of adherence, to guide the implementation of improvements in care and medicine dispensing; and (c) study of compliance with prescribing and dispensing standards and guidelines. The basis for the proposed algorithm is the studies to measure adherence, with regard to which basic details of the protocol were agreed upon. It is proposed that this protocol be followed in future studies to be conducted in the region.

Based on the evidence generated by the studies conducted in the region and others carried out elsewhere in the world, the AMI countries have modified their therapeutic regimens to improve adherence to treatment without decreasing treatment efficacy. The study titled *Situación de la Gestión del Suministro de Medicamentos para el Tratamiento de la Malaria en Países de la Cuenca Amazónica*, conducted by the Strengthening Pharmaceutical Systems (SPS) Program of Management Sciences for Health (MSH) in 2008,<sup>5</sup> relates how many of these countries have made changes to therapeutic guidelines for treatment of both *P. falciparum* and *P. vivax* malaria (typically from 14-day to 7-day regimens).

MSH, through its SPS Program, has been a technical partner of AMI since 2002, focusing on providing support for pharmaceutical supply management. Together with other AMI partners, MSH has contributed to strengthening the capacity of national malaria control programs to manage medicines and supplies. Within the framework of this assistance, MSH/SPS held a regional workshop on July 28–30, 2009, in Rio de Janeiro, Brazil, with the goal of analyzing current practices involving prescribing and dispensing of antimalarials in the region and their contribution to improving adherence to treatment. Participants were informed of the results of the studies of the antimalarial prescribing and dispensing practices and of adherence to antimalarial treatment conducted in 2009 in Colombia, Peru, Ecuador, and Brazil. During the workshop, participants identified a need to disseminate results of similar studies that were carried out, but not published, during 2004 to 2006. MSH/SPS, using resources made available by USAID, provided technical assistance for compiling and systematizing, in a single document, the studies previously conducted in AMI member countries between 2004 and 2009.

---

<sup>5</sup> Ibid.



## **OBJECTIVE**

To systematize interventions that can contribute to improving the prescribing and dispensing of antimalarials, as well as patient adherence to antimalarial treatment, as identified in studies conducted in AMI member countries over the 2004–2009 period.



## METHODOLOGY

The following methodology was used to prepare the systematization of these studies—

1. **Request for submission of studies of adherence carried out in AMI member countries between 2004 and 2009:** During the Rio de Janeiro workshop on best practices for prescribing and dispensing antimalarials and improving adherence to antimalarial treatment, participants were asked to forward to MSH/SPS all studies on patient adherence carried out between 2004 and 2009.
2. **Review of documents:** With support provided by PAHO/AMI focal points on site in member countries, a total of 13 research studies carried out during the period 2004–2009 were identified and reviewed. The primary sources of these studies were the final reports submitted by direct collaborators or authors; some were summaries published in the RAVREDA Newsletter.
3. **Gathering of complementary information:** A search was conducted of other studies that might have been conducted in the region during the chosen period and published in PubMed, Cochrane, WHO, PAHO/Virtual Health Library, Partnership for Social Sciences in Malaria Control, or Project-Info databases.
4. **Consolidation and analysis:** For processing purposes, a consolidation and analysis matrix was prepared containing columns for title, intervention, author(s), year, country, design, findings/results, and conclusions (included as annexes 1 and 2 to this report).
5. **Review and testing of the final document:** The final document was reviewed by PAHO-AMI focal points. Their comments and suggestions were incorporated into a final report. The report was organized according to the periods over which the studies were carried out and the countries involved, resulting in three broad groups: (a) adherence studies conducted in 2004, (b) adherence studies conducted in 2005–2006, and (c) adherence studies conducted in 2009.



## ADHERENCE STUDIES CONDUCTED IN THE REGION (AMI MEMBER COUNTRIES)

### Initial Adherence Studies Conducted in 2004

#### **Bolivia**

The first adherence study reported was conducted in the cities of Guayaramerín and Riberalta, both located in Bolivia's Amazon region.<sup>6</sup> The study used an exploratory, transversal design and included a quantitative-qualitative analysis. Two groups of patients treated with CQ and PQ were studied. The first group of 90 patients received a 14-day course of therapy with PQ, while a second group of 89 patients received a course of therapy of only 7 days for which the dose was doubled. Results based on statistical association showed that, with the standard treatment, there were 43 cases (48 percent) of nonadherence, whereas the shortened regimen produced 32 cases of nonadherence (36 percent). The most important reasons for adherence failure were forgetting to take the medicines, loss of medicines, and occurrence of side effects. Most cases of treatment abandonment occurred between the fifth and the eighth day of treatment. On the basis of these results, the National Malaria Prevention and Control Program implemented a shortened 7-day regimen, and new measures aimed at preventing abandonment of treatment were put into place.

#### **Colombia**

In 2004, a study was conducted of adherence to treatments for *P. falciparum* malaria in the municipality of Guapí, in the department of Cauca, with support provided by the International Center for Medical Training and Research (Centro Internacional de Entrenamiento e Investigaciones Médicas; CIDEIM) and Universidad del Valle. The sample consisted of 32 patients, and the regimen to be evaluated was the first-line treatment for *P. falciparum* malaria (amodiaquine 3 days + sulfadoxine/pyrimethamine). The study design was descriptive and used a combination of quantitative and qualitative methods. The results reported nine failures to adhere to treatment (28.1 percent of the study sample). Health agents responsible for prescribing treatment did not always adhere to the official regimen and on some occasions continued to prescribe CQ instead of amodiaquine (AQ). In addition, a lack of coordination exists both within and among health institutions regarding the supply of medicine to patients, as well as information regarding requirements and steps to be taken with respect to both diagnosis and treatment. These findings highlight the importance of working to develop strategies for improving medicine prescription and use.<sup>7</sup>

---

<sup>6</sup> Matías, A., A. Achocalla, J. P. Escobar, and E. Martínez. 2004. *Disminución de las fallas en la adherencia al tratamiento de malaria por Plasmodium vivax en Bolivia con esquema acortado de tratamiento. Guayaramerín y Riberalta, Bolivia.* Ministry of Health and Sports and PAHO/WHO.

<sup>7</sup> Anacona, A., L. Osorio, and E. Sevilla. 2004. *Adherencia al tratamiento de malaria no complicada por P. falciparum en el municipio de Guapí en el departamento del Cauca.* Cali, Colombia. CIDEIM, Universidad del Valle and the Cauca Departmental Health Directorate.

## **Ecuador**

In a study conducted in Quinindé canton, in the province of Esmeraldas, located in the northwestern region of Ecuador, a total of 249 individuals clinically diagnosed as having *P. vivax* malaria, confirmed by thick blood smear, were prescribed treatment with CQ + PQ for 7 days in accordance with the therapeutic regimen in effect in the National Malaria Eradication Service (Servicio Nacional de Erradicación de la Malaria; SNEM). Patients were treated without being given a written prescription. The study design was observational and based on interviews conducted in homes one day following the scheduled completion of treatment and observation of the number of tablets remaining. The results showed that of the 249 patients in the sample, 85 (34.1 percent) were nonadherent. The remaining 164 patients (65.9 percent) were in compliance with the course of therapy prescribed by SNEM health service providers. The number of patients infected with *P. falciparum* was very similar to the number infected with *P. vivax*. This was not the case with the distribution of adherent and nonadherent patients based on the species of the infecting parasite: those infected with *P. falciparum* (74 percent) showed a greater degree of adherence than those infected with *P. vivax* (58 percent). Overall, for every three adherent patients, two were nonadherent. Nonadherence was associated primarily with the adverse effects of the medicines prescribed, forgetting to take the medicines, and having achieved an “immediate cure.” The study recommended that malaria program authorities establish “memory aid” mechanisms that would ensure self-administration of tablets for the prescribed number of days and at the appropriate intervals (e.g., individualized, prepackaged therapeutic packets, accompanied by a diagram providing dosage guidance, plus information, education, and communication [IEC] materials for the patient).<sup>8</sup>

An additional study was conducted in 2004 in the villages of Milagro, Esmeraldas, and Huaquillas to measure adherence to 7-day and 14-day treatment regimens for *P. vivax*.<sup>9</sup> The study design was observational, based on interviews conducted in homes one day following scheduled completion of treatment and verification of the number of tablets remaining. The study did not control for the terms of prescription. The results showed that compliance with the 14-day regimen totaled 72 percent (65/90) in Milagro, 25 percent (18/71) in Huaquillas, and 52 percent (34/65) in Esmeraldas. Noncompliance with the 7-day regimen was 12 percent (11/90) in Milagro and 20 percent (18/90) in Esmeraldas. Most cases of nonadherence in these studies were confirmed by the number of tablets remaining and by prescription errors. The study recommended the design of strategies that would improve prescribing practices as well as changes to the therapeutic guidelines for treatment of *P. vivax* from 14 to 7 days.

## **Summary**

Within the framework of RAVREDA-AMI, the problem of adherence was addressed first in 2004 by means of evaluations carried out in Bolivia, Colombia, and Ecuador. These initial studies were important in terms of increasing interest in this issue within malaria control

---

<sup>8</sup> Yépez, M. C., D. Zambrano, F. Carrasco, and R. F. Yépez. 2000. Factores asociados con el cumplimiento del tratamiento antipalúdico en pacientes ecuatorianos. *Revista Cubana de Medicina Tropical* 52(2): 81–9.

<sup>9</sup> RAVREDA-AMI, SNEM. *Adherencia al tratamiento de P. vivax en las comunidades de Milagro, Huaquillas y Esmeraldas en el Ecuador, 2004.*

programs. The studies identified problems involving the inappropriate use of antimalarials linked to poorly prepared prescriptions (table 1).

**Table 1. Adherence Studies Conducted by AMI-RAVREDA in 2004**

Country	Town	Year	Species	Therapeutic Regimen	Prescription Control	Number Evaluated	Adherence Failures		Tablets Remaining	Absence of Prescription
							No.	%		
Colombia	Guapí	2004	<i>P. falciparum</i>	AQ/CQ+SP	No	32	9	28.1	0	5
Ecuador	Milagro	2004	<i>P. vivax</i>	CQ+PQ 14 days	No	90	65	72.2	61	1
Ecuador	Milagro	2004	<i>P. vivax</i>	CQ+PQ 7 days	No	90	11	12.2	11	0
Ecuador	Huaquillas	2004	<i>P. vivax</i>	CQ+PQ 14 days	No	71	18	25.4	16	4
Ecuador	Esmeraldas	2004	<i>P. vivax</i>	CQ+PQ 14 days	No	65	34	52.3	17	27
Ecuador	Esmeraldas	2004	<i>P. vivax</i>	CQ+PQ 7 days	No	90	18	20.0	12	14
Bolivia	Guayaramerín	2004	<i>P. vivax</i>	CQ+PQ 7 days	No	89	32	36.0	17	12
Bolivia	Riberalta	2004	<i>P. vivax</i>	CQ+PQ 14 days	No	90	43	47.8	10	16



## **Adherence Studies Conducted in 2005**

In April 2005,<sup>10</sup> during the RAVREDA meeting in Caracas, Venezuela, a standard methodology was defined to assess access to and use of antimalarials in AMI member countries. It was agreed that patients would be classified according to a combination of findings from reviews of the amount of medicine remaining and interviews. Any patient who had tablets remaining in the package was to be classified as *nonadherent*. When the package/blister was not available or was empty, patients were to be classified as follows—

- *Probably nonadherent*: when the patient reported that he or she had not taken all doses within the proper time frame and in the proper amount; or
- *Probably adherent*: when the patient reported that he or she had taken all doses within the proper time frame and in the proper amount.

This standard methodology was recommended for all studies conducted subsequent to that date.

### **Brazil**

In 2005, two studies were conducted to evaluate adherence to the course of therapy used to treat *P. vivax*—CQ + PQ for seven days—in the city of Colniza and in Augusto Correia, in Mato Grosso state. The study did not control for prescription quality. Adherence was monitored through home visits beginning on the eighth day and interviews with patients. In Augusto Correia, 94 patients were evaluated; in four cases (4 percent), leftover tablets were found. The remaining patients (96 percent) were considered to be probably adherent. In Colniza, of 115 patient evaluated, 8 (7 percent) were classified as nonadherent and 107 (93 percent) as probably adherent. The study highlighted problems involving adherence to treatment (PQ) attributable to numerous factors, including the information provided by prescribers and dispensers, which patients did not understand well.<sup>11</sup>

### **Ecuador**

In 2005 and 2006, studies were conducted in the villages of Esmeraldas, Machala, Milagro, and Santo Domingo, using the methodology proposed in the Caracas meeting, for the purpose of measuring adherence to the seven-day treatment with PQ (0.5 mg/kg/day).<sup>12</sup> Staff from program health posts were trained to prescribe and dispense precisely in accordance with the recommendations contained in Ministry of Health guidelines. The study method consisted of interviews and verification of the number of tablets remaining. The results show that, of 101 patients evaluated, 20 (20 percent) were classified as nonadherent, 20 as probably nonadherent,

---

<sup>10</sup> RAVREDA-AMI/PAHO. 2005. *Guía para la realización de estudios de adherencia a los antimaláricos* (borrador). OPS/DPC/CD/M/392/06.

<sup>11</sup> RAVREDA-AMI. 2005. *Estudios para evaluar la adherencia al régimen de tratamiento P. vivax, cloroquina y primaquina + 7 días, en Mato Grosso, en la ciudad de Colniza y Pará, en Augusto Correia*. Ministry of Health, Brazil.

<sup>12</sup> RAVREDA-AMI, Ministry of Health. *Estudios de adherencia al tratamiento de P. vivax en los pueblos de Esmeraldas, Machala, Milagro y Santo Domingo en 2005 y 2006, Ecuador*.

and 61 (60 percent) as probably adherent. Based on these results, a decision was made to improve prescribing practices by introducing written instructions and providing staff training.

**Ministerio de Salud Pública**  
**Servicio Nacional Control de Enfermedades Transmitidas por Vectores Artrópodos**

Nombre : \_\_\_\_\_ Fecha: \_\_\_\_\_  
 Edad: \_\_\_\_\_ Sexo: \_\_\_\_\_ Peso: \_\_\_\_\_

DIA					NOMBRE PASTILLAS
1	⊕	⊕	⊕	⊕	CLOROQUINA PRIMAQUINA
	⊕	⊕			
2	⊕	⊕	⊕		CLOROQUINA PRIMAQUINA
	⊕	⊕			
3	⊕	⊕	⊕		CLOROQUINA PRIMAQUINA
	⊕	⊕			
DIAS	⊕ ⊕	⊕ ⊕	⊕ ⊕	⊕ ⊕	PRIMAQUINA
	04	05	06	07	

**TRATAMIENTO VIVAX**

**Graphic1. Graphic instructions in Ecuador**

## **Colombia**

In the municipality of Apartadó, Antioquia, a descriptive study was carried out following the methodology established at the Caracas meeting but with no control for prescription quality. The study evaluated the 14-day CQ + PQ treatment for *P. vivax* as well as the single-dose treatment for *P. falciparum* with AQ (3 days) + sulfadoxine/pyrimethamine (SP).<sup>13</sup> Compliance was verified by means of interviews carried out in the home and verification of the number of tablets remaining. The evaluation covered 61 patients receiving CQ + PQ for 14 days, of which 6 (10 percent) were classified as nonadherent, 4 (6 percent) as probably nonadherent, and 51 (84 percent) as probably adherent. Regarding treatment of *P. falciparum*, the evaluation covered a total of 22 patients, of which 1 (5 percent) was classified as nonadherent, 2 (9 percent) as probably nonadherent, and 19 (86 percent) as probably adherent. These results suggested the implementation of strategies to ensure proper prescribing and dispensing practices and the use of patient education materials.

In February 2005, a study was conducted in the municipality of Tierralta, Córdoba, on adherence to treatment for 14 days with CQ + PQ for *P. vivax*.<sup>14</sup> The study design was transversal and

<sup>13</sup> Restrepo, M., M. Arboleda and J. Osorio. 2005. *Estudio del tratamiento al P. vivax de CQ+PQ 14 días y el tratamiento a P. falciparum de AQ+SP (amodioquina 3 días+ sulfadoxina-pirimetamina) en el municipio de Apartadó, Colombia*. RAVREDA-AMI, Colombian Institute of Tropical Medicine, Antioquia Sectional Health Directorate and PAHO/WHO.

<sup>14</sup> Pérez, L. 2005. *Adherencia al tratamiento de malaria no complicada por P. vivax en el municipio de Tierralta y al tratamiento de malaria no complicada por P. falciparum en el municipio de Puerto Libertador en el departamento de Córdoba, Colombia*. Córdoba Health Development Secretariat, Colombian Ministry of Social Protection, PAHO/WHO.

included an analysis of access to antimalarials and the dispensing of medicines not included in official regimens. Problems involving the prescribing, dispensing, and use of antimalarials were recorded. Adherence was measured by counting tablets and by conducting home interviews on the day following completion of treatment. No provisions were made to control for prescription quality. Eighty patients were recruited into the 14-day CQ + PQ regimen, and 42 (52 percent) of these were affected by prescription errors. Of the 38 patients for whom a correct prescription was verified, 15 (39 percent) still had tablets on hand, while 18 (47 percent) had no tablets left but the patients reported having followed the course of therapy incorrectly, which thus led to total failure to adhere to the treatment regimen in 87 percent (33/38) of patients. In addition to the problem of nonadherence, the study revealed a high percentage of patients receiving incorrect prescriptions, significant problems involving medicine management, poor-quality handwriting on prescriptions, prescribing of medicines not recommended by the central level, inappropriate packaging, and a lack of information on adverse reactions. It was concluded that all of these factors acted directly on failure to adhere to the course of therapy. The study recommended that improvements be made to management processes involved in the medicine cycle on all levels, together with the development of educational, management, and normative strategies for application to the health system, prescribing personnel, dispensing personnel, patients, and the community at large.

1. Patients included in the study: 80
2. Patients affected by prescription errors: 52.5 percent (42/80)
3. Patients for whom adherence was assessed (those who received correct prescriptions): 47.5 percent (38/80) *Note:* The figure of 38 is the result of subtracting 42 from 80.
4. Patients with tablets still remaining: 39.4 percent (15/38)
5. Patients with tablets remaining but who indicated that they had taken the medicine incorrectly: 47.36 percent (18/38)
6. Adherent patients (medicine properly prescribed and correctly taken): 13.15 percent (5/38)

### **Summary**

Following the Caracas meeting, adherence studies were conducted between 2005 and 2006 in Bolivia, Brazil, Colombia, and Ecuador (table 2). Of these studies, the suggested methodology was rigorously applied only in Ecuador.

**Table 2. Adherence Studies, 2005–2006**

Country	Town	Year	Species	Therapeutic Regimen	Prescription Control	Number Evaluated	Adherence Failures			Probably Adherent (%)
							Nonadherent	Probably Nonadherent	Nonadherent (% of Total)	
Brazil	Bragança - Augusto Correia	2005	<i>P. vivax</i>	CQ+PQ 7 days	No	94	4	0	4 (4.0%)	90 (96%)
	Colniza	2005	<i>P. vivax</i>	CQ+PQ 7 days	No	115	8	0	8 (7.0%)	107 (93%)
Colombia	Apartadó	2005	<i>P. vivax</i>	CQ+PQ 14 days	No	61	6	4	10 (16.3%)	51 (84%)
	Apartadó	2005	<i>P. falciparum</i>	AQ+SP	No	22	1	2	3 (13.3%)	19 (86%)
	Tierralta	2005	<i>P. vivax</i>	CQ+PQ 14 days	No	38	33	0	33 (87%)	5 (13.15%)
Ecuador	Esmeraldas, Santo Domingo, Milagro, Machala	2005	<i>P. vivax</i>	CQ+PQ 7 days	Yes	101	20	20	48 (39.8%)	61 (60.3%)

Source: RAVEDRA/AMI. 2005. The data for the Adherence Failures columns of table 2 were reordered and reorganized for better understanding using data from the original studies.

## Adherence Studies Conducted in 2009

During the period 2008–2009, studies were conducted in Colombia, Peru, Ecuador, and Brazil. Unlike the studies carried out in prior years, these studies evaluated prescribing and dispensing practices as well as adherence. The methodology and the criteria used to measure adherence were similar, although they were applied to different population groups and, occasionally, for different therapeutic regimens (table 3).

### Colombia

During the first quarter of 2009, a descriptive study was conducted in the municipalities of Tumaco, in the department of Nariño, and Pizarro, in the department of Chocó. The study design was descriptive, transversal, and retrospective and included an analysis of adherence to the following treatments: (a) 7-day short treatment with CQ + PQ for *P. vivax* in Tumaco; (b) 14-day treatment with CQ + PQ for *P. vivax* in Pizarro; and (c) 3-day treatment with artemether and lumefantrine for *P. falciparum* in both municipalities. In Pizarro, 9 patients were interviewed and an adherence failure rate was recorded in 6 (33 percent) for treatment of *P. vivax* and of 100 percent for treatment of *P. falciparum* (this study evaluated a sample of only two patients). In Tumaco, the sample consisted of 78 patients, 74 under treatment for *P. falciparum* and 4 for *P. vivax*. Failure to adhere to treatment was reported in zero patients (0 percent) for *P. vivax* and in one patient (1.4 percent) for *P. falciparum*. Of all patients, 97 percent (in the case of *P. falciparum*) and 85 percent (in the case of *P. vivax*) correctly understood how the medicines prescribed were to be taken.<sup>15</sup> The study revealed difficulties involving prescribing and dispensing practices, as well as suboptimal levels of adherence related primarily to (a) failure to update guidelines for providing care and to standardize treatment regimens, (b) quality-related prescribing errors, and (c) problems in dispensing of treatment regimens attributable to stock-outs of certain medicines.<sup>16</sup>

### Ecuador

A descriptive, transversal, retrospective study was conducted from December 2008 to March 2009 in the five provinces located in Ecuador's Amazon region (Napo, Orellana, Sucumbios, Pastaza, and Morona Santiago). The study design was descriptive, transversal, and retrospective. Interviews with 124 patients and tablet counting indicated that 117 patients (94 percent) had adhered to the seven-day treatment of CA + PQ for *P. vivax*, in accordance with the prescribed regimen. Seven patients (6 percent) were nonadherent. Failure to adhere to treatment was attributed to the adverse effects of the medicines. The study revealed that prescription of antimalarial medicines currently shows a high degree of compliance with established guidelines (97.2 percent), that graphic instructions continue to be used to promote adherence to treatment,

---

<sup>15</sup> The percentage figures resulting from the study were based on a small sample, as a result of which statistically valid inferences cannot be made.

<sup>16</sup> Antioquia Hospital Cooperative (COHAN). 2009. *Estudio de prácticas de prescripción, dispensación y adherencia al tratamiento antimalárico en Colombia* (borrador). MSH/SPS, Arlington, VA.

and that these graphic instructions are likely to have effectively enhanced the rate of adherence to treatment, which now totals 94 percent of all patients receiving treatment.<sup>17</sup>

### **Peru**

From September to November of 2008, a descriptive, transversal, and retrospective study was conducted in the Loreto Health Region located in Maynas province. The study included a comprehensive analysis of prescribing and dispensing practices plus an evaluation of adherence to the seven-day short regimen of CQ + PQ for *P. vivax* and to the three-day regimen of MQ + AS for *P. falciparum*. In total, 197 interviews were done.

The study highlighted a number of problems regarding proper prescribing practices in 40.4 percent of the prescriptions reviewed. In addition, it showed that direct supervision of treatment was carried out in only 54.5 percent of the cases studied, and that the information given to patients was considered complete in only 22.6 percent of all cases. Home interviews showed 88.5 percent adherence to treatment. An investigation was done of the blisters and tablets in the house without finding any pharmaceuticals because all of the patients said they took the medicines under direct supervision of health service staff. Twenty-three patients (11.5 percent) did not complete treatment and were considered nonadherent because they were referred to higher-level treatment facilities without adequate record of the referral having been made. The study concluded that only 60 percent of prescriptions were in compliance with national therapeutic recommendations for treatment of malaria. If to this is added the fact that 12 percent of patients failed to adhere to the prescribed treatment, it can be stated that for every 100 patients with a diagnosis of malaria, only 53 receive the benefits of efficient treatment management.<sup>18</sup>

### **Brazil**

This study was conducted in the city of Goiania, in Pará state, and in Manaus, in Amazonas state. The study design was transversal, and the method used to quantify adherence was based on household interviews and a review of unused tablets. The study used the Caracas definitions of nonadherent, probably adherent, and probably nonadherent. The regimen to be evaluated was the treatment for *P. vivax* malaria consisting of CQ for three days and PQ for seven days. The study covered five patients treated in health centers in the city of Goianésia and 11 health posts in the city of Manaus. The study was carried out in coordination with national and local authorities.

A total of 118 patients were evaluated in Goiania. Adherence failure (nonadherents plus probable nonadherents) was observed in 26 patients, accounting for 18.8 percent of all patients evaluated. In 6.1 percent of the total (7 nonadherents), a blister containing tablets was found, while 13.8 percent had failed to take these medicines in accordance with the instructions they were given (19 probably nonadherent).

In Manaus, the total sample consisted of 165 patients. The total number of patients with treatment failure (nonadherents plus probable nonadherents) was 31, or 18.8 percent; 6.1 percent

---

<sup>17</sup> Avecillas, J., and K. Sacoto. 2009. *Estudio de prácticas de prescripción, dispensación y adherencia al tratamiento antimalárico en Ecuador* (borrador). MSH/SPS, Arlington, VA.

<sup>18</sup> Neyra, D. 2009. *Estudio de prácticas de prescripción, dispensación y adherencia al tratamiento antimalárico en la República del Perú* (borrador). MSH/SPS, Arlington, VA.

(10 patients) were classified as nonadherent because they had blisters still containing tablets, while 12.72 percent (21 patients) indicated that they never correctly took the medicine as prescribed. “The study revealed problems with adherence to treatment (PQ) associated with a variety of factors, ranging from the instructions provided by dispensers that the patients do not really understand to patient failure to understand the medicine dosage form.”<sup>19</sup>

---

<sup>19</sup> Paola Marchesini. 2009. *Estudio de prácticas de prescripción, dispensación y adherencia al tratamiento antimalárico en el Brasil*. MSH/SPS, Arlington, VA.

Summary

Table 3. Adherence Studies, 2009

Country	Town	Year	Species	Medicine	Prescription Control	Number Studied	Adherence Failure			Probably Adherent (%)
							Nonadherent	Probably Nonadherent	Adherence Failure (% of the Total)	
Brazil	Goiania	2009	<i>P. vivax</i>	CQ+PQ 7 days	Yes	118	7	19	18.8	92 (78%)
	Manaus	2009	<i>P. vivax</i>	CQ+PQ 7 days	Yes	165	10	21	18.8	134 (81.2%)
Colombia	Tumaco	2009	<i>P. falciparum</i>	AS+ lumefantrine 3 days	Yes	74	1	0	1 (1.4%)	73 (98.6%)
			<i>P. vivax</i>	CQ+PQ 7 days	Yes	4	0	0	0%	100%
	Pizarro	2009	<i>P. falciparum</i>	AS+ lumefantrine 3 days	Yes	2	2	0	2 (100%)	0%
			<i>P. vivax</i>	CQ+PQ 14 days	Yes	9	3	0	3 (33%)	6 (67%)
Ecuador	Napo, Orellana, Sucumbios, Pastaza and Morona, Santiago	2009	<i>P. vivax</i>	CQ+PQ 7 days	Yes	124	7	0	7 (6%)	117 (94%)
Peru	Maynes, Loreto	2009	<i>P. vivax</i>	CQ+PQ 7 days	Yes	197	23	0	23 (11.6%)	174 (88.5%)
			<i>P. falciparum</i>	AS+MQ 3 days	Yes					

Source: MSH/USAID/AMI. 2009. The data in the Adherence Failures columns of table 3 were reordered and reorganized for better understanding using the data from the original studies.



## ANALYSIS

The initial studies of treatment adherence conducted in 2004 were carried out in different stages, and although they were not designed using strong or strictly standardized methodologies, their results revealed low levels of adherence to treatment of uncomplicated malaria caused by *P. vivax* and *P. falciparum*, as well as problems involving prescribing, dispensing, and availability of antimalarial medicines. The findings led to interventions aimed at strengthening management of the supply chain, prompted other studies of adherence carried out subsequently in the same region, and caught the attention of national programs regarding the need to focus on strategies for improving the prescription and use of medicines.

In 2005, studies were conducted in Brazil, Colombia, and Ecuador, using a standardized methodology, in which treatment protocols were the primary tool for measuring proper prescribing of treatment regimens recommended by official malaria control programs in those countries. Not all studies strictly observed the Caracas recommendation regarding prescription control, but all used the classification for degree of adherence agreed to at the Caracas meeting, and the results were highly relevant.

In 2008–2009, studies were conducted in Brazil, Colombia, Peru, and Ecuador using the adherence definition agreed upon in Caracas, although the methodology, study population, and geographic areas prevented comparisons with the results of prior studies. The results obtained from the studies carried out in Brazil, for example, showed a higher percentage of nonadherents and probable adherents to treatment for *P. vivax* malaria vis-à-vis the studies conducted previously, in 2005. However, it cannot be said that adherence decreased or deteriorated during that period, since in analyzing the results it is necessary to take into account social and cultural factors affecting adherence that were not considered in this study.

Only in some of the countries was it possible to establish a cause-effect relationship with regard to the results obtained from these interventions and the decisions made by national authorities based on those results. These include the studies conducted in Ecuador (2005), which revealed problems caused by the absence of written prescriptions and failures to adhere to antimalarial treatment regimens. Based on these findings, Ecuador's National Malaria Control Program implemented the use of graphic instructions and co-blisters with a view toward improving patient adherence to treatment regimens; these interventions continue to be used to date.<sup>20</sup>

Beginning with the inclusion of graphic instructions, one can compare studies conducted in 2005—which evaluated adherence to the 7-day regimen for treatment of *P. vivax* malaria, resulting in a rate of 61 percent adherent and 39.8 percent nonadherent—with the data reported in the studies carried out in 2008–2009, which revealed a 94 percent level of adherence and a 6 percent level of nonadherence to the 7-day regimen for treatment of *P. vivax*. The findings suggest that significant improvements were made regarding adherence to treatment for *P. vivax*, which can be attributed to the graphic prescription method put into place and incorporated into the national program following the adherence studies carried out in 2005–2006.

---

<sup>20</sup> RAVREDA-AMI; Ministry of Health. 2005. *Estudios de adherencia al tratamiento de P. vivax en los pueblos de Esmeraldas, Machala, Milagro y Santo Domingo en 2005 y 2006, Ecuador*.

In Bolivia, based on the results of the study carried out in 2004, the National Program for the Prevention and Control of Malaria implemented a shortened seven-day regimen and took steps to prevent abandonment of treatment, including training health personnel to improve prescribing and dispensing practices and implementing IEC activities.<sup>21</sup>

In the studies conducted in 2004 in both Ecuador and Bolivia, high levels of adherence to the shortened 7-day treatment of *P. vivax* malaria were observed, as compared to the 14-day regimen, thus suggesting the use of short, easy-to-manage regimens as a factor for increasing the degree of proper adherence to antimalarial treatment.

The results from the studies conducted in Colombia have contributed to improvements in prescribing and dispensing practices through the use of a standard protocol, along with a change in the treatment of *P. vivax* malaria, from 14 days to 7 days with CQ + PQ, in certain departments of the country.<sup>22,23</sup>

International experiences with interventions to improve adherence to antimalarial treatment are consistent with those implemented in the countries of the region, based on studies conducted.

- Studies show high levels of adherence: 76.3 percent for CQ + PQ for 7 days compared with 70.5 percent for CQ + PQ for 14 days.<sup>24</sup>
- A study conducted in Ghana showed that clear information, use of simple language by prescribers when addressing patients, and improved labeling of medicines for home-based treatment of malaria, together with the use of graphic instructions, contributed to an increase in adherence, in all clinics included in the study, from 42 percent to 91 percent.<sup>25</sup>
- Prepackaged treatment plus printed information increases adherence to antimalarial treatment compared to nonprepackaged treatment and lack of information. Results showing 94.5 percent adherence attributable to the use of prepackaged treatment plus printed information compared with 76.5 percent for nonprepackaged treatment and lack of information;<sup>26</sup> 82 percent prepackaged/blister compared with 60.5 percent using

---

<sup>21</sup> Matías, A., A. Achocalla, J. P. Escoba, and E. Martínez. 2004. *Disminución de las fallas en la adherencia al tratamiento de malaria por Plasmodium vivax en Bolivia con esquema acortado de tratamiento.*

<sup>22</sup> RAVREDA-AMI/OPS. 2007. *Mejora del acceso a y uso de los antimaláricos.* <http://www.paho.org/spanish/ad/dpc/cd/ravreda-antimal-acceso-uso.pdf>.

<sup>23</sup> Barillas, E., C. Valdez, and S. Holland. 2008. *Situación de la gestión del suministro de medicamentos para el tratamiento de la malaria en países que comparten la Cuenca Amazónica.* Submitted to the United States Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington VA: Management Sciences for Health.

<sup>24</sup> RAVREDA and PAHO. 2004. *Estudios de adherencia al tratamiento de la malaria no complicada por Plasmodium falciparum y P. vivax en Venezuela. Bolívar and Amazonas states, Venezuela.*

<sup>25</sup> Agyepong, I.A., E. Ansah, M. Gyapong, S. Adjei, G. Barnish, and D. Evans. 2002. Strategies to Improve Adherence to Recommended Chloroquine Treatment Regimes: A Quasi-Experiment in the Context of Integrated Primary Health Care Delivery in Ghana. *Social Science and Medicine* 55(12): 2215–26.

<sup>26</sup> Lauwo, J. A., F. W. Hombhanje, S. P. Tulo, G. Maibani, and S. Bjorge. 2006. Impact of Pre-packaging Antimalarial Drugs and Counselling on Compliance with Malaria Treatment at Port Moresby General Hospital Adult Outpatient Department. *Papua and New Guinea Medical Journal* 49(1–2): 14–21.

traditional packaging;<sup>27</sup> and 83 percent traditional packaging compared with 97 percent prepackaged/blister<sup>28</sup>, support the use of these interventions.

To conclude, from the initial studies addressing the issue of adherence to the most recent studies conducted in the region in 2009, improvements have been sought in policies involving dispensing and use, aimed at improving adherence to antimalarial treatment (table 4). These improvements include the following: introduction of treatments packaged in blisters for specific age groups (prepackaged) for treatment of uncomplicated *P. falciparum* malaria (Coartem) in Brazil, Colombia, Guyana, and Suriname; implementation of a CQ + PQ regimen (seven days) in Bolivia, Ecuador, and certain departments of Colombia for treatment of *P. vivax* malaria; use of written instructions in the treatment of *P. vivax* malaria; and supervised treatment (Ecuador). In Guyana, PQ packaged in co-blisters was incorporated to improve patient adherence to treatment.

**Table 4. Adherence Studies Conducted and Interventions Implemented, by Country**

Country	Date of Study	Intervention
Bolivia	2004	Change in PQ regimen from 14 to 7 days
Ecuador	2004	CQ + PQ (7 days) for <i>P. vivax</i>
Brazil	2004	Co-blisters packaging with AS derivatives
Colombia	2005	Co-blisters packaging with AS derivatives
Ecuador	2005	Use of written instructions for treatment of <i>P. vivax</i> malaria, plus supervised treatment
Colombia (certain departments)	2005	CQ + PQ (7 days) for <i>P. vivax</i>

Source: RAVREDA-AMI/USAID/PAHO. 2007. *Mejora del acceso a y uso de los antimaláricos*.

As described in table 4, educational interventions; prepackaged treatment accompanied by graphic instructions; information provided in simple, easy-to-understand language by prescribers; and use of audiovisual media or materials at the community level constitute interventions of proven effectiveness for improving adherence to antimalarial treatment.

Developing a standard methodology—containing elements that make it possible to study adherence-related social and cultural factors, recently applied practices, and/or interventions not yet evaluated—and conducting adherence studies in low-incidence contexts provide an opportunity for evaluating the initiatives that have been carried out in countries of the Amazon Basin to inform decision making by national authorities.

---

<sup>27</sup> Yeboah-Antwi, K., J. O. Gyapong, I. K. Asare, G. Barnish, D. B. Evans, and S. Adjei. 2001. Impact of Prepackaging Antimalarial Drugs on Cost to Patients and Compliance with Treatment. *Bulletin of the World Health Organization* 79(5): 394–9.

<sup>28</sup> Qingjun, L., et al. 1998. The Effect of Drug Packaging on Patients' Compliance with Treatment for Plasmodium vivax Malaria in China. *Bulletin of the World Health Organization* 76 (Suppl. 1): 21–27.



## ANNEX 1: ANALYSIS OF THE RESULTS OF ADHERENCE STUDIES IN THE LATIN AMERICAN REGION

Title of Study*	Interventions	Country	Authors	Year	Financing	Study/Sample Design	Sample	Findings/ Adherence Level	Conclusions
Decrease in failure to adhere to treatment of <i>Plasmodium vivax</i> malaria in Bolivia using a shortened treatment regimen	<i>P. vivax</i> CQ 25 mg/kg distributed over 3 days (10 mg on the first day, 7.5 mg/kg on the second day, and 7.5 mg/kg on the third day + PQ at 0.25 mg/kg for 14 days vs. CQ 25 mg/kg distributed over 3 days (10 mg on the first day, 7.5 mg/kg on the second day, and 7.5 mg/kg on the third day) + PQ for 7 days at 0.50 mg/kg per day	Bolivia	Matías A.; Achocalla A.; Escobar J.P.; Martínez E.	2004	RAVREDA-AMI	Exploratory transversal with quantitative-qualitative analysis	Riberalta (n=49) and Guayaramerín (n=61)	24% adherent with 14-day regimen (Riberalta) and 57% adherent with 7-day regimens (Guayaramerín)	The shortened 7-day treatment regimen with a double dose of PQ for <i>P. vivax</i> malaria reduced the percentage of treatment adherence failure and is thus deemed to constitute a recommendable measure that can contribute to curing malaria. It suggests that the shortened treatment with CQ + PQ may be a factor contributing to increased adherence.

<b>Title of Study*</b>	<b>Interventions</b>	<b>Country</b>	<b>Authors</b>	<b>Year</b>	<b>Financing</b>	<b>Study/Sample Design</b>	<b>Sample</b>	<b>Findings/ Adherence Level</b>	<b>Conclusions</b>
Adherence to treatment of uncomplicated <i>P. falciparum</i> malaria in the municipality of Guapí in the department of Cauca, Colombia	Treatment of <i>P. falciparum</i> : AQ 3 days + SP	Colombia	CIDEIM and Universidad del Valle	2004	Ministry of Social Protection, Departmental Health Secretariats, RAVREDA-AMI	Interview-based, descriptive, and quantitative-qualitative	Municipality of Guapí (n=32)	28% adherence failure	The results showed a treatment adherence failure rate of 28.1%, with causes including the fact that health agents responsible for prescribing treatment do not always apply the official course of treatment and on some occasions continue to prescribe CQ instead of AQ. The findings point to the importance of working to develop strategies that will improve the prescribing and use of medicines.

Title of Study*	Interventions	Country	Authors	Year	Financing	Study/Sample Design	Sample	Findings/ Adherence Level	Conclusions
Factors associated with adherence to antimalarial treatment in Ecuadoran patients	Shortened 7-day treatment with CQ +PQ. CQ:150 mg tabs, 4 tabs on day 0, subsequently 3 tabs/day + PQ: 75 mg per day for 7 days	Ecuador	Yépez, M.C.; Zambrano, D.; Carrasco, F.; Yépez, R. F.	2000	RAVREDA-AMI	Observational follow-up and household interviews	Quinindé canton, province of Esmeraldas in northwestern Ecuador (n=249)	34.2% treatment failure and 58.8% adherence	For every three adherent patients, two were nonadherent; nonadherence was significantly associated with age, sex, schooling, ethnicity, urban or rural residence, or level of financial income. Knowledge of the seriousness of the infection did contribute to adherence. Reasons for nonadherence were associated primarily with the medicines (side effects/reluctance to take them); other reasons included forgetting to take the medicine and having "been cured immediately."

*Systematization of Studies of Adherence to Antimalarial Treatment Conducted from 2004 to 2009 in Countries of the Amazon Basin*

<b>Title of Study*</b>	<b>Interventions</b>	<b>Country</b>	<b>Authors</b>	<b>Year</b>	<b>Financing</b>	<b>Study/Sample Design</b>	<b>Sample</b>	<b>Findings/ Adherence Level</b>	<b>Conclusions</b>
Adherence to <i>P. vivax</i> treatment in the Ecuadoran communities of Milagro, Huaquillas, and Esmeraldas	Shortened 7-day treatment with CQ + PQ and 14-day treatment with CQ + PQ	Ecuador	RAVREDA-AMI, SNEM	2004	RAVREDA-AMI	Observational follow-up and household interviews	Milagro (n=90), Esmeraldas (n=65 and n=65), and Huaquillas (n=71)	Results for the 14-day regimen were 72% in Milagro (65/90), 25% in Huaquillas (18/71), and 52% in Esmeraldas (34/65). Failure to adhere to the 7-day treatment regimen was 12% (11/90) in Milagro and 20% (18/90) in Esmeraldas.	The shortened 7-day treatment regimen with a double dose of PQ for <i>P. vivax</i> malaria reduced the percentage of failure to adhere to treatment and is thus deemed to constitute a recommendable measure that can contribute to curing malaria. It suggests that the shortened treatment with CQ + PQ may be a factor contributing to increased adherence.
Studies to evaluate adherence to the treatment regimen for <i>P. vivax</i> , CQ + PQ for 7 days, in the city of Colniza in Mato Grosso state, and in Augusto Correia in Pará state.	Shortened 7-day treatment with CQ + PQ	Brazil	RAVREDA-AMI, Ministry of Health	2005	RAVREDA-AMI	Observational follow-up and household interviews	Augusto Correia (n=94) and Colniza (n=115)	In Augusto Correia, unused tablets were found in 4 cases (4%). The remaining patients (96%) were classified as probably adherent. In Colniza, of the 115 patients evaluated, 8 (7%) were classified as nonadherent and 107 (93%) as probably nonadherent.	The study showed that problems involving adherence to treatment (PQ) arose in association with a number of factors, most notably the actual instructions provided by dispensers and patient failure to understand the medicine dosage form.



Title of Study*	Interventions	Country	Authors	Year	Financing	Study/Sample Design	Sample	Findings/ Adherence Level	Conclusions
Adherence to treatment of uncomplicated <i>P. vivax</i> malaria in the municipality of Tierralta and to treatment of uncomplicated <i>P. falciparum</i> malaria in the municipality of Puerto Libertador in the department of Córdoba, Colombia	14-day treatment of <i>P. vivax</i> with CQ + PQ	Colombia	Colombian Ministry of Social Protection PAHO representative in Colombia	2005	RAVREDA-AMI	Transversal study based on structured interviews with patients in their homes on the final day of treatment, plus counting of remaining unused tablets	Tierralta (n=80)	87% nonadherence CQ + PQ, 14 days	This study revealed a high percentage of patients with an incorrect prescription, significant medicine management problems, poor handwriting used to write prescriptions, use of medicines not recommended by the central level, inadequate packaging, and lack of information on adverse effects. The study concluded that all of these factors act directly on failure to adhere to treatment. Data from Puerto Libertador are not included in the study results.
Study of the 14-day treatment of <i>P. vivax</i> with CQ + PQ and treatment of <i>P. falciparum</i> with AQ + SP (AQ 3 days + SP) in the municipality of Apartadó, Colombia	14-day treatment of <i>P. vivax</i> with CQ + PQ and treatment of <i>P. falciparum</i> with AQ (3 days) + SP	Colombia	RAVREDA-AMI, Ministry of Health	2005	Ministry of Social Protection, departmental health secretariats, RAVREDA-AMI	Descriptive study based on structured interviews of patients in their homes on the final day of treatment, plus counting of remaining unused tablets	Apartadó (n=61 and n=22)	61 patients receiving 14-day course of therapy with CQ + PQ were evaluated; of these, 6 (10%) were classified as nonadherent, 4 (6%) as probably nonadherent, and 51 (84%) as probably	The study conclusions suggest that proper prescribing in a clear and simple manner could contribute to enhanced adherence

Title of Study*	Interventions	Country	Authors	Year	Financing	Study/Sample Design	Sample	Findings/ Adherence Level	Conclusions
								adherent. Regarding treatment of <i>P. falciparum</i> , 22 patients were evaluated, of which 1 (4.5%) was classified as nonadherent, 2 (9%) as probably nonadherent, and 13 (86%) as probably adherent.	
Studies of adherence to treatment of <i>P. vivax</i> in the towns of Esmeraldas, Machala, Milagro, and Santo Domingo, Ecuador, in 2005 and 2006	CQ + PQ for 7 days with PQ (0.5 mg/kg/day)	Ecuador	RAVREDA-AMI, Ministry of Health	2005	RAVREDA-AMI	Descriptive, based on structured interviews of patients in their homes on the final day of treatment, plus counting of remaining unused tablets	Esmeraldas, Machala, Milagro, and Santo Domingo (n=101)	Results show that 101 patients were evaluated, of which 20 (20%) were classified as nonadherent, 20 as probably nonadherent, and 61 (60%) as probably adherent.	In the studies of 7-day treatment regimens, prescribing practices were improved with the introduction of written instructions and staff training.

Title of Study*	Interventions	Country	Authors	Year	Financing	Study/Sample Design	Sample	Findings/ Adherence Level	Conclusions
Study of prescribing and dispensing practices and adherence to antimalarial treatment in Colombia	7-day short course of therapy with CQ + PQ for <i>P. vivax</i> in Tumaco; 14-day course of therapy with CQ + PQ for <i>P. vivax</i> in Pizarro; and 3-day course of therapy with artemether and lumefantrine for <i>P. falciparum</i>	Colombia	RAVREDA-AMI, MSH	2009	USAID	Descriptive, based on a review of records, direct observations of visits to clinics, and exit interviews of patients leaving the clinic and in patients' homes	Tumaco (n=28) and Pizarro (n=85)	The results from Pizarro showed a lack of adherence totaling 33% of the sample as regards treatment for <i>P. vivax</i> , and 100% of the sample as regards treatment for <i>P. falciparum</i> . In Tumaco, failure to adhere to treatment was 0% for <i>P. vivax</i> and 1.4% for <i>P. falciparum</i> . 97% of patients (in the case of <i>P. falciparum</i> ) and 85% (in the case of <i>P. vivax</i> ) understood the proper way to take the medicines prescribed.	The study revealed the existence of difficulties in prescribing and dispensing practices and suboptimal levels of adherence associated primarily with failure to update guidelines for care provision and to standardize treatment regimens; deficiencies in the quality of prescribing; and problems involving dispensing of treatment regimens owing to the stock-out of medicines.

*Systematization of Studies of Adherence to Antimalarial Treatment Conducted from 2004 to 2009 in Countries of the Amazon Basin*

<b>Title of Study*</b>	<b>Interventions</b>	<b>Country</b>	<b>Authors</b>	<b>Year</b>	<b>Financing</b>	<b>Study/Sample Design</b>	<b>Sample</b>	<b>Findings/ Adherence Level</b>	<b>Conclusions</b>
Study of prescribing and dispensing practices and adherence to antimalarial treatment in Peru	<i>P. vivax</i> with CQ + PQ for 7 days and <i>P. falciparum</i> with MQ + AS for 3 days	Peru	RAVREDA-AMI, MSH	2009	USAID	Descriptive, transversal, and retrospective	Maynas, department of Loreto (n=915)	88.5% adherence to treatment	The study concluded that only 60% of prescriptions are consistent with national therapeutic recommendations for the treatment of malaria. If to this is added the fact that 12% of patients did not adhere to the prescribed treatment, it can be stated that for every 100 patients diagnosed with malaria, only 53 received the benefit of efficient treatment management.
Study of prescribing and dispensing practices and adherence to antimalarial treatment in Ecuador	<i>P. vivax</i> with CQ + PQ for 7 days	Ecuador	RAVREDA-AMI, MSH	2009	USAID	Descriptive, transversal, and retrospective	Napo, Orellana, Sucumbios, Pastaza, and Morona Santiago (n=720)	The interviews and the counting of tablets showed that 94% of patients were in compliance with treatment for <i>P. vivax</i> in accordance with the course of therapy prescribed. Nonadherence to treatment was attributed to untoward effects, the most important of	The study revealed that prescription of antimalarial medicines currently reflects a high percentage of consistency (97.2%) with established guidelines, that graphic instructions continue to be used to promote adherence to treatment, and that these instructions have likely contributed to a level of adherence to treatment that totals 94% of all patients receiving treatment.

Title of Study*	Interventions	Country	Authors	Year	Financing	Study/Sample Design	Sample	Findings/ Adherence Level	Conclusions
								which were nausea or vomiting (44.5%), bad-tasting medicine (44.5%), and muscle pain (2%).	
Study of prescribing and dispensing practices and adherence to antimalarial treatment in Brazil	<i>P. vivax</i> with CQ + PQ for 7 days	Brazil	RAVREDA-AMI, MSH	2009	USAID	Descriptive, transversal, and retrospective	Goiania (n=118) and Manaus (n=165)	Goiania: Adherence failure (nonadherents + probable nonadherents) was observed in 26 patients, accounting for 18.8% of the total; 6.1% (7 nonadherents) had a blister pack containing unused tablets, and 13.8% failed to take the medicine in accordance with instructions received (19 probable nonadherents).  Manaus Adherence failure (nonadherents +	The study revealed the existence of problems involving adherence to treatment (PQ) associated with a number of factors, which ranged from the actual instructions provided by dispensers to patient failure to understand the medicine dosage form.

Title of Study*	Interventions	Country	Authors	Year	Financing	Study/Sample Design	Sample	Findings/ Adherence Level	Conclusions
								probable nonadherents) was recorded for 31 patients, accounting for 18.8% of the total; 6.1% (10) were classified as nonadherent because they had blister packs containing unused tablets, and 12.72% (21) indicated that they had not properly taken the medicine.	

\* These are translations of the study names; the studies are written in Spanish or Portuguese.

## ANNEX 2: ANALYSIS OF THE RESULTS OF INTERNATIONAL INTERVENTIONS

Interventions	Country/Author/Year	Study/Sample Design	Findings/ Adherence Level e	Conclusions
<b>1. Prescription: Adherence associated with therapeutic regimens prescribed in health facilities</b>				
a. Therapeutic regimens of CQ + PQ prescribed in health facilities				
Shortened 14-day treatment with CQ + PQ CQ (25 mg base/kg for 3 days) + PQ (0.25 mg/kg per day for 14 days)	Thailand (Khantikul N, 2009)	Retrospective study (n=206)	23.80% adherent	<p><i>P. vivax</i> malaria. Two of the studies revealed that the shortened 3-day and 5-day CQ + PQ regimens resulted in a 74% level of adherence, in contrast with the results obtained for the 7-day (58%) and 14-day (23.8%) regimens. This suggests that the shortened CQ + PQ treatment can be a factor contributing to increased adherence. The efficacy of CQ + PQ in the treatment of <i>P. vivax</i> is well known and widely described. Even so, insufficient information is available to demonstrate that shortened treatment, compared to traditional courses of therapy, is a factor contributing to an increased level of adherence to antimalarial treatment. The methods used in this intervention were not sufficiently rigorous to reach such a conclusion.</p>
Shortened 7-day treatment with CQ + PQ CQ: 150 mg tabs, 4 tabs on day 0, followed by 3 tabs/day + PQ: 75 mg per day for 7 days	Ecuador (Yépez M, 2004)	Observational follow-up (n=129)	58% adherent	
Shortened 5-day treatment with CQ + PQ CQ: 4 mg on days 0-1, 2 mg on days 2-4. PQ: 75 mg per day for 5 days	Sri Lanka (Reilly, 2002)	Interviews (n=271)	74% adherent	
Shortened 3-day treatment with CQ + PQ	Ecuador (Yépez M, 2004)	Observational follow-up (n=121)	74% adherent	
b. Therapeutic regimens using ACT prescribed by health facilities				
Treatment with artemether + lumefantrine (Coartem) for 3 days (2/day for 3 days)	Uganda (Fogg, 2003)	Clinical follow-up (n=210)	90% adherence	<p>Results revealed that treatment with Coartem led to a 90% level of adherence compared to combined treatments with MQ (80% and 87%). This suggests that the fixed-dose combination (FDC), taken over a short</p>
Treatment with AS + MQ (MAS) for 3 days. (AS: 12mg/kg for 3 days; MQ: 25 mg/kg for 2 days)	Cambodia (Yeung, 2004)	Clinical follow-up (n=361)	80% adherence	

Interventions	Country/Author/Year	Study/Sample Design	Findings/ Adherence Level e	Conclusions
Treatment with artesunate + mefloquine (MAS) for 2 days. (Artesunate: 300mg (50mg tabs x 6), single dose on day 0. Mefloquine: 750mg (250mg tabs x 3) after 24 hours and 500 mg after 30 hours)	Thailand (Na-Bangchang, 1997)	Clinical follow-up (n=126)	87%	period of time, could contribute to an increased level of adherence to antimalarial treatment.
<b>2. Prescription: Adherence associated with patient education provided by health facility prescriber</b>				
a. Oral and written information provided by prescriber	Ghana (Agyepong IA, Ansah, 2001)	Quasi-experimental (n=299)	42% oral + information vs. 91% oral + graphic information on dosage	Adherence level was 42% with oral dosage form vs. 91% with tablets + information for patient + medicine labeling. The results suggest that at the community level for outpatient care, presentation in tablet form + graphic information on labeling regarding dose contributed to increased adherence as compared to oral liquid dosage form.
	Gambia (Conteh L, 2007)	Interviews (n=1,337)	Not applicable	Clear information presented to clients in simple, easy-to-understand language by the prescriber, together with improved labeling of medicines for home treatment of acute episodes of malaria contribute to increased adherence. The results show that the intervention led to an increase in adherence in all clinics.
	Nigeria (Okonwo, 2001)	Interviews (n=632)	73.3% picture + oral information 51.9% picture only	The introduction of a pictogram targeting the illiterate population, who are unable to understand the use of age or weight in dispensing medicines, can be substituted for written information delivered to the patient. This strategy increased adherence from 51% to 73%.



Interventions	Country/Author/Year	Study/Sample Design	Findings/ Adherence Level e	Conclusions
<b>3. Dispensing: Adherence associated with dispensing strategies</b>				
a. DOTS/supervised	Thailand/Bangladesh (Rahman MM, 2008)	Controlled randomized study (n=320)	93% unsupervised	The studies conducted in Myanmar and Bangladesh proved the existence of factors associated with good adherence without supervision, such as correct prescribing, using dosage forms with FDCs of ACT, and taking the medicine for fewer days. The study conducted in Peru did not benefit from a rigorous design; even so, it corroborates and supports the findings of the Ghana study, which concluded that adherence to supervised treatment is almost 90% vs. 84% for unsupervised, and that home-based treatment without supervision probably contributes to poor adherence to treatment.
	Myanmar (Smithuis F, 2006)	Open, comparative randomized study (n=656)	No difference between supervised and unsupervised	
	Ghana (Oduro AR, 2008)	Randomized comparative study (n= 638)	91.3% supervised 84% unsupervised	
	Peru (Llanos-Zavalaga F, 2001)	Qualitative transversal study (n=35)	Supervision contributes to increased adherence	
b. Dispensing by community medicine distributors	Sub-Saharan Africa (Uganda, Ghana, and Nigeria) (Ajayi IO, 2008)	Large-scale multicenter study (n=1,289)	Average of 94%	The effectiveness of ACTs dispensed by community distributors is reflected in an average adherence to treatment of 94% in the three study countries.
c. Prepackaged	Uganda (Kolaczinski JH, 2006) CQ + SP (HOMAPAK)	Survey (n=241)	96.30%	The four studies concluded that prepackaged or blister packaging was considered to be useful, because medicines can be kept clean and dry, contamination of the medicine can be eliminated, and costs can be reduced by 50%. Adherence to treatment using the prepackaged dosage form totaled 94.5%, compared with 76.5% using traditional packaging (Lauwo JA, 2006) and 60.5% with traditional packaging vs. 82% with prepackaged/blister (Yeboah-Antwi. K
	Papua New Guinea (Lauwo JA, 2006)	Controlled randomized study (n=322)	94.5% prepackaged + printed information vs. 76.5% among patients not given printed information	
	Ghana (Yeboah-Antwi. K et al., 2001)	Controlled randomized study (n=654)	60.5% traditional packaging vs. 82% prepackaged/blister	

<b>Interventions</b>	<b>Country/Author/Year</b>	<b>Study/Sample Design</b>	<b>Findings/ Adherence Level e</b>	<b>Conclusions</b>
	China (Quinjun L et al., 1998)	Controlled randomized study (n=138)	83% traditional packaging vs. 97% prepackaged/blister	et al., 2001).
<b>4. Education: Adherence associated with community education (IEC) and education provided in facilities</b>				
a. Community educators/IEC/businesses	Kenya (Marsh, 2004)	Household survey (n=109)	4% prior to the intervention 75% subsequent to the intervention	Materials distributed by community educators (IEC). Graphics showing treatment dose plus delivery of prepackaged treatment led to a 75% level of adherence compared with 4% prior to the intervention.
b. Audiovisual educational materials in health facilities and communities (IEC)	Cambodia (Dennis, 1998)	Comparative randomized study (n=325)	10% prior to the intervention 39% subsequent to the intervention	Adherence was 39% for educational materials consisting of posters and videos, compared to 10% when only posters were used.